United States
Environmental Protection
Agency

FINAL
ECAO-CIN-414
April, 1988

EPA

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR POLYCHLORINATED BIPHENYLS (PCBS)

Prepared for

OFFICE OF DRINKING WATER

Prepared by

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DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1986; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

TABLE OF CONTENTS (cont.)

TABLE OF CONTENTS (cont.)

LIST OF TABLES

LIST OF TABLES (cont.)

LIST OF TABLES (cont.)

LIST OF TABLES (cont.)

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAH	Aryl hydrocarbon hydroxylase
BCF	Bioconcentration factor
BHC	Benzene hexachloride
BOD	Biologic oxygen demand
bw	Body weight
CAS	Chemical Abstracts Service
CB	Chlorinated biphenyl
d	Deuterium
DCB	Dichlorinated biphenyl
DEN	Diethylnitrosamine
DMBA	Dimethylbenzanthracene
DMN	Dimethylnitrosamine
DNA	Deoxyribonucleic acid
DP	Diphenyl
DWEL	Drinking water equivalent level
EROD	Ethoxyresorufin o-deethylase
eV	Electron volts
EXAMS	Exposure Assessment Modeling System
2-FAA	N-2-fluoroenylacetamide
GC	Gas chromatography
GI	Gastrointestinal
gmw	Gram molecular weight
H	Proton
HA	Health Advisory
HCB	Hexachlorinated biphenyl
HPLC	High performance liquid chromatography
I.D.	Internal diameter
i.p.	Intraperitoneal
K_{ow}	Octanol water coefficient
KC	Kanechlor
LD_{50}	Lethal dose for 50% of recipients
LOAEL	Lowest-observed-adverse-effect level

LOEL	Lowest-observed-effect level
$(M + H)^+$	Molecular weight ion plus 1
$(M + H_2 - Cl)^+$	Molecular weight ion plus 2 minus chlorine
3-MC	3-methylcholanthrene
MCB	Monochlorinated biphenyl
3'-MeDAB	3'-methyl-4-dimethylaminoazobenzene
MFO	Mixed function oxidase
MNNG	N-methyl-N'-nitro-N'-nitrosoguanidine
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCB	Polychlorinated biphenyl
PCDF	Polychlorinated dibenzofuran
PCE	Polychromatic erythrocytes
PCQ	Polychloroquaterphenyl
PeCB	Pentachlorinated biphenyl
pH	$-\log (H^+)$
ppb	ng/mℓ (liquids); nℓ/ℓ (gases/vapors); ng/g (solids)
ppm	µg/mℓ (liquids); µℓ/ℓ (gases/vapors); µg/g (solids)
RfD	Reference dose
RNA	Ribonucleic acid
s.c.	Subcutaneous
S_N1	Substitution nucleophilic first order reaction
S_N2	Substitution nucleophilic second order reaction
SNARL	Suggested no adverse response level
STEL	Short-term exposure limit
TCB	Tetrachlorinated biphenyl
TEM	Triethylenemelamine
TPA	12-O-tetradecanoylphorbol-13-acetate
triCB	Trichlorinated biphenyl
TWA	Time weighted average
UV	Ultraviolet

DEFINITIONS

Isomers	PCBs having the same molecular weight and chlorine number but with the chlorines substituted differently
Congeners	PCBs having different numbers of chlorines

I. SUMMARY

Evaluation of the health effects of polychlorinated biphenyls (PCBs) in the environment represents a highly complex problem. The empirical formula for PCBs is $C_{12}H_{10-n}Cl_n$ (n=1-10), which in theory allows for the formation of 209 different individual PCBs. Commercial formulations of PCBs enter the environment as mixtures consisting of a variety of individual PCB congeners and impurities, including polychlorinated dibenzofurans (PCDFs). The toxicity of some individual PCB congeners and specific impurities such as the PCDFs has been examined using laboratory animals.

Various commercial mixtures of PCBs have been marketed under a number of trade names including Aroclor (Britain and USA), Phenochlor or Pyralene (France), Clophen (FRG), Kanechlor or Santotheam (Japan), Fenclor (Italy) and Sovol (USSR). Since commercial formulations contain a complex mixture of PCBs, the physical properties of a given formulation will vary depending on the components and composition of the mixture. The physical properties of the biphenyl family vary considerably, having a molecular weight range of 154 for biphenyl to 499 for decachlorobiphenyl (the PCB with the most chlorines), a log octanol/water partition coefficient range of 3.76-8.26 for PCBs, and an aqueous solubility range of 9.77×10^{-10} to 4.68×10^{-3} mol/l.

Commercial PCB mixtures are estimated to volatilize from ambient water, with half-lives ranging from 2 months to >150 years for low and high molecular weight mixtures, respectively. The most important input parameter affecting volatilization rates is the octanol/water partition coefficient, since this reflects the amount of PCBs partitioning into the water from sediments and biota, and the amount available for volatilization. Sediments

and other organic matter adsorb PCBs effectively, the more highly chlorinated congeners being adsorbed better than the lower chlorinated biphenyls. Thus, the adsorption of PCBs onto sediments and matter with high organic content is perhaps the dominant process for removal of highly chlorinated biphenyls from water.

As with volatilization and water solubilization, biodegradation is significant for only the less chlorinated, low molecular weight PCBs. PCBs containing three or fewer chlorines will tend to be degraded more than the highly chlorinated PCBs.

The analysis for PCBs in the environment or biological tissues must be performed on a specific or surrogate congener basis using capillary GC/MS, because the patterns characteristic of Aroclor are not retained in most situations except for highly contaminated conditions.

PCBs form PCDFs when heated, but both are destroyed at a 2-second residence time at 1200°C with 3% excess oxygen or a 1.5-second residence time at 1600°C with 2% excess oxygen. PCDFs can be produced from PCBs by sunlight photodecomposition though the environmental importance of the process is unknown.

PCBs have been detected in almost all components of the global ecosystem, including water.

The major exposure routes to humans are through food and by inhalation. Dermal exposure is also important in occupational exposures, for swimmers in polluted waters, and in cleaning up PCB spills or from leaking hazardous

waste sites containing PCBs. In all cases, total PCB levels are best characterized by specific congener analysis or total PCB by perchlorination rather than in terms of Aroclors, because the congener patterns in environmental media and biological tissues usually do not match those in Aroclor fluids unless massive contamination has occurred (typical of spills and some occupational situations). Thus, predictive models based on specific congener data must also be utilized.

The less chlorinated congeners predominate in air samples from known contaminated areas, and in water and wet deposition samples with the temperature and amount of sediment in river and water samples being important covariables. In contrast, the more highly chlorinated isomers with substituents at the 2,4,5- or 2',4',5'-positions tend to bioaccumulate in some crop vegetables, game animals, fish and in human tissue samples. PCBs in contaminated soils can be absorbed by plants and vegetables with shallow-root systems, although volatilization in this situation is also favored; erosion of such particles will also cause contamination of sediments. The more chlorinated congeners will dominate in soils and sediments and the resident biota (cash crops, vegetables, fish, aquatic life). The absolute levels in any situation depend on which of the competing processes dominates as estimated in Table IV-7. Congeners of Aroclor 1016 have been detected in finished drinking water obtained from the Hudson River and samples from well water taken during the National Organic Monitoring Survey. The finished drinking water from Dority Reservoir treatment and distribution in upstate New York was reported to contain Aroclor 1016. Water from the public water supply system of the village of Fort Edward, located near the township of Moreau of Saratoga County, New York is obtained from Dority Reservoir treatment and distribution system. The level of Aroclor 1016 in this finished

drinking water corresponded well to the median level in the Dority River water.

Because of their lipophilic and relatively stable nature, PCBs rapidly bioaccumulate in biota and the tissues of humans. PCBs are effectively absorbed following oral, dermal and inhalation exposure. In most animal species that have been investigated there is an initial uptake of PCBs into the liver and muscle because of high perfusion in the liver and the relatively large muscle volume. Subsequent redistribution of PCBs into adipose tissue and skin reflects the high affinity of the PCBs for lipophilic tissues. At equilibrium the elimination of PCBs from all tissues will be dependent on the structure-dependent metabolism rates of individual PCB congeners. For example, biological half-lives in the rat range from 0.15 days for 2,2'-di-CB to ~460 days for 2,2',4,4',5,5'-hexa-CB.

Metabolism is apparently the primary rate-limiting event regulating the elimination of PCBs from mammalian systems. The in vitro metabolism of PCBs has been investigated in liver microsomes from the human, monkey, dog, and rat. The data suggest that the human metabolism of PCBs would most closely resemble that of the rat. Therefore, the rat should be a good model for predicting the disposition of PCBs in humans.

The position and degree of chlorination substantially influence the rate and extent of PCB metabolism. As the degree of chlorination increases on both phenyl rings the rate of metabolism decreases, though there is also a selectivity with respect to type of substitution for isomers. The availability of two vicinal unsubstituted carbon atoms facilitates metabolism of the PCB substrate but is not a necessary requirement for metabolism.

Although phenolic products are the major PCB metabolites, sulfur-containing metabolites, trans-dihydrodiols, polyhydroxylated PCBs and their methyl ether derivatives have been identified. The presence of trans-dihydrodiol metabolites strongly suggests metabolism through an arene oxide intermediate. Arene oxides have been implicated in cellular necrosis, mutagenicity and carcinogenicity; however, the role of metabolism in the genotoxicity of PCBs has not been delineated.

Studies using laboratory animals clearly demonstrate that PCBs can cross the placental barrier and accumulate in the fetus. Another major route of exposure occurs by lactation in which the highly lipophilic PCBs are readily transferred from maternal milk to the neonate. The latter route represents the most important route of PCB exposure for the young.

Preferential structure-dependent bioaccumulation of PCB congeners has been observed in human liver, adipose tissue, serum and milk. 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5'-hexa-CB, 2,2',3,3',4,4',5-hepta-CB and 2,2',3,4,4',5,5'-hepta-CB are major components of both a high molecular weight commercial PCB mixture (Aroclor 1260) and human milk. On the other hand, 2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2,2',4,4',5-penta-CB, 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB are identified as major components of human milk extract, while representing only minor components of Aroclor 1260. Human studies also clearly indicate the importance of lactation as the major route of infant PCB exposure, and represent a major route of depuration for mothers with high body burden of PCBs.

In evaluating the health effects of PCBs in animals, it is important to consider the isomer specific composition of the PCBs and potential impuri-

ties, the length of exposure, and the species under investigation. In general, PCB mixtures have low to moderate acute toxicity in mammalian species. Single dose oral LD_{50}s of commercial PCB mixtures in rats range from 1.0-11.3 g/kg bw. Limited data also suggest that the acute toxic potency of PCB mixtures is similar in other species following oral, dermal or i.p. exposure.

Data on purified PCB isomers have established that the toxic, metabolic and toxicokinetic behavior of the different component molecules varies not only with the degree of chlorination (greater toxic potency with greater degree of chlorination) but also with the position of the chlorine atoms. The relative toxicity and persistence of four pure hexa-CB isomers was examined in mice; 3,4,5-sym-hexa-CB was found to be the most acutely toxic (LD_{50} = 19 mg/kg bw/day) and persistent (levels in liver and adipose tissue) isomer, followed by 2,4,6-sym-hexa-CB > 2,4,5-sym-hexa-CB, > 2,3,6-sym-hexa-CB. Although structure-activity relationships are most interesting for this class of compounds, it is also important to note that highly toxic, coplanar PCB isomers, such as 3,4,5-sym-hexa-CB, have only been detected as very minor constituents of commercial PCB formulations.

Animals are sensitive to subchronic and chronic exposures to PCBs. This is due in part to the rapid bioaccumulation of PCBs to toxic levels following long-term, low-level exposure.

A major target organ for PCBs is the liver; an increase in the liver-to-body weight ratio is one of the most sensitive indicators of PCB exposure. Hepatomegaly has been observed in rats ingesting diets containing as little as 20 ppm Aroclor 1254 (PCB mixture with an average chlorine content of 54%)

for 4 days (1 mg/kg bw/day). Hepatomegaly results from liver cell hypertrophy, which is caused by fatty infiltration and proliferation of the smooth endoplasmic reticulum. The latter response is associated with the induction of certain hepatic enzymes, particularly the microsomal mixed function oxidases. Hepatic fluorescence, which is suggestive of porphyria has also been reported after exposure of rats for 16 weeks to 10 ppm of Aroclor 1254 (0.5 mg/kg bw/day). Focal necrosis and iron-containing deposits in Kuppfer cells have been observed at higher levels of exposure.

PCBs have also been shown to produce immunosuppression, which maybe associated with thymic atrophy, lymphocytopenia and splenomegaly. Other PCB-related toxicity include a reduction in food and water intake, reduced rate of body weight gain (wasting syndrome), and decreased body temperature. Another sensitive indicator of PCB exposure is an enlarged thyroid. Ultrastructural evidence suggestive of increased thyroid gland activity has been reported in rats maintained on diets containing as little as 5 ppm Aroclor 1254 (0.25 mg/kg bw/day) for 4 weeks.

In a chronic study that defined a NOAEL, BALB/CJ mice were maintained for 9 months on diets containing 0, 3.75, 37.5 or 375 ppm of the Aroclors 1221, 1242 or 1254 (0.45, 4.57 or 45.7 mg/kg bw/day). The Aroclor with the lowest chlorine content (1221) produced no liver lesions, while exposure to Aroclor 1242 resulted in increased liver weight in the high-dose group. In mice exposed to Aroclor 1254, increased mortality was observed in the high-dose group, mild hepatopathology observed in the median-dose group, and no liver lesions detected in the low-dose group. The NOEL observed in the study using mice of 0.45 mg/kg bw/day is nearly identical to the LOELs of

0.5 mg/kg bw/day associated with porphyria in rats and 0.25 mg/kg bw/day associated with enlarged thyroid.

Monkeys have been found to be highly sensitive to the toxic effects of PCBs. Signs of toxicity with chronic exposure to Aroclor 1248 include severe facial and subcutaneous edema, comedones and cysts of the meibomian glands, gastric lesions, body weight loss and reduced hemoglobin and leukocytes. The lesions are unique to the monkey and resemble chloracne in man. In the monkey, chronic exposure as low as 0.1 mg/kg bw/day of Aroclor 1248 produce frank toxic effects; no studies have been conducted from which a NOAEL can be derived or to indicate how close 0.1 mg/kg bw/day is to the NOAEL for monkeys.

There are two reports of a slight increase in the incidence of cleft palate in the progeny of mice exposed to PCBs during gestation. Several studies have reported fetal toxicity, which consisted of resorptions, abortions, reduced birth weight, and decreased postnatal survival, in several species that was attributed to PCBs. The mink and monkey are the most sensitive species tested to the reproductive toxicity of PCBs. Complete reproductive failure was observed in mink maintained on a diet containing 5 ppm Aroclor 1242 (0.75 mg/kg bw/day) for 18 months. Rhesus monkeys maintained on diets containing 2.5 or 5 ppm Aroclor 1248 (0.1 or 0.2 mg/kg bw/day) for 18 months had increased abortions at the low dose and maternal toxicity with no live births at the high dose.

Aroclor 1016 is less toxic than Aroclor 1242, which caused 100% mortality in female mink at the same exposure level. Chronic exposure to 2 ppm Aroclor 1016 in the diet (0.3 mg/kg bw/day) appears to be a NOAEL in the

mink. Adult monkeys exposed to Aroclor 1016 in the diet did not have any clinical growth or reproductive abnormalities. However, infants born to the 1 ppm Aroclor 1016 group (0.042 mg/kg bw/day, assuming a monkey consumes 4.2% of its body weight/day) were significantly smaller than controls. Thus, 0.25 ppm (0.0105 mg/kg bw/day) appears to be a NOAEL for chronic oral exposure to Aroclor 1016 in rhesus monkeys.

Reports of mutagenicity in the Ames assay are conflicting. Most reports indicate a lack of mutagenicity. No report of cytogenetic changes or dominant lethal effects attributable to PCBs have been located in the available literature.

Human exposure to PCBs may come from contact with industrial products, accidental contamination of foodstuffs or from association with contaminated environmental components. Similar signs of toxicity are associated with oral, inhalation or dermal exposure. Chloracne is the most commonly encountered dermatologic symptom. These lesions comprise follicular keratosis with comedone formation and acneform eruptions. Other reported dermatologic symptoms include rash, burning sensation, pigmentation (darkening), thickening, and discoloration of the fingernails. It is not clear whether PCB mixtures are solely responsible for chloracne or whether contamination of PCBs with polychlorinated dibenzofurans (PCDFs) resulted in chloracne and other adverse health effects. In Yusho and Yu-cheng poisoning incidents, the presence of PCDFs in the PCB contaminated rice oil and in the liver and other tissues of the victims indicates that PCDFs were the responsible toxic compounds. Hepatic effects associated with PCB exposure include hepatomegaly, hepatic enzyme induction with accelerated rate of drug metabolism, and hepatic dysfunction indicated by an increase in serum hepatic enzyme

activities. A decrease in pulmonary function (forced vital capacity), cough, wheezing, tightness in chest, and upper respiratory or eye irritation were also reported in capacitor manufacturing workers.

Two separate groups of high-risk subpopulations for exposure to PCBs may be identified. The first group includes those persons with the potential for frequent or high exposure, namely, occupationally-exposed workers and breast-fed infants, as PCBs are excreted in the breast milk of lactating humans. The second group includes those individuals with a limited ability to metabolize and excrete PCBs, such as fetuses and neonates (2-3 months old).

Infants born to women exposed to PCB during pregnancy (Yusho incident) were generally small for gestational age and exhibited dark brown pigmentation on the skin and mucous membranes, gingival hyperplasia, early eruption of teeth, and facial edema. The PCDF impurities may also determine the severity of these effects.

The available data are insufficient to develop a 1-day HA for PCBs. It is recommended that the 10-day HA for the 10 kg child be used for the 1-day HA for a 10 kg child. A 10-day HA of 100 µg/L for a 10 kg child has been recommended. The toxicity of the PCBs found in water may differ from the commercial PCBs because the congener and impurity composition may be very different from the original Aroclor. Longer-term HAs on Aroclor 1016 for a 70 kg adult and 10 kg child are 0.0035 mg/L and 0.001 mg/L, respectively.

PCBs (Aroclor 1260, Kanechlor 500, Aroclor 1254, Clophen A-30 and Clophen A-60) have been evaluated for carcinogenicity in several animal bioassays. Aroclor 1260 induced a statistically significant increase of heptocellular carcinomas in two rat (Sherman, Sprague-Dawley) feeding studies. Kanechlor 500 produced a statistically significant liver tumor response in dd mice when given in the diet for 32 weeks. Aroclor 1254 fed in the diet to mice (Balb/cj) and rats (Fischer 344) induced increased incidences of liver tumors, and while the incidences are dose-related they were not statistically significant. Clophen A-30 and A-60 induced hepatocellular carcinomas in rats after 832 days of feeding 100 ppm in the diet. This level of carcinogenic evidence in rats and mice for some commercial PCBs (Aroclor 1260, Kanechlor 500 and Aroclor 1254, Clophen A-30 and Clophen A-60) constitute sufficient evidence for carcinogenicity of these commercial PCBs in animals using weight of evidence criteria in the U.S. EPA's guidelines for carcinogen risk assessment (U.S. EPA, 1986a). Only one recent epidemiologic study reports the presence of a carcinogenic risk of liver cancer to humans by ingestion. A significant risk of liver cancer was observed among victims of the Yusho accident in Japan, which involved exposure to contaminated rice oil. There is some uncertainty regarding concurrent exposure to other possibly carcinogenic substances. The authors of the study have not derived conclusions regarding the relationship of exposure to PCB-contaminated rice oil and increased cancer risk. At present, the human epidemiologic evidence is suggestive, but from a weight of evidence classification of the data must be currently regarded as inadequate because of the tentative nature of the data. The authors of these studies have urged caution in the interpretation of their results.

The positive evidence in rats and mice, together with inadequate evidence in humans, places Aroclor 1254 and 1260, Kanechlor 500, and Clophen A-30 and A-60 in the weight-of-evidence category B2, as a probable human carcinogen. PCB mixtures containing significant amounts of components present in Aroclor 1254 and 1260, Kanechlor 500, and Clophen A-30 and A-60 are likely to present a carcinogenic hazard to the human population upon exposure to PCBs. Recognizing the variety and variability of PCB mixtures, it is recommended that all commercial PCB mixtures be considered to have a carcinogenic potential (category B2) similar to that of the five compounds herein evaluated. This is thought to be a prudent public health judgment for which changes could be made if additional scientific evidence is forthcoming.

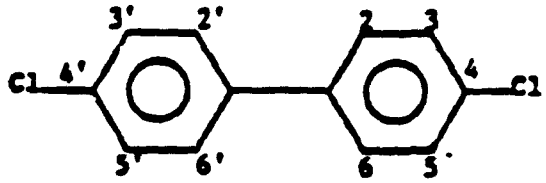
A cancer-based criterion has been calculated for excess lifetime upper-limit cancer risks of 10^{-4}, 10^{-5} and 10^{-6}. The respective water concentrations are 0.5, 0.05 and 0.005 µg/ℓ. These calculations use the linearized multistage dose-response model with data from a study in which hepatocellular carcinomas were caused by chronic dietary administration of the PCB mixture Aroclor 1260 to female Sprague-Dawley rats. Given a lack of information about which constitutents of Aroclor 1260 or any other PCB mixture are carcinogenic, Aroclor 1260 is assumed to be representative of other PCB mixtures. Currently, there is no published report in the literature that shows the presence of Aroclor 1260 in finished drinking water.

II. PHYSICAL AND CHEMICAL PROPERTIES

Structure and Identification

Polychlorinated biphenyls (PCBs) are a family of compounds based on biphenyl as the parent compound. There are 209 possible PCB isomers and congeners of which some 187 have been chromatographically separated and all have been synthesized (Mullin et al., 1984). A listing of all PCB congeners is given in Table II-1 along with their Chemical Abstract Services (CAS) Registry numbers and an identifying numbering system developed by Ballschmiter and Zell (1980).

The structure and numbering of a typical PCB (4,4'-dichlorobiphenyl) is as follows:



Here, an unprimed locant is preferred to its primed locant, with as few primed locants used as possible but keeping the sum of the locant number (primed plus unprimed) a minimum. For rings with equal substitution the ring with the lower numbered locants receives the unprimed numbers. If both rings are equal, the locant cited first is unprimed.

PCBs used commercially are complex mixtures consisting of various PCB congeners and isomers. Monsanto (the former British and U.S. manufacturer) designated a 4-digit code to refer to its PCBs marketed under the tradename Aroclor. In West Germany the name is Clophen; in France, Phenochlor or Pyralene; in Japan, Kanechlor or Santotherm; and in Italy, Fenclor. For Aroclors the first two digits (12) indicate that the preparation is a

TABLE II-1

Numbering of PCB Isomers*

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Monochlorobiphenyls			**Trichlorobiphenyls (cont.)**		
1	2	2051-60-7	22	2,3,4'	38444-85-8
2	3	2051-61-8	23	2,3,5	55720-44-0
3	4	2051-62-9	24	2,3,6	55702-45-9
			25	2,3',4	55712-37-3
Dichlorobiphenyls			26	2,3',5	38444-81-4
			27	2,3',6	38444-76-7
4	2,2'	13029-08-8	28	2,4,4'	7012-37-5
5	2,3	16605-91-7	29	2,4,5	15862-07-4
6	2,3'	25569-80-6	30	2,4,6	35693-92-6
7	2,4	33284-50-3	31	2,4',5	16606-02-3
8	2,4'	34883-43-7	32	2,4',6	38444-77-8
9	2,5	34882-39-1	33	2',3,4	38444-86-9
10	2,6	33146-45-1	34	2',3,5	76708-77-5
11	3,3'	2050-67-1	35	3,3',4	55712-37-3
12	3,4	2974-92-7	36	3,3',5	38444-87-0
13	3,4'	2974-90-5	37	3,4,4'	38444-90-5
14	3,5	34883-41-5	38	3,4,5	53555-66-1
15	4,4'	2050-68-2	39	3,4',5	38444-88-1
Trichlorobiphenyls			**Tetrachlorobiphenyls**		
16	2,2',3	38444-78-9	40	2,2',3,3'	38444-93-8
17	2,2',4	37680-66-3	41	2,2',3,4	52663-59-9
18	2,2',5	37680-65-2	42	2,2',3,4'	36559-22-5
19	2,2',6	38444-73-4	43	2,2',3,5	70362-46-8
20	2,3,3'	38444-84-7	44	2,2',3,5'	41464-39-5
21	2,3,4	55702-46-0	45	2,2',3,6	70362-45-7

TABLE II-1 (cont.)

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Tetrachlorobiphenyls (cont.)			**Tetrachlorobiphenyls (cont.)**		
46	2,2',3,6'	41464-47-5	74	2,4,4',5	32690-93-0
47	2,2',4,4'	2437-79-8	75	2,4,4',6	32598-12-2
48	2,2',4,5	70362-47-9	76	2',3,4,5	70362-48-0
49	2,2',4,5'	41464-40-8	77	3,3',4,4'	32598-13-3
50	2,2',4,6	62796-65-0	78	3,3',4,5	70362-49-1
51	2,2',4,6'	68194-04-7	79	3,3',4,5'	41464-48-6
52	2,2',5,5'	35693-99-3	80	3,3',5,5'	33284-52-5
53	2,2',5,6'	41464-41-9	81	3,4,4',5	70362-50-4
54	2,2',6,6'	15968-05-5			
55	2,3,3',4	74338-24-2		**Pentachlorobiphenyls**	
56	2,3,3',4'	41464-43-1			
57	2,3,3',5	70424-67-8	82	2,2',3,3',4	52663-62-4
58	2,3,3',5'	41464-49-7	83	2,2',3,3',5	60145-20-2
59	2,3,3',6	74472-33-6	84	2,2',3,3',6	52663-60-2
60	2,3,4,4'	33025-41-1	85	2,2',3,4,4'	65510-45-4
61	2,3,4,5	33284-53-6	86	2,2',3,4,5	55312-69-1
62	2,3,4,6	54230-22-7	87	2,2',3,4,5'	38380-02-8
63	2,3,4',5	74472-34-7	88	2,2',3,4,6	55215-17-3
64	2,3,4',6	52663-58-8	89	2,2',3,4,6'	73575-57-2
65	2,3,5,6	33284-54-7	90	2,2',3,4',5	68194-07-0
66	2,3',4,4'	32598-10-0	91	2,2',3,4',6	68194-05-8
67	2,3',4,5	73575-53-8	92	2,2',3,5,5'	52663-61-3
68	2,3',4,5'	73575-52-7	93	2,2',3,5,6	73575-56-1
69	2,3',4,6	60233-24-1	94	2,2',3,5,6'	73575-55-0
70	2,3',4',5	32598-11-1	95	2,2',3,5',6	38379-99-6
71	2,3',4',6	41464-46-4	96	2,2',3,6,6'	73575-54-9
72	2,3',5,5'	41464-42-0	97	2,2',3',4,5	41464-51-1
73	2,3',5',6	74338-23-1	98	2,2',3',4,6	60233-25-2

TABLE II-1 (cont.)

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Pentachlorobiphenyls (cont.)			**Hexachlorobiphenyls**		
99	2,2',4,4',5	38380-01-7	128	2,2',3,3',4,4'	38380-07-3
100	2,2',4,4',6	39485-83-1	129	2,2',3,3',4,5	55215-18-4
101	2,2',4,5,5'	37680-73-2	130	2,2',3,3',4,5'	52663-66-8
102	2,2',4,5,6'	68194-06-9	131	2,2',3,3',4,6	61798-70-7
103	2,2',4,5',6	60145-21-3	132	2,2',3,3',4,6'	38380-05-1
104	2,2',4,6,6'	56558-16-8	133	2,2',3,3',5,5'	35694-04-3
105	2,3,3',4,4'	32598-14-4	134	2,2',3,3',5,6	52704-70-8
106	2,3,3',4,5	70424-69-0	135	2,2',3,3',5,6'	52744-13-5
107	2,3,3',4',5	70424-68-9	136	2,2',3,3',6,6'	38411-22-2
108	2,3,3',4,5'	70362-41-3	137	2,2',3,4,4',5	35694-06-5
109	2,3,3',4,6	74472-35-8	138	2,2',3,4,4',5'	35065-28-2
110	2,3,3',4',6	38300-03-9	139	2,2',3,4,4',6	56030-56-9
111	2,3,3',5,5'	39635-32-0	140	2,2',3,4,4',6'	59291-64-4
112	2,3,3',5,6	74472-36-9	141	2,2',3,4,5,5'	52712-04-6
113	2,3,3',5',6	68194-10-5	142	2,2',3,4,5,6	41411-61-4
114	2,3,4,4',5	74472-37-0	143	2,2',3,4,5,6'	68194-15-0
115	2,3,4,4',6	74472-38-1	144	2,2',3,4,5',6	68194-14-9
116	2,3,4,5,6	18259-05-7	145	2,2',3,4,6,6'	74472-40-5
117	2,3,4',5,6	68194-11-6	146	2,2',3,4',5,5'	51908-16-8
118	2,3',4,4',5	31508-00-6	147	2,2',3,4',5,6	68194-13-8
119	2,3',4,4',6	56558-17-9	148	2,2',3,4',5,6'	74472-41-6
120	2,3',4,5,5'	68194-12-7	149	2,2',3,4',5',6	38380-04-0
121	2,3',4,5',6	56558-18-0	150	2,2',3,4',6,6'	68194-08-1
122	2',3,3',4,5	76842-07-4	151	2,2',3,5,5',6	52663-63-5
123	2',3,4,4',5	65510-44-3	152	2,2',3,5,6,6'	68194-09-2
124	2',3,4,5,5'	70424-70-3	153	2,2',4,4',5,5'	35065-27-1
125	2',3,4,5,6'	74472-39-2	154	2,2',4,4',5,6'	60145-22-4
126	3,3',4,4',5	57465-28-8	155	2,2',4,4',6,6'	33979-03-2
127	3,3',4,5,5'	39635-33-1	156	2,3,3',4,4',5	38380-08-4

TABLE II-1 (cont.)

No.*	Structure	CAS No.
Hexachlorobiphenyls (cont.)		
157	2,3,3',4,4',5'	69782-90-7
158	2,3,3',4,4',6	74472-42-7
159	2,3,3',4,5,5'	39635-35-3
160	2,3,3',4,5,6	41441-62-5
161	2,3,3',4,5'6	74472-43-8
162	2,3,3',4',5,5'	39635-34-2
163	2,3,3',4',5,6	74472-44-9
164	2,3,3',4',5',6	74472-45-0
165	2,3,3',5,5'6	74472-46-1
166	2,3,4,4',5,6	41411-63-6
167	2,3',4,4',5,5'	52663-72-6
168	2,3',4,4',5',6	59291-65-5
169	3,3',4,4',5,5'	32774-16-6
Heptachlorobiphenyls		
170	2,2',3,3',4,4',5	35065-30-6
171	2,2',3,3',4,4',6	52663-71-5
172	2,2',3,3',4,5,5'	52663-74-8
173	2,2',3,3',4,5,6	68194-16-1
174	2,2',3,3',4,5,6'	38411-25-5
175	2,2',3,3',4,5',6	40186-70-7
176	2,2',3,3',4,6,6'	52663-65-7
177	2,2',3,3',4',5,6	52663-70-4
178	2,2',3,3',5,5',6	52663-67-9
179	2,2',3,3',5,6,6'	52663-64-6
180	2,2',3,4,4',5,5'	35065-29-3
181	2,2',3,4,4',5,6	74472-47-2
182	2,2',3,4,4',5,6'	60145-23-5
183	2,2',3,4,4',5',6	52663-69-1
184	2,2',3,4,4',6,6'	74472-48-3
185	2,2',3,4,5,5',6	52712-05-7
186	2,2',3,4,5,6,6'	74472-49-4
187	2,2',3,4',5,5',6	52663-68-0
188	2,2',3,4',5,6,6'	74487-85-7
189	2,3,3',4,4',5,5'	39635-31-9
190	2,3,3',4,4',5,6	41411-64-7
191	2,3,3',4,4',5',6	74472-50-7
192	2,3,3',4,5,5',6	69782-91-8
193	2,3,3',4',5,5',6	69782-91-8
Octachlorobiphenyls		
194	2,2',3,3',4,4',5,5'	35694-08-7
195	2,2',3,3',4,4',5,6	52663-78-2
196	2,2',3,3',4,4',5,6'	42740-50-1
197	2,2',3,3',4,4',6,6'	33091-17-7
198	2,2',3,3',4,5,5',6	68194-17-2
199	2,2',3,3',4,5,6,6'	52663-73-7
200	2,2',3,3',4,5',6,6'	40186-71-8
201	2,2',3,3',4,5,5,6'	52663-75-9
202	2,2',3,3',5,5',6,6'	2136-99-4
203	2,2',3,4,4',5,5',6	52663-76-0
204	2,2'3,4,4',5,6,6'	74472-52-9
205	2,3,3',4,4',5,5',6	74472-53-0

TABLE II-1 (cont.)

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Nonachlorobiphenyls				**Decachlorobiphenyl**	
206	2,2',3,3',4,4',5,5',6	40186-72-9	209	2,2,3,3',4,4'5,5',6,6'	2051-24-3
207	2,2',3,3',4,4',5,6,6'	52663-79-3			
208	2,2',3,3',4,5,5',6,6'	5121-88-0			

*Ballschmiter Number (Ballschmiter and Zell, 1980)

biphenyl-C_{12} mixture and the second two digits indicate the chlorine content percentage by mass. Thus, Aroclor 1242 is a biphenyl mixture with an average chlorine content of 42%. Monsanto also developed a mixture that was primarily mono-, di- and tri-chloro isomers, Aroclor 1016. The chromatographic pattern and the actual percent chlorine (41%) is very similar to Aroclor 1242.

The CAS numbers and the Registry of Toxic Effects of Chemical Substances (RTECS) numbers for representative Aroclors are given in Table II-2. Toxic polychlorinated dibenzofurans (PCDFs) have been found in all PCB formulations (Tables II-3, II-4 and II-5).

Physical and Chemical Properties

Some physical properties of some Aroclors are summarized in Table II-6. Molecular formulas of PCB congeners in various Aroclors and Kanechlors are listed in Table II-7. The properties of the Aroclors listed are average values, however, since the Aroclors are mixtures. For example, the molecular mass of the PCB congeners ranges from 154 for biphenyl to 499 for decachlorobiphenyl. Thus, the vapor pressure and water solubilities of an Aroclor reflect the lower chlorinated components of greatest abundance.

Individual PCB congeners increase in vapor pressure with decreasing chlorination (Hutzinger et al., 1974; Westcott et al., 1981; Foreman and Bidleman, 1985; Burkhard et al., 1985a). The vapor pressure of biphenyl is 1.01 pascal at 25°C, whereas that for decachlorobiphenyl is 5.30×10^{-8} pascal (Burkhard et al., 1985a). The Henry's Law constants at 25°C do not

TABLE II-2

CAS and RTECS Numbers for Some Aroclors*

Aroclor No.	CAS No.	RTECS No.	Reference
1016	12674-11-2	NA	NIOSH, 1983
1221	11104-28-2	TQ 1352000	NIOSH, 1983
1232	11141-16-5	TQ 1354000	NIOSH, 1983
1242	53469-21-9	TQ 1356000	NIOSH, 1983
1248	12672-29-6	TQ 1358000	NIOSH, 1983
1254	11097-69-1	TQ 1360000	NIOSH, 1983
1260	11096-82-5	TQ 1362000	NIOSH, 1983
1262	37324-23-5	NA	Alford-Stevens et al., 1986a
1268	11100-14-4	NA	Alford-Stevens et al., 1986a

NA = Not available

TABLE II-3

PCDF Content in Some PCBs and in Kanemi Oil[a]

Substrate	PCDF Content (ppm)					Reference
	Tri-	Tetra-	Penta-	Hexa-	Total	
Yu-Cheng oil[b] (3)					0.14-0.18	Miyata et al., 1985
Kanemi oil[b] (4) (Yusho)					2-7	Miyata et al., 1985
Unused Kanechlor 400[b]					33	Miyata et al., 1985
Used Kanechlor 400[b] (3)					20-510	Miyata et al., 1985
Kanemi oil (Yusho)	0.15	1.4	2.5	1.6	5.7	Buser et al., 1978
Kanemi oil (Yusho)	--	--	--	--	5.0	Nagayama et al., 1976
Used Japanese PCB (Mitsubishi-Monsanto T-1248)	4.2	4.5	5.5	1.4	16	Buser et al., 1978
Kanemi oil	0.02	0.52	1.3	0.81	2.7	Morita et al., 1977a
Kanechlor 300	--	6.7	1.6	-	8.3	Morita et al., 1977a
Kanechlor 300	--	--	1.3	--	1.3	Nagayama et al., 1976
Kanechlor 400	0.3	12.2	10.4	0.9	24	Morita et al., 1977a
Kanechlor 400	--	--	--	-	18	Nagayama et al., 1976
Kanechlor 400	--	1	--	--	--	Roach and Pomerantz, 1974
Kanechlor 500	0.2	1.7	1.1	3.1	6.1	Morita et al., 1977a
Kanechlor 500	-	--	--	--	3.3	Nagayama et al., 1976
Kanechlor 600	--	0.2	0.5	0.4	1.1	Morita et al., 1977a
Kanechlor 600	--	--	--	--	4.0	Nagayama et al., 1976
Phenoclor DP-4	--	1.7	1.6	0.5	3.8	Morita et al., 1977a
Phenoclor DP-5	--	4.6	2.7	2.6	9.9	Morita et al., 1977a

TABLE II-3 (cont.)

Substrate	PCDF Content (ppm)					Reference
	Tri-	Tetra-	Penta-	Hexa-	Total	
Phenoclor DP-6	0.2	2.1	2.6	5.6	11	Morita et al., 1977a
Phenoclor DP-6	--	0.7	10	2.9	14	Bowes et al., 1975
Aroclor T-1200	--	0.1	0.4	0.5	1.0	Bowes et al., 1975
Aroclor T-1241	--	2.4	2.7	0.8	5.9	Morita et al., 1977a
Aroclor T-1242	--	2.3	2.3	--	4.5	Morita et al., 1977a
Aroclor T-1248	--	0.5	2.3	--	2.8	Morita et al., 1977a
Aroclor T-1248[c]	0.3	5.8	5.6	0.7	12	Morita et al., 1977a
Aroclor T-1254	--	0.1	0.2	1.4	1.7	Bowes et al., 1975
Aroclor T-1254	--	0.2	0.4	0.9	1.5	Bowes et al., 1975
Aroclor T-1254	--	0.1	3.6	1.9	5.6	Morita et al., 1977a
Aroclor T-1260	--	0.2	0.3	0.3	0.8	Bowes et al., 1975
Aroclor T-1260	--	0.8	0.9	0.5	2.2	Morita et al., 1977a
Aroclor T-1264	--	4.8	9.4	2.0	16	Morita et al., 1977a
Clophen A-30	1.6	2.3	1.0	--	4.9	Morita et al., 1977a
Clophen A-40	1.5	5.4	6.9	--	14	Morita et al., 1977a
Clophen A 50	0.7	8.3	4.1	1.8	15	Morita et al., 1977a
Clophen A-60	--	1.4	5.0	2.2	8.4	Bowes et al., 1975

[a] No data found for hepta-

[b] Yu-Cheng oil also contained 22-113 ppm PCBs and 9-38 ppm PCQs. Kanemi oil also contained 151-968 ppm PCBs and 490-866 ppm PCQs. Kanechlor 400 also contained 999,800 ppm PCBs and 209 ppm PCQs. Used Kanechlor 400 also contained 961,900-999,000 ppm PCBs and 690-31,000 ppm PCQs.

[c] Used PCB

TABLE II-4

Suspected Maximum Levels of Toxic PCDFs in Various PCBs and in Rice Oils
(Kanemi oil also contained 900 ppm PCBs and 800 ppm PCQs;[a]
Yu-Cheng rice oil also contained 60-100 ppm PCBs and 90-180 ppm PCQs)

Formulation	PCDF Levels (ppm)		Total	Percentages of Total PCDFs for These Two Derivatives
	2,3,7,8-[b,c] TCDF	2,3,4,7,8-[b,d] PeCDF		
Yu-Cheng rice oil (2)[a]	0.001-0.005	0.02-0.70	0.08-0.10	20-25
Kanemi oil[a]	0.2	0.7	2.02	45
Kanemi oil[b]	0.28	0.42	2.68	26
Phenoclor[a]				
DP-4	0.7	0.4	3.8	29
DP-5	2.2	0.8	9.9	30
DP-6	0.9	0.6	10.5	14
Kanechlor[b]				
KC-300	2.2	0.6	8.3	34
KC-400	1.6	0.9	23.8	11
KC-500	0.7	0.7	6.1	23
KC-600	0.1	0.1	1.1	18
Aroclor[b]				
T-1241	1.1	0.4	5.9	25
T-1242	0.2	0.1	4.5	7
T-1248	0.2	0.8	2.8	36
T-1248[e]	1.1	1.4	12	20
T-1254	--	1.6	5.6	29
T-1260	--	0.1	2.2	5
T-1264	2.4	2.3	16	29

TABLE II-4 (cont.)

Formulation	PCDF Levels (ppm) 2,3,7,8-[b,c] TCDF	PCDF Levels (ppm) 2,3,4,7,8-[b,d] PeCDF	Total	Percentages of Total PCDFs for These Two Derivatives
Clophen[b]				
A-30	1.0	0.1	4.9	22
A-40	2.1	0.7	14	20
A-50	3.6	0.6	15	28

[a]Masuda et al., 1982

[b]Calculated from Morita et al., 1977a

[c]Based on GC retention time, but subsequently confirmed by Buser et al. (1978). This was subsequently found to include also the 2,3,4,8-TCDF.

[d]The order of elution obtained by Buser et al. (1978) is assumed to pertain to the GC column utilized.

[e]Used PCB

-- Below detection limit

TABLE II-5

Specific PCDFs in Commercial PCBs (ng/g)*

PCB-typ	Tri-	Tetra-		Penta-			Hexa-					Hepta-	
	Total	2378	Total	12348 12378	23478	Total	123479 123478	123678	123789	234678	Total	Total	Rec 2378-TCDD-%
Pyralene	700	53	630	10	T	35	ND	ND	ND	ND	ND	ND	79
A1254	63	19	1,400	690	490	4000	2500	2100	190	130	10,000	960	78
A1260	10	13	110	48	56	260	500	120	190	27	1,500	1300	88
A30	500	35	573	14	20	160	50	59	ND	ND	220	T	79
A40	1300	100	2,600	96	8	1700	79	68	ND	T	310	ND	79
A50	7400	3300	20,000	760	1100	8000	700	360	10	90	3,100	75	95
A60	770	840	6,900	1100	990	8100	1600	330	170	330	6,800	2000	95
T64	47	23	360	97	122	840	520	390	50	41	2,600	220	72
Clophen C	710	54	1,200	34	30	270	Nd	T	ND	ND	T	ND	79
Blank	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	90
Blank	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	87

*Source: Rappe et al., 1984

ND = Not detected

TABLE II-6

Some Physical Properties of Aroclors[a,b,c]

Property	VALUE						
	1016	1221	1232	1242	1248	1254	1260
Appearance	clear oil	clear oil	clear oil	clear oil	clear oil	light yellow viscous liquid	light yellow sticky resin
Chlorine (percent)	41	20.5-21.5	31.4-31.5	42	48	54	60
Density (g/ml) (25°C)	1.33	1.15	1.24	1.35	1.41	1.50	1.58
Distillation range (°C)	325-356	275-320	290-325	325-366	340-375	365-390	385-420
Evaporation loss % at 100°C/6 hours		1-1.5	1-1.5	0-0.4	0-0.3	0-0.2	0-0.1
Aqueous solubility (mg/l)	0.42[d]	0.59[e]	NA	0.24,0.34[d] 0.13[c]	0.054	0.012, 0.024[f] 0.0569	0.027
Lipid solubility (organic solvents)	very soluble	very soluble	very soluble	very soluble	very soluble	very soluble	very soluble
Vapor pressure (mm Hg at 25°C)	[4x10^{-4}]	[6.7x10^{-5}]	[4.06x10^{-5}]	4.06x10^{-4}	4.94x10^{-4}	7.71x10^{-5}	4.05x10^{-5}
Log octanol/water partition coefficient	4.38[d] >5.58[i,j]	[2.8] 4.09[j,k]	[3.2] >4.54[j,k]	4.11[d] >5.58[i,j]	[5.75][h] >6.11[i,j]	[6.03][h]	[7.14][h] >6.11[i,j]
Adsorption capacity of activated carbon (mg/g)	NA	242[l]	630[l]	NA	NA	NA	NA
Conversion factors 1 ppm = 1 mg/m^3 =	10.85 mg/m^3 0.0948 ppm	8.21 mg/m^3 0.122 ppm	9.50 mg/m^3 0.105 ppm	10.9 mg/m^3 0.0917 ppm	12.2 mg/m^3 0.0816 ppm	13.4 mg/m^3 0.0745 ppm	15.4 mg/m^3 0.0651 ppm

[a]Adapted from Callahan et al., 1979
[b]All values not superscripted are from Monsanto, 1974.
[c]Bracketed data are estimated.
[d]Paris et al., 1978
[e]Mollifield, 1979
[f]Dexter and Pavlov, 1978
[g]Haque et al., 1974
[h]Hansch et al., 1974; Chiou et al., 1977
[i]Chiou et al., 1977
[j]Partition coefficient of lowest chlorinated biphenyl present in significant quantities.
[k]Yalkowsky and Dannenfelser, 1978a
[l]Ramanathan, 1984
NA = Not available

TABLE II-7

Percent Composition of Aroclors and Kanechlors[a]

Empirical Formula	Mass Percentage in Aroclor							Kanechlor Number		
	1016	1221	1232	1242	1248	1254	1260[b]	300	400	500
$C_{12}H_{10}$	<0.1	11	<0.1	<0.1	ND	<0.1	ND	NR	NR	NR
$C_{12}H_9Cl$	1	51	31	1	ND	<0.1	ND	NR	NR	NR
$C_{12}H_8Cl_2$	20	32	24	16	2	0.5	ND	16.6	3.0	NR
$C_{12}H_7Cl_3$	57	4	28	49	18	1	ND	59.8	32.8	5.0
$C_{12}H_6Cl_4$	21	2	12	25	40	21	1	23.0	43.8	26.5
$C_{12}H_5Cl_5$	1	<0.5	4	8	36	48	12	0.6	15.8	55.0
$C_{12}H_4Cl_6$	<0.1	ND	<0.1	1	4	23	38	NR	4.6	12.8
$C_{12}H_3Cl_7$	ND	ND	ND	<0.1	ND	6	41	NR	NR	NR
$C_{12}H_2Cl_8$	ND	ND	ND	ND	ND	ND	8	NR	NR	NR
$C_{12}H_1Cl_9$	ND	ND	ND	ND	ND	ND	ND	NR	NR	NR
Percent chlorine	41	20.5-21.5	31.4-32.5	42	48	54	60	NA	49	54

[a]Source: Callahan et al., 1979; IARC, 1974; Masuda et al., 1974

[b]Kanechlor 600 (Japanese), Phenoclor DP6 (French) and Clophen A60 (German); all contain ~60% Cl (Masuda et al., 1974; Fishbein, 1974).

ND = None detected; NR - Not reported

depend on molecular weight but do for ortho-substituted PCBs (Burkhard et al., 1985b; Arbuckle, 1986). Vapor-particle partitioning of PCBs depends markedly on temperature (Bidleman et al. 1986); at 20°C, only 2.1% of Aroclor 1254 was retained on a filter, whereas at 0°C the percentage was 25%. Differential volatilization of the less chlorinated components of Aroclor 1254 has been observed during air sampling with Tenax-GC, XAD-2 resin, and deactivated Florisil (Brownlow and Que Hee, 1985; Lin and Que Hee, 1987). Enrichment in the higher chlorinated congeners is observed also in the residue after volatilization of the less chlorinated compounds (Lin and Que Hee, 1987).

Individual PCB congeners increase in water solubility, with decreasing chlorination and increasing temperature (Yalkowsky et al., 1983; Mackay et al., 1980; Dickhut et al., 1986). Beyond the Cl_4-PCBs, most of the PCBs tend to be relatively insoluble (Dickhut et al., 1986); for example, 3,3',4,4'-Cl_4-PCB has a solubility of (1.95×10^{-9}) M at 25°C; decachlorobiphenyl similarly has a solubility of (1.30×10^{-12}) M. Octanol/water coefficients increase with increasing chlorination (Rapaport and Eisenreich, 1984). Miller et al. (1985) showed that log K_{ow} values at 25°C varied between 3.76 (biphenyl) and 8.26 for decachlorobiphenyl. The Cl_4-PCBs had a log K_{ow} of ~5.7; the Cl_5-PCBs of ~6.0, and the Cl_6-PCBs of ~7.0. In all of these systems the chlorine substitution in an isomeric class also influences physical property.

PCBs are aromatic and hence can be detected with great sensitivity using ultraviolet (UV) detectors (λ_{max} are at 197-222, 214-265 and 267-302 nm for PCBs), and give strong molecular ions in mass spectra, but because of

the number of possible congeners, infrared spectroscopy (1200-300 cm^{-1}) and nuclear magnetic resonance spectroscopy (7.0-7.6 ppm relative to tetramethylsilane) are poor at sensitively distinguishing congeners (Hutzinger et al., 1974). Mullin et al. (1984) have measured the 'H-NMR spectra for individual Cl_4, Cl_5, Cl_6 and Cl_7-PCBs. As for the Cl_8 and Cl_9-PCBs, the 2,2',6 and 6' protons exhibited the lowest chemical shifts with respect to tetramethylsilane. Protons at the para positions gave the highest chemical shift values. The spectra for the mono-, di- and tri-PCBs were extremely complex.

PCB Analysis

Capillary gas chromatography with nonpolar columns is invariably the last step used to attain optimum separation (Mullin et al., 1984); currently only 187 congeners of the 209 are resolvable. The capillary column used was 50 m x 0.2 mm I.D. fused silica coated with SE-54 and a temperature program of 1.0°C/min from 100-200°C (injector, and ^{63}Ni-electron capture detector temperatures were 270 and 330°C, respectively). The synthesis of all 209 congeners is also provided. The relative retention times are highly dependent on congener structure. Within each series of isomers, there was generally an increase in retention time with a decrease in the number of o-chloro substituents. The electron-capture relative response factors increase with increasing chlorination, but there are wide variations within isomeric classes. Cooper et al. (1985) selected 31 surrogate congeners for each isomeric class based on electron-capture response. Pellizari et al., (1981, 1985) have also discussed these problems. The molecular ion (M) and M-2Cl have been most utilized for specific ion monitoring mass spectroscopy after capillary column separation. Electron impact (70eV) fragmentation is

the most commonly used technique (Alford-Stevens et al., 1986a,b; Gebhart et al., 1985; Silven et al., 1985). However, it is 2-3 orders of magnitude less sensitive than the electron capture detector. Electron impact (70eV) fragmentation is recommended as the basis of U.S. EPA method 680 (Alford-Stevens et al., 1986b). It was shown that the mass spectrometric response factors within an isomeric class varied between 1.3 and 4.6 (Gebhart et al., 1985). Nevertheless, nine surrogate congeners can represent all PCBs in mass spectroscopic response; therefore, the recommendation is that detection limits be found in terms of these nine surrogates. The nine surrogates in terms of chlorine substitution are as follows: 2-, 2,3-, 2,4,5-, 2,2',4,6-, 2,2',3,4,5'-, 2,2',4,4',5,6'-, 2,2',3,4',5,6,6'-, 2,2',3,3',4,5',6,6'- and decachlorobiphenyl (for Cl_9 and Cl_{10}). The only isotopically labeled PCB available is 3,3',4,4'-Cl_4 PCB-d_6 (Gebhart et al., 1985). The recovery of Aroclors from waters shows a negative bias between 15 and 27% when analysed as Aroclors, thus necessitating specific congener analysis (Alford-Stevens et al., 1986b).

Positive methane chemical ionization-GC/MS of PCBs has been reported by Voyksner et al. (1986). The $(M+H)^+$ and $(M+H_2-Cl)^+$ ions were monitored. The relative response for all congeners varies between 0.14 and 1.79 (compare electron impact range of 0.22-4.08), and was generally 2-6 times more sensitive than electron impact detection (but still not as sensitive as electron capture detection).

Environmental samples often require many clean-up steps before interfering peaks can be removed. For example, sediments require Soxhlet extraction or ultrasonic homogenization in hexane/acetone or isopropanol/dichloro-

methane followed by Florisil column chromatography, and removal of sulfur before GC/MS analysis (Alford-Stevens et al., 1985). Using a Webb-McCall Analysis (Webb and McCall, 1973), direct comparison with Aroclor standards or specific congener analysis can then be performed (Alford-Stevens et al., 1985). The Soxhlet extraction is recommended for sediments. In general, direct comparison with Aroclor standards gives higher results than the Webb-McCall method alone. The more heavy the contamination, the better is the accuracy of the Aroclor standards comparison. The noncorrespondence of blood PCB profiles with original Aroclor is well-known from occupational studies (Wolff et al., 1986) and from the Yusho incidents (Chen et al., 1985; Miyata et al., 1985; Kashimoto et al., 1985; Hara, 1985). In general, the sample (tissue or blood) is saponified, extracted with hexane, concentrated and then subjected to Florisil chromatography before GC/MS analysis. Pattern recognition of the GC and GC/MS data from environmental (Capel et al., 1985) and tissue (Wolff et al., 1986) samples has been discussed.

Solvent extraction with dichloromethane is recommended for PCB isolation from environmental waters in U.S. EPA method 680 (Alford-Stevens et al., 1986b). An XAD-4 sorbent method yielded competitive results with the dichloromethane solvent extraction method for Aroclor 1232 in distilled water but not in natural water at a concentration of 10 ppb (Woodrow et al., 1986). Clean-up on HPLC is required for levels below the ppt level.

UV detectors in HPLC can be effectively utilized for sensitive detection of PCBs because of their strong ultraviolet absorption. Normal phase silica columns are usually used with hexane as mobile phase together with methyl t-butyl ether in a linear gradient program (Woodrow et al., 1986). A fluor-

escence detector with excitation at 340 nm has also been used after a 37-50 μBondapak/Corasil column or a μBondapak C_{18} column (Miller et al., 1985).

Two dimensional TLC using a hexane/ethyl acetate mobile phase and silica gel plates has been reported (Lay et al., 1976); the fluorescence characteristics of PCBs in α-cyclodextrin using room temperature phosphorescence can discriminate some individual PCB congeners (Femia et al., 1985).

Other analytical methods of some use are perchlorination (Lin and Que Hee, 1985) and dechlorination (Seymour et al., 1986). Perchlorination has been used extensively, especially for Yusho samples (Miyata et al., 1985; Kashimoto et al., 1985).

Chemical Reactions

Pyrolysis. A route with environmental implications is the thermal production of PCDFs from PCBs. Buser et al. (1978) and Buser and Rappe (1979) showed that when specific PCBs were pyrolyzed in quartz ampules between 500 and 700°C, PCDF yields in the 1-10% range could be obtained, though they were accompanied by many other products including chlorinated benzenes, naphthalenes and hydroxy PCBs. Buser et al. (1978) described the products of pyrolysis at 600°C identified by GC/MS. There appear to be four major paths for production of PCDFs from PCBs: loss of two ortho chlorines, loss of ortho hydrogen as well as chlorine, loss of an ortho hydrogen as well as chlorine but involving a shift of chlorine from the 2- to the 3-position and loss of two ortho hydrogens. These paths are summarized in

Figure II-1 for 2,2',4,4',5,5'-hexachlorobiphenyl. Such paths are environmentally important in the origin of toxic PCDFs from various PCB formulations. Mazer and Hileman (1982), Mazer et al. (1983a,b) and Hileman et al. (1985) have utilized the technique after HPLC separation and confirmation by GC/MS and Kovats indices to produce 110 pure TCDFs to act as chromatographic standards.

The levels of PCDFs in PCBs increase with the length of time in service at high temperatures as heat exchange media (Morita et al., 1977b; Buser et al., 1978), as originally suggested by Kuratsune et al. (1976). A contrary finding has been reported by Cull and Dobbs (1984). Aroclor 1254 on pyrolysis also contained the major toxic PCDFs, but the relative amounts of the products differed somewhat from those obtained from the Mitsubishi-Monsanto T-1248 (Buser and Rappe, 1979). The major PCDFs identified in the used Mitsubishi-Monsanto T-1248 were the 2,3,7,8-TCDF (1.25 ppm), the 2,3,4,7,8-PeCDF (the pyrolysis product of 2,4,5,2',4',5'-hexachlorobiphenyl), 1,2,3,7,8-PeCDF, 2,3,4,6,8-PeCDF, 1,2,3,4,8-PeCDF, 1,3,4,7,8-PeCDF (also from pyrolysis of 2,4,5,2',4',5'-hexachlorobiphenyl) and the 2,3,4,6,7,8-HxCDF. The 2,3,4,8- and 2,3,7,8-TCDFs were later shown to co-elute (Mazer et al., 1983a,b; Rappe et al., 1984). The exact composition of the 2,3,7,8-TCDF peak is still unreported. Whereas the used Mitsubishi-Monsanto T-1248 was exposed for years to elevated temperatures in the liquid phase, the laboratory pyrolyses of Aroclor 1254 and 1260 were performed in the gas phase for a few seconds up to a maximum temperature of 700°C (Buser and Rappe, 1979). With Aroclor 1254 (tri- to nepta-PCBs), mostly MCDFs to PeCDFs were formed at a level of ~2%. With Aroclor 1260 (penta- to octa-PCBs), mostly TrCDFs to HpCDFs were produced at a similar level. The toxic

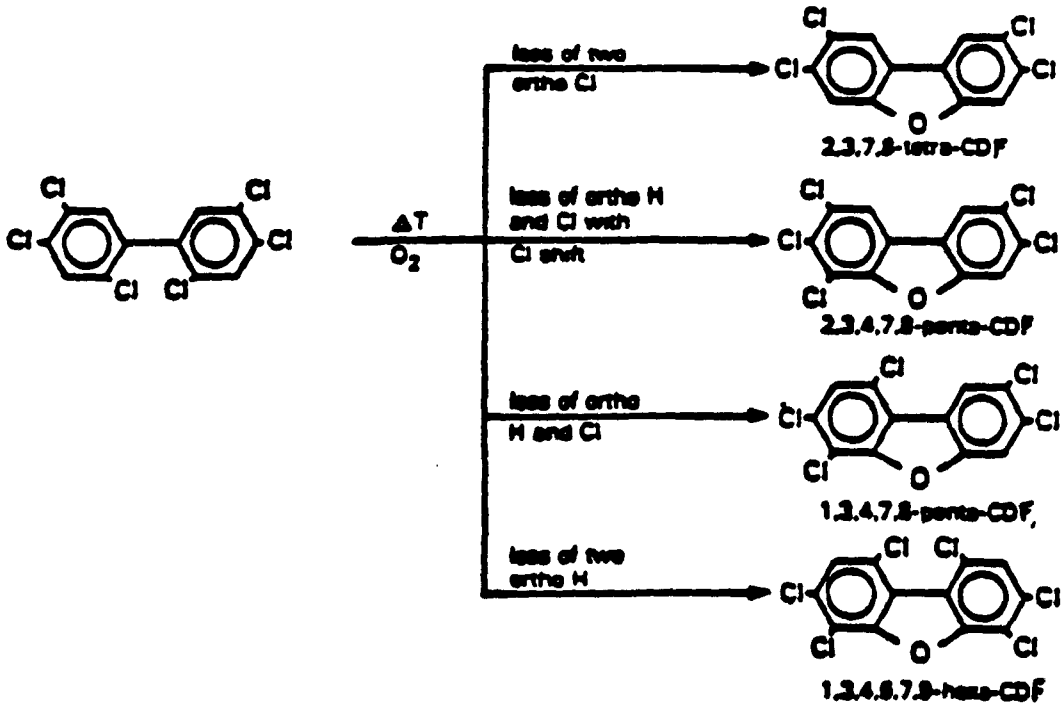


FIGURE II-1

Possible Reaction Schemes to Produce PCDFs from the Pyrolysis of 2,2', 4,4', 5,5'-Hexachlorobiphenyl

Source: Adapted from Buser and Rappe, 1979

2,3,7,8-TCDF was the most abundant TCDF and was most likely derived from 2,4,5,2',4',5'-hexachlorobiphenyl or 2,3',4,4',5'-pentachlorobiphenyl. The acutely toxic 1,2,3,7,8- and 2,3,4,7,8-PeCDFs were the major PeCDFs. The former probably is produced from pyrolysis of 2,3,4,2',4',5'-hexachlorobiphenyl, and the latter from 2,4,5,2',4',5'-hexa- or 2,3,4,5,2',4',5'-heptachlorobiphenyl. Pyrolyzed Aroclor 1254 also contained significant amounts of 1,3,4,7,9-PeCDF. These results were confirmed by Paasivirta et al. (1985) who also found small amounts of chlorinated phenols, naphthalenes, and MCDFs and DCDFs produced between 500 and 700°C.

PCBs are destroyed at a 2 sec residence time at 1200°C with 3% excess oxygen and at 1.5 sec residence time at 1600°C with 2% excess oxygen (Johnston, 1985). Johnston (1985) has also reviewed the disposal methods for PCB waste including thermal incineration. Rubey et al., (1985) showed that in addition to PCDFs, lower PCBs, chlorinated benzenes, naphthalenes, phenyl ethynes and biphenylenes were produced from pyrolysis of 2,3',4,4'5-penta-CB. HCl loss was the dominant mechanism between 750 and 850°C. PCDF and PCB levels declined exponentially >900°C at a 2 sec residence time.

Stability in Water

Commercial Aroclors are complex mixtures of PCBs rather than single components. Therefore, the composition of an Aroclor will change with time because of selective adsorption, evaporation, solubility and biodegradation of specific congeners. Water solubility and vapor pressure increase with decreasing chlorination (Hutzinger et al., 1974). In summary, lower chlorinated PCBs are mostly removed from the water bodies by biodegradation,

volatilization and solubilization (Hutzinger et al., 1974), although sedimentation removal also occurs. Higher molecular weight PCBs will principally adsorb to sediments and biota, although some volatilization (Hutzinger et al., 1974) may occur.

Photodecomposition. PCBs in water at sunlight wavelengths can be photochemically degraded (Crosby and Moilanen, 1973), resulting in reductive or hydroxylative dechlorination as well as dibenzofurans. The hydroxylated products can also form dibenzofurans on boiling or at high pH. Reductive dechlorination occurs in organic solvents at 300 nm; the chlorines next to the biphenyl bridge are cleaved preferentially (Hutzinger et al., 1974).

PCBs in water can be photolyzed (Crosby and Moilanen, 1973; Hutzinger et al., 1974; Pomerantz et al., 1978; Callahan et al., 1979). Hydroxylative dechlorination can also occur as well as reductive dechlorination (Crosby and Moilanen, 1973; Hutzinger et al., 1974). The rate and extent of PCB photodegradation by sunlight are extremely difficult to assess in the environment. Complicating factors include the diversity of environmental conditions and the propensity of PCBs (particularly the more photolabile highly-chlorinated biphenyls) to adsorb to sediments and organic materials (Hutzinger et al., 1974). Hutzinger (1972) observed 0.2% 2-PCDF production after 7 days of ultraviolet irradiation (310 nm) of aqueous solutions of 2,5,2'5'-tetrachloro- and 2,5-dichlorobiphenyls (5 mg/ℓ). These products were confirmed by Crosby and Moilanen (1973). However, Hutzinger (1972) found no PCDFs after some aqueous PCB samples (167 mg/ℓ) had been exposed to sunlight for >2 months. This discrepancy may have arisen because of the different irradiation times and different wavelengths used. The yield of

the products was wavelength-dependent. Irradiation at 254 nm (mercury arc) decomposed PCDF photoproducts but only slowly at 310 nm or at the wavelengths encountered at sea level for sunlight, or for a solar simulator. Triplet sensitizers (for example, 4,4'-dichlorobenzophenone) induced faster photodecomposition of 2,8-DCDF in methanolic solution (Crosby and Moilanen, 1973). Thus, the presence of other compounds may be important.

Oxidation and Hydrolysis

Oxidation is not likely to be an important environmental conversion process for PCBs since severe conditions are necessary (Hutzinger et al., 1974). PCDFs are formed in very low yields during oxidation of PCBs (Pomerantz et al., 1978). Thus, although PCDFs are present in commercial PCB mixtures, the evidence for their environmental formation is tenuous.

PCBs are also unlikely to be affected by hydrolysis as an environmental process because S_N1 and S_N2 reactions do not take place readily at sp^2 hybridized carbons (Morrison and Boyd, 1973) and they are not water soluble enough to allow water to interact. However, hydroxylative dechlorination in water has been noted at 254 and 310 nm wavelengths (Hutzinger et al., 1974).

Volatilization

The collection of PCBs in the atmosphere and during several laboratory studies have confirmed the importance of volatilization as a removal process for PCBs from water (Doskey and Andren, 1981; Callahan et al., 1979; Atlas et al., 1983; Eisenreich et al., 1981; Mackay and Leinonen, 1975). Volatilization half-life data for environmental waters are not available.

Modeling is complicated by the numerous contradictory solubilities, octanol/water partition coefficients, and Henry's Law constants for each Aroclor (Callahan et al., 1979; Doskey and Andren, 1981; Mabey et al., 1981; Burkhard et al., 1985c; Mackay et al., 1986). This arises because Aroclors are mixtures. Thus, some Henry's Law constants varied over 4 orders of magnitude for the same Aroclor (Doskey and Andren, 1981). The volatilization half-lives for various Aroclors calculated, based on a number of input values for these parameters (Burns et al., 1981), appear to be in the following ranges: Aroclor 1221 and Aroclor 1232, 2 months to 1 year; Aroclor 1016, <2-7 years; Aroclor 1242, 2-7 years; Aroclor 1248, 3-8 years; Aroclor 1254, >4-11 years; Aroclor 1260, >60 to >150 years. However, exact data can only be obtained by consideration of specific congeners.

One of the major controlling factors found to determine the volatilization half-life (Burns et al., 1981) was the octanol/water partition coefficient, since this is inversely related to the amount of PCBs partitioning into the water from sediments and biota and the level available for volatilization. This applies for laboratory as well as environmental conditions. Again, as expected of mixtures, several laboratory values for the octanol/water partition coefficient varying over 2 orders of magnitude were found for the Aroclors (Callahan et al., 1979; Garten and Trabalka, 1983; Miller et al., 1985). The advantage of using the Burns et al. (1981) approach is that adsorption is also taken into account when calculating volatilization half-lives, while models for volatilization alone do not consider adsorption or do so indirectly (Mackay and Leinonen, 1975). The reduction of volatilization half-lives in the presence of adsorption has been studied in the laboratory. Oloffs et al. (1972, 1973) showed that

Aroclor 1260 (100 µg/ℓ) volatilized 67% from river water after 12 weeks but only 34% when sediment was added. Tucker et al. (1975) reported that Aroclors 1221 and 1016 volatilized 4.2 and 3.6% from aerated samples containing activated sludge.

Adsorption

Adsorption onto sediments and other organic matter, including treatment plant sludge, coagulant and possibly plastic water pipe and coal tar coated water pipe, may be an important removal process for high molecular weight PCBs in waters. Using the octanol/water partition coefficients available (Callahan et al., 1979; Mabey et al., 1981; Mackay, 1982; Burns et al., 1981; Miller et al., 1985), the following amounts of PCB that would be adsorbed onto sediments have been predicted: Aroclor 1221, 45-95%; Aroclor 1232, 70-98%; Aroclor 1016 and 1242, 96->99%; Aroclor 1248, 97->99%; Aroclor 1254, 98->99% and Aroclor 1260, >99%. These values are dependent on the choice of partition coefficient and on the amount of organic matter present in the sediment. These results appear to be consistent with other experimental data (Oloffs et al., 1973; Haque et al., 1974; Moein et al., 1976; Hetling et al., 1978; Paris et al., 1978). The adsorption characteristics of each PCB congener of the Aroclors will, of course, vary considerably. The lower chlorinated components will adsorb less strongly to the organic matter than the more highly chlorinated ones. In addition, the more strongly adsorbed components are also less biodegradable and hence more persistent. The same considerations have been noted in laboratory investigations using glass equipment (Hutzinger et al., 1974).

Exchange Between Media

Air/water exchange of PCBs has been modeled by Mackay et al. (1986). The example has been provided of a Cl_5-PCB in the Great Lakes Basin. This PCB air concentration is 5.7% sorbed and 94.3% in gaseous form at 15°C; in the water, 19.7% is sorbed and 80.3% is dissolved. While there is a net volatilization effect, this is countered (25%) by wet and dry deposition. On the average, rainfall contains 68.2 ng PCB/ℓ, mostly all associated with washed out particles. Lower temperatures will enhance adsorption and sorption. Higher temperatures will enhance volatilization and solubilization. Thus, a complex cycling of a PCB in an ecosystem is expected. Burkhard et al. (1985c) have noted that the relative proportions of the PCBs in environmental mixtures and Aroclors are different. They also modeled how specific Cl_4, Cl_5 and Cl_6 PCB congeners would be depleted or enriched in a 3-phase system (water/air/suspended particulate matter). The binding of 2,2',5,5'-tetrachlorobiphenyl to dissolved humic acid was studied by Hassett and Millicic (1985), using an aspiration method. The equilibrium binding constant is 7.1×10^4. The rate constant for release of bound PCB congener by humic acid is 3.5×10^{-3} min^{-1}; the rate constant for binding of dissolved PCB congener by humic acid is 1.7×10^{-4} ℓ (mg dissolved organic carbon)$^{-1}$ min^{-1}.

Biodegradability

A number of investigators have reported on biodegradability and its mechanism for PCBs (Hutzinger et al., 1972, 1974; Kaiser and Wong, 1974; Branson et al., 1975; Berlin et al., 1975; Wong and Kaiser, 1976; Furukawa et al., 1978, 1983; Tabak et al., 1981a,b). Biodegradability is generally related to the number of hydrogens available. These positions appear to be

hydroxylated by microsomal oxidation. If an adjacent position is unchlorinated, degradation is then facilitated by allowing the formation of an arene oxide. Biodegradation rates vary considerably and are dependent upon many factors including the amount of chlorination, concentration, type of microbial population, available nutrients and temperature. An example of this variation in biodegradation rate was reported by Tucker et al. (1975) for Aroclors using the Soap and Detergent Association semicontinuous activated sludge procedure and modified feed with 48-hour exposure: Aroclor 1221, 81±6%; Aroclor 1016, 33±14%; Aroclor 1242, 26±16% and Aroclor 1254, 19±38%. Tabak et al. (1981a,b) found virtually complete degradation for Aroclors 1221 and 1232 at 5 and 10 mg/ℓ concentrations using a static-culture, flask-screening procedure employing BOD dilution water and a settled domestic wastewater inoculum over 28 days. By contrast, Aroclors 1016 and 1242 showed moderate degradation (~40%), while Aroclors 1248, 1254 and 1260 showed almost no degradation.

This type of degradation pattern has been reported by Oloffs et al. (1972), Moein et al. (1976) and Wong and Kaiser (1976). The results show that mono-, di- and tri-CBs (Aroclors 1221 and 1232) biodegrade relatively rapidly, tetra-CBs (Aroclors 1016 and 1242) biodegrade slowly and higher chlorinated biphenyls (Aroclors 1248, 1254 and 1260) are recalcitrant.

Summary

Aroclors once marketed in the United States principally by Monsanto are a family of compounds consisting of a mixture of various PCB congeners and isomers. The physical properties of the congeners vary considerably with a molecular mass range of 154-499, a log octanol/water partition coefficient

range of 3.76-8.26, and a solubility range of 9.77×10^{-10} to 4.68×10^{-5} moles/ℓ (moles/ℓ x molecular weight x 10^6/ℓ = μg/ℓ) (Yalkowsky et al. 1983).

PCBs will volatilize from ambient waters with half-lives ranging between 2 months and >150 years (Burns et al., 1981; Doskey and Andren, 1981; Callahan et al., 1979; Mabey et al., 1981). The most important parameter affecting volatilization rates was found to be the octanol/water partition coefficient, showing that the partitioning of the PCBs from the sediments and biota into the water was the limiting factor affecting volatilization.

Adsorption appears to be the dominant removal mechanism for highly chlorinated PCBs. Using the input parameters from the previously mentioned sources, sorption to sediment effectively binds between 45 and >99% of the PCBs present in water depending on the PCB and the organic matter present in the sediment. The higher the organic matter in the sediment or the higher the chlorination, the more strongly sorbed will be the PCB. PCBs have been demonstrated to undergo complete cycling in ecosystems.

As for volatilization and sorption, biodegradation is also a significant removal mechanism for the less chlorinated species (Callahan et al., 1979; Hutzinger et al., 1972, 1974; Kaiser and Wong, 1974; Tabak et al., 1981a,b). Based on published reports, PCBs containing $\leq$3 chlorines tend to be degraded in the environment, although estimation of half-lives is very difficult given the great variability in the reported literature. PCBs with four chlorines appear to be somewhat less degradable. PCBs with five or more chlorines appear to be recalcitrant.

III. TOXICOKINETICS

Introduction

As explained in Chapter II, polychlorinated biphenyls are highly complex mixtures of isomers and congeners that have been widely identified in almost all components of the global ecosystem (Hutzinger et al., 1974; Risebrough et al., 1968; Fishbein, 1972; Buckley, 1982; Ballschmiter et al., 1981; Wasserman et al., 1979; Higuchi, 1976; Cordle et al., 1978; Holdrinet et al., 1977; Safe, 1982). Since PCBs are highly lipophilic and relatively stable, these pollutants rapidly bioaccumulate and are routinely detected in fish, wildlife and human milk, adipose tissue and blood serum (Risebrough et al., 1968; Fishbein, 1972; Buckley, 1982; Ballschmiter et al., 1981; Wasserman et al., 1979; Higuchi, 1976; Cordle et al., 1978; Holdrinet et al., 1977; Safe, 1982). Since commercial PCBs are highly complex mixtures, the gas chromatographic (GC) identification and quantitation of PCB residues has primarily relied upon specific peak or pattern matching techniques using commercial PCB mixtures as standards (Chapter II of this document). However, it is apparent from analytical studies of environmental samples and residues in laboratory animals treated with these compounds that there can be major differences between their composition and that of the commercial PCB products (Hansen et al., 1975; Hansen, 1979; Stalling et al, 1979; Burse et al., 1976). The development of high resolution glass capillary, GC analytical procedures and the recent synthesis and characterization of the 209 PCB standards (Mullin et al., 1984) has remarkably demonstrated this latter observation as discussed in Chapter II. Table III-1 provides a comparative analysis of PCBs in Aroclor 1260 and an extract of human breast milk. Congener-specific high resolution GC analysis of the commercial PCB Aroclor 1260 identified at least 90 different PCBs (Safe et al., 1985b). In

TABLE III-1

Quantitative and Qualitative Analysis of PCBs in Aroclor 1260 and a Human Breast Milk Extract[a]

Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]	Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]
PCB-018	0.12	ND	PCB-118	0.49	6.5
PCB-017	0.05	ND	PCB-134	0.35	ND
PCB-024	0.01	ND	PCB-114	ND	0.33
PCB-016	0.04	ND	PCB-131	0.07	ND
PCB-029	0.02	ND	PCB-122	0.12	0.53
PCB-026	0.02	ND	PCB-146	1.3	1.9
PCB-028	0.04	8.8	PCB-153	9.6	12
PCB-021	0.01	ND	PCB-141	2.5	0.29
PCB-033	0.09	2.2	PCB-176	0.33	ND
PCB-053	0.04	ND	PCB-137	0.22	0.87
PCB-022	0.01	0.65	PCB-130	ND	0.59
PCB-045	0.07	ND	PCB-138	6.5	10
PCB-046	0.02	0.25	PCB-158	0.70	0.55
PCB-052	0.25	1.9	PCB-129	0.20	ND
PCB-043	0.02	ND	PCB-178	1.2	ND
PCB-049	0.06	0.66	PCB-175	0.49	ND
PCB-048	0.29	0.37	PCB-187	4.5	1.5
PCB-044	0.11	0.78	PCB-183	2.3	1.4
PCB-037	0.04	2.9	PCB-128	0.47	0.33
PCB-042	0.04	ND	PCB-167	0.16	0.85
PCB-041	0.25	1.3	PCB-185	4.1	0.11
PCB-040	0.03	ND	PCB-174	5.5	0.39
PCB-100	0.02	ND	PCB-177	1.9	0.61
PCB-074	0.03	11	PCB-171+202	1.2	0.37
PCB-070+076	0.15	0.61	PCB-156	0.45	4.87
PCB-095	2.7	ND	PCB-173	0.06	ND
PCB-091	0.07	ND	PCB-200	0.78	ND

TABLE III-1 (cont.)

Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]	Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]
PCB-056+060	0.14	0.71	PCB-157	ND	0.47
PCB-084	0.65	ND	PCB-172	0.78	0.31
PCB-101	2.5	0.97	PCB-180	9.1	5.3
PCB-099	0.13	4.8	PCB-193	0.47	0.19
PCB-119	ND	0.08	PCB-191	0.10	0.90
PCB-083	0.04	ND	PCB-199	0.33	ND
PCB-097	0.45	ND	PCB-170	6.8	5.3
PCB-087	0.45	0.82	PCB-201	2.9	0.85
PCB-085	0.13	ND	PCB-203	3.1	0.79
PCB-136	1.4	ND	PCB-196	2.5	0.18
PCB-110	1.7	1.0	PCB-189	0.15	2.4
PCB-154	0.02	ND	PCB-195	3.1	0.31
PCB-082	0.11	ND	PCB-207	0.08	ND
PCB-151	2.5	0.59	PCB-194	1.7	0.48
PCB-144+135	1.5	0.51	PCB-205	0.11	0.06
PCB-107	0.03	0.31	PCB-206	0.85	0.24
PCB-149	7.4	ND	PCB-209	0.06	0.09

[a]Source: Safe et al., 1985b

[b]Congener names adapted from Ballschmiter and Zell (1980). See Table II-1 in this document.

[c]Human milk sample collected and extracted by the Michigan Department of Public Health under Cooperative Agreement CR807192 with the Large Lakes Research Station, U.S. EPA.

ND = Not detected

contrast, the gas chromatogram of a composite human milk sample does not resemble the pattern of any commercial PCB, and pattern matching methods would not yield meaningful quantitative results. However, the high-resolution isomer-specific GC approach permitted quantitation of all the individual PCB components present in this mixture. Several PCB congeners, including 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5'- hexa-CB, 2,2',3,3',4,4',5-hepta-CB and 2,2',3,4,4',5,5'-hepta-CB are major components of both Aroclor 1260 and the human milk extract.

Another major PCB present in the human milk extract, (4.87%), (2,3,3',4,4',5-hexa-CB) is a minor component of Aroclor 1260 and other commercial PCBs (Ballschmiter and Zell, 1980; Jensen and Sundstrom, 1974) and has previously been identified as a major PCB contaminant of Japanese human milk extracts (Safe, 1982). The four remaining major PCB congeners identified in the human milk extract (2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2,2',4,4',5-penta-CB and 2,3',4,4',5-penta-CB) are minor components of Aroclor 1260 (<0.49% for all four isomers). It is likely that these penta- and tri-PCB congeners are derived from the lower chlorinated PCB formulations; however, it is noteworthy that with the exception of 2,4,4'-tri-CB, all of these compounds also contain 2,4,5-trichloro-substitution on one of the phenyl rings and a p-chloro group on the second phenyl ring. This high-resolution analytical study has also identified 2,4,4'-tri-CB as a major PCB component and confirms a previous report that identified this compound in a Japanese human milk extract (Yakushiji et al., 1979). The reasons for the persistence of this congener are not apparent. It was also of interest to note that several other compounds including 2,2',3,5',6-penta-CB (2.7%), 2,2',3,4',5',6-hexa-CB (7.4%), 2,2',3,3',4,5,5'-hepta-CB (5.5%) and

2,2',3,3',4,4',5,6-octa-CB (3.1%) constitute 22.8% of the PCBs present in Aroclor 1260 but are only minor components (0.81%) of the human milk PCB extract.

These results clearly demonstrate that there is a preferential structure-dependent bioaccumulation of specific PCB congeners in human milk. Several studies have also shown that the biologic and toxic effects of PCBs are also structure-dependent because of their stereoselective interaction with a cytosolic receptor protein (Safe et al., 1982; Poland et al., 1979, 1983; Safe, 1984). Not surprisingly, the absorption, tissue distribution, metabolism and excretion of individual PCBs and their mixtures is dependent on their physicochemical and biologic properties, and an assessment of the toxicokinetics of this class of chemicals must recognize these important structure-dependent effects (Matthews and Dedrick, 1984; Schnellmann et al., 1985; Safe, 1980).

Absorption

Gastrointestinal. The GI absorption of commercial PCB mixtures and individual congeners has been extensively investigated in laboratory animal studies (Albro and Fishbein, 1972; Berlin et al., 1974; Matthews and Anderson, 1975; Gage and Holm, 1976; Allen et al., 1974a,b; Tanabe et al., 1981). Oral administration of a complex mixture of Kanechlors 300, 400, 500 and 600 (1.1.1:1 by weight) in corn oil to immature male Wistar rats (Tanabe et al., 1981) resulted in >84% of the total dose being absorbed from the GI tract with <16% of the dose excreted in the feces. GC-MS analysis of the PCB in the fecal material demonstrated that the absorption efficiency of the individual PCBs varied from 66-96%. The major structural determinant that

governed absorption efficiencies was the degree of chlorination, since there was an increase in absorption of PCBs with increasing ring chlorination and molecular size. It is also conceivable that other structural factors may also play an important role in PCB absorption. For example, ortho-chlorine substitution decreases PCB ring coplanarity and there is evidence in both fish and rats that there may be decreased absorption of isomers with increasing ortho-chloro substituents (Tulp and Hutzinger, 1978a,b; Sparling and Safe, 1980b; Shaw and Cornell, 1980). Several rodent and monkey studies using either commercial PCB mixtures, reconstituted mixtures or individual compounds confirm that PCBs are readily absorbed from the GI tract and are distributed rapidly by the blood to diverse tissues. Liver and sometimes muscle act as major depots for PCB accumulation after initial exposure and absorption; these highly lipophilic compounds are then redistributed into adipose tissue and skin (Matthews and Dedrick, 1984). The effect of the vehicle on the GI absorption of PCBs has not been systematically evaluated.

Dermal. Several dermal studies with PCB congeners or mixtures demonstrate that these compounds are readily absorbed and elicit toxic or biologic effects at dermal and distal sites (Nishizumi, 1976; Miller, 1944; Puhvel et al., 1982; Wester et al., 1983). A recent study by Wester et al. (1983) reported the dermal absorption in guinea pigs and monkeys of synthetic ^{14}C-labeled PCBs containing 42 and 54% chlorine (by weight). Dermal absorption was estimated using the following relationship:

$$\% \text{ Dose Absorbed} = \frac{\text{total } ^{14}C \text{ urinary excretion following topical administration} \times 100}{\text{total } ^{14}C \text{ urinary excretion following parenteral administration}}$$

The estimated absorption of the 42 and 54% ^{14}C mixtures was 33 and 56%, respectively, in the guinea pigs and the absorption of the 42% mixture varied between 15 and 34% depending on the dose (4.1 $\mu g/cm^2$ or 19.3 $\mu g/cm^2$). Immediate washing of the applied ^{14}C-labeled PCB (42% Cl content) with water and acetone removed 59% of the dose whereas washing 24 hours after dermal application of the 42 and 54% ^{14}C-labeled preparations removed only 1 and 20% of the applied label, respectively.

Inhalation. Benthe et al. (1972) exposed male Wistar rats to Pidranil A200 as an aerosol (0.5-3μ particles, 30 g/m^3). Hepatic levels at 15 minutes were >50% of the maximum obtained after 2 hours. The pharmacokinetics of the inhaled PCBs were comparable to those observed by absorption by other routes; initial high PCB concentrations in liver and brain peaked and decreased within 48 hours after exposure and adipose tissue became the major reservoir for these compounds.

Tissue Distribution and Excretion

Transport of PCBs from the site of application to distal sites occurs by a number of processes. The facile GI absorption of PCBs (Matthews and Dedrick, 1984; Albro and Fishbein, 1972; Berlin et al., 1974; Matthews and Anderson, 1975; Gage and Holm, 1976; Allen et al., 1974a,b; Tanabe et al., 1981) is consistent with passive absorption into the lipophilic cell membranes followed by transport to all tissues by blood. *In vitro* studies have shown that 2,2',4,4',5,5'-hexa-CB is taken up into very low density lipoproteins (VLDL), low density lipoproteins (LDL), high density lipoproteins (HDL) and other plasma proteins (Vomachka et al., 1983; Becker and Gamble, 1982). 2,2',4,4',5,5'-hexa-CB injected intravenously resulted in initial

association primarily with LDL; however, between 6 and 24 hours after administration the hexa-CB was redistributed from LDL to HDL and other protein-rich plasma fractions (Spindler-Vomachka et al., 1984). Recent studies using domestic animals have also demonstrated the importance of the lymphatic system as a transport route for PCBs (Ziprin et al., 1980, 1986), and this may contribute to the immunotoxic effects of PCBs.

The initial distribution of PCB mixtures and individual PCB congeners in diverse animal species is dependent on the structure(s) of the compounds and most importantly the biophysical factors that affect distribution of compounds in a multicompartment system (Matthews and Dedrick, 1984). Figure III-1 summarizes a flow diagram for the pharmacokinetics of PCBs in animals in which the initial distribution of serum containing PCBs is dependent on blood flow rates, blood volumes, PCB-blood serum absorption affinities, tissue/blood partition ratios, perfusion rates and tissue volumes (Matthews and Dedrick, 1984). In most animal species that have been investigated there is an initial uptake of PCBs into the liver and muscle which is due to high perfusion in the liver and the relatively large muscle volume. Subsequent redistribution of PCBs into adipose tissue and skin reflects the high affinity of the lipophilic PCBs for lipophilic tissues. At equilibrium the elimination of PCBs from all tissues will be dependent on the structure-dependent rates of metabolism of individual PCB congeners (see the Metabolism Section).

Several studies on the pharmacokinetics in rats and mice have been reported (Matthews and Dedrick, 1984; Schnellmann et al., 1985; Safe, 1980; Albro and Fishbein, 1972; Berlin et al., 1974; Matthews and Anderson, 1975;

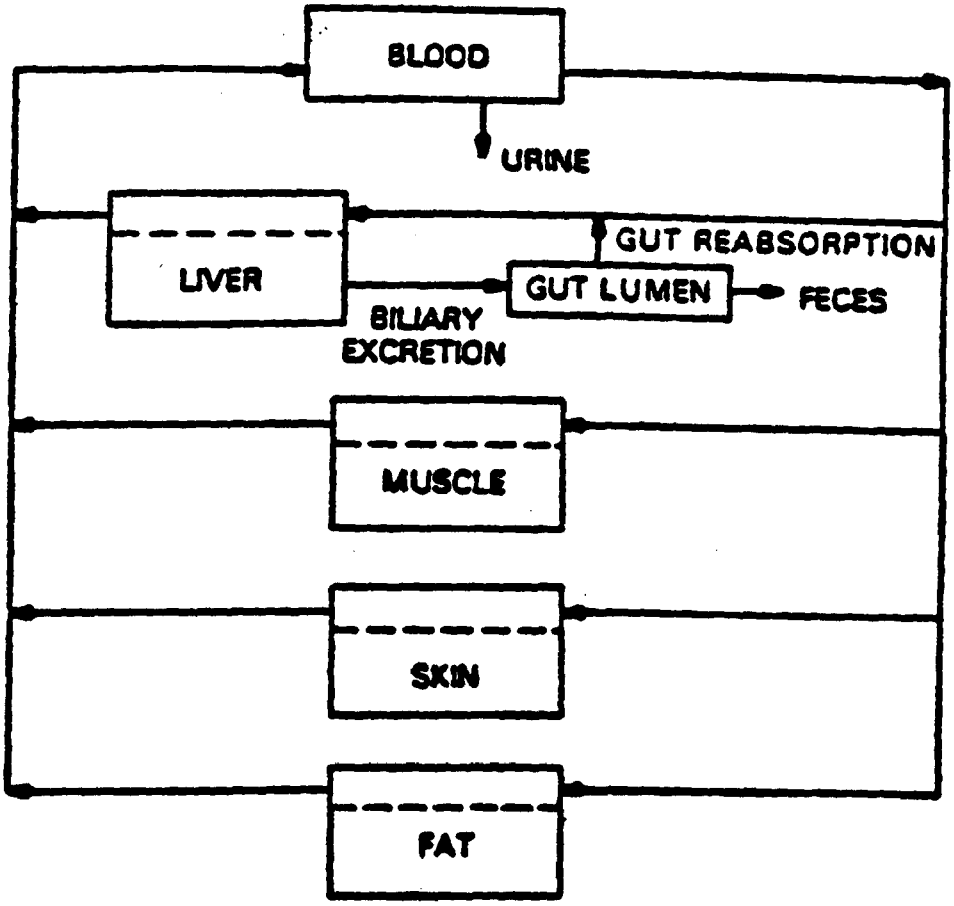


FIGURE III-1

PCB Pharmacokinetic Flow Diagram

Source: Lutz et al., 1977

Gage and Holm, 1976; Allen et al., 1974a,b; Tanabe et al., 1981; Sparling and Safe, 1980a,b; Matthews and Tuey, 1980; Lutz et al., 1977; Muhlebach and Bickel, 1981; Tuey and Matthews, 1977a,b, 1980; Morales et al., 1979; Moritta and Oishi, 1977; Lucier et al., 1978; Clarke et al., 1984; Sugiura et al., 1975, 1976; Mizutani et al., 1977; Felt et al., 1977, 1979). Most of the reports using individual PCB congeners gave comparable results. Matthews and Anderson (1975) administered 0.6 mg/kg i.v. of the following ^{14}C-labeled PCB congeners to Sprague-Dawley rats: 4-CB (1-CB) 4,4'-di-CB (2-CB) 2,2',4,5,5'-penta-CB (5-CB) and 2,2',4,4',5,5'-hexa-CB (6-CB). Early time points illustrate the relatively high levels of all compounds in liver and muscle; the subsequent decrease of PCBs in these tissues was followed by preferential bioaccumulation of the PCB congeners in adipose tissue and skin. Lutz et al. (1977) proposed one model based on the pharmacokinetic data obtained for these isomers, the flow diagram illustrated in Figure III-1 and the known compartment sizes and perfusion rates from the experimental animal (Sprague-Dawley rat). This pharmacokinetic model has also been reviewed by Matthews and Dedrick (1984). The tissue/blood distribution ratio and kinetic parameters are summarized in Tables III-2 and III-3. The results illustrate a number of important points, namely:

1. The highly lipophilic parent compounds tend to preferentially bioconcentrate in lipophilic tissues (adipose tissue and skin) whereas the more polar metabolites are found in the hydrophilic cell tissues/compartments;

2. The magnitude of the metabolic clearance parameters (Km) are dependent on structure; the Km for the more rapidly metabolized CB-1 congener is 10.0 whereas these values decrease with increasing ring chlorination; the Km value for 2,2',4,4',5,5'-hexa-CB was <0.2% of the Km for 4-CB;

3. The mathematical model developed for PCB pharmacokinetics using the multicompartment system (see Figure III-1) can simulate and predict the behaviour of both parent compound and metabolite. For example, the mass balance equation for a tissue in which metabolism occurs (for example, liver, L) takes the form.

TABLE III-2

Pharmacokinetic Compartment Size Distribution for Individual PCB Congeners in the Rat*
(tissue/blood distribution ratios)

Compartment	Parent				Metabolite			
	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut/lumen	1	1	1	1	1	1	1	1
Muscle	1	2	1	4	0.14	0.40	0.10	0.30
Liver	1	3	6	12	2	5	2	4
Skin	10	10	7	30	0.25	0.30	0.10	2
Adipose	30	70	70	400	0.40	0.60	0.40	2

*Source: Adapted from Lutz et al., 1977

1-CB:(4-CB)
2-CB:(4,4'-di-CB)
5-CB:(2,2',4,5,5'-penta-CB)
6-CB:(2,2',4,4',5,5'-hexa-CB)

TABLE III-3

Pharmacokinetic Parameters for Individual PCB Congeners in the Rat*

Rate constant	1-CB	2-CB	5-CB	6-CB
Metabolic clearance, Km, mL/min	10.0	2.0	0.39	0.045
Kidney clearance, Kk, mL/min	0.20	0.133	0.033	0.030
Biliary clearance, KB, mL/min	0.20	0.35	0.30	0.30
Gut reabsorption, KG, min^{-1}	0.00016	0.00016	0.00016	0.00016
Fecal transport, KF, min^{-1}	0.0008	0.0008	0.0008	0.0008

*Source: Adapted from Lutz et al., 1977

1-CB:(4-CB)
2-CB:(4,4'-di-CB)
5-CB:(2,2',4,5,5'-penta-CB)
6-CB:(2,2',4,4',5,5'-hexa-CB)

$$\frac{d}{dt}(V_L C_L) = Q_L[C_B - \frac{C_L}{R_L}] - Km \frac{C_L}{R_L}$$

where:

t = time
V = tissue volume or mass
C = concentration
Q = blood flow rate
Km = metabolic clearance
R = equilibrium tissue-blood distribution ratio.

For highly lipophilic tissues, such as adipose tissue and PCBs, which are poorly metabolized, the Km C_L/R_L term approaches 0 and can be neglected (Matthews and Dedrick, 1984).

It was also apparent from most of the rodent pharmacokinetic data that tissue persistence of individual PCB congeners was a function of their structure and relative rates of metabolism. Although the degree of chlorination of individual PCBs is an important determinant in tissue persistence (and rate of metabolism) it is evident from several reports that the orientation or chlorine substitution pattern is also an important structural feature. Matthews and Tuey (1980) reported the distribution and excretion of 2,2',3,3',5,5'-, 2,2',3,3',6,6'-, 2,2',4,4',5,5'- and 2,2',4,4',6,6'-hexa-CB in adult male Sprague-Dawley rats. The 2,2',3,3',6,6'-hexa-CB isomer was more rapidly metabolized and eliminated than the other three isomers, which were highly tissue persistent and resistant to metabolic breakdown. It was evident that the presence of two adjacent unsubstituted carbon atoms in the 2,2',3,3',6,6'-hexa-CB isomer greatly facilitated the rate of metabolism in the rat.

Table III-4 summarizes the biological half-lives of 93 PCB congeners that were identified in a mixture of Kanechlors 300, 400, 500 and 600

TABLE III-4

Biological Half-Lives of Individual Chlorobiphenyls in Rats[a,b]

Peak No.	Type	Type A and Type B (I) t_1 (day)	Type A and Type B (I) Duration[c] (day)		Type B (II) and Type C t_2 (day)	Type B (II) and Type C Duration[c] (day)		Structure
11[d]								
21	A	0.15	0.13-0.5	0.94				2,2'
22[d]								2,5
23	A	0.34	0.12-0.5	0.86				2,4 2,3'
24	A	0.18	0.13-1	0.99				2,4'
25[e]								4,4'
31	A	0.11	0.13-0.25	1.00				2,2',6
32	A	0.18	0.13-1	0.98				2,2',5
33	A	0.21	0.13-1	0.92				2,2',4
34	A	0.21	0.12-1	0.99				2,2',3 2,3',6
35	A	0.23	0.13-1	0.99				2,4',6
36	A	0.32	0.13-1	0.97				2,3',5 2,3',5'
37	A	0.29	0.13-1	0.81				2,3',4
38	B	1.4	0.13-1	0.97	6.0	7-15	1.00	2,3,3' 2,4,4'
39	A	0.20	0.13-1	0.98				2,3',4'
310	A	0.34	0.13-1	0.99				3,4,4'
41	A	0.12	0.13-0.25	1.00				2,2',4,6
42	A	0.12	0.13-0.25	1.00				
43	B	0.89	0.13-3	0.72	3.4	3-15	1.00	2,2',5,5' 2,2',3,5
44								2,2'4,5 2,2',4,5
45	B	3.8	0.13-7	0.73	70	7-90	0.73	2,3,3',6 2,3',4,6 2,3',5',6
46								2,4,4',6 2',2,3,5' 2,3',4,6 2,2',4,4'
47	A	1.4	0.13-3	0.90				2,2',3,4'
48								2,2',3,3' 2,2',3,4
49	A	0.83	0.13-3	0.92				
410	B	3.1	0.13-7	0.93	37	7-45	0.98	2,3',4',5 2,4,4',5
411								2,3',4',5' 2,3,3',4
412	A	0.29	0.13-0.25	1.00				2,3,4,4'
413	B	2.4	0.13-7	0.98	25	7[10]-45	0.99	2,3,3',4'
414[e]								3,3',4,4'
51[d]								
52[d]								
53	B	1.4	0.13-7	0.91	16	7-15	1.00	2,2',3,5',6
54	A	1.4	0.13-3	0.64				2,2',3,5',6
55	A	2.1	0.13-7	0.99				2,2',3,5,5'
56	B	2.6	0.13-7	0.95	35	7-90	0.95	2,2',4,5,5'

Peak No.	Type	Type A and Type B (I) t_1 (day)	Duration[c] (day)		Type B (II) and Type C t_2 (day)	Duration[c] (day)		Structure
57	C				>90	0.13-90		2,2',4,4',5
58	A	2.1	0.13-3	0.82				2,2',3,4,5' 2,2',3,4',5'
59	B	2.5	0.13-7	0.95	64	7-90	0.98	2,2',3,3',4 2,3,3',4',6
510[a]								2,3,3',4',5
511	B	6.6	0.13-7	0.98	>90	7-90		2,3',4,4',5
512	B	5.6	0.13-7	0.97	>90	7-90	0.96	2,3,3',4,4'
61	A	2.6	0.13-7	0.75				2,2',3,3',6,6'
62	B	2.5	0.13-7	0.96	59	7-15	1.00	2,2',3,3',5,6'
63	B	2.7	0.13-7	0.92	23	7-45	1.00	2,2',3,4',5,6' 2,2',3,5,5',6
64	A	1.9	0.13-7	0.91				2,2',3,3',5,6
65								2,2',3,3',4,6'
66	C				>90	0.13-90		2,2',3,4',5,5'
67	C				>90	0.13-90		2,2',4,4',5,5' 2,2',3,4,5,5'
68	B	12	0.13-7	0.98	>90	7-90		2,2',3,3',4,5'
69	C				>90	0.13-90		2,2',3,4,4',5'
610	B	8.3	0.13-7	0.83	>90	7-45		
611	B	6.3	0.13-7	0.83	>90	7-90		2,2',3,3',4,4'
612	C				>90	0.13-90		2,3',4,4',5,5'
613	C				>90	0.13-90		2,3,3',4,4',5
71	B	3.3	0.13-7	0.87	66	7-15	1.00	2,2',3,3',5,6,6'
72	B	5.1	0.13-7	0.92	>90	7-90		2,2',3,3',4,6,6'
73	C				>90	0.13-90		2,2',3,3',5,5',6
74	C				>90	0.13-90		2,2',3,4',5,5',6
75	B	9.3	0.13-7	0.97	>90	7-90		2,2',3,3',4,5,6' 2,2',3,4,4',5',6
76	C				>90	0.13-90		2,2',3,3',4,5',6'
77	B	13	0.13-7	0.97	>90	7-90		2,2',3,3',4,4',6
78	C				>90	0.13-90		2,2',3,3',4,5,5'
79	C				>90	0.13-90		2,2',3,4,4',5,5'
710	C				>90	0.13-90		2,2',3,3',4,4',5
711	C				>90	0.13-90		
712[a]								2,3,3',4,4',5,5'
81	C	3.3			>90	0.13-90		2,2',3,3',5,5',6,6'
82	B	6.4	0.13-7	0.84	>90	7-90		2,2',3,3',4,5',6,6'
83[f]								2,2',3,3'4,5,6,6' 2,2',3,3',4,4',6,6'
84	C				>90	0.13-90		2,2',3,3',4,5,5',6'
85	B	9.4	0.13-7	0.80	>90	7-90		2,2',3,3',4,4',5,6'
86[f]								2,2',3,4,4',5,5',6
87[f]								2,2',3,3',4,4',5,6

TABLE III-4 (cont.)

Peak No.	Type	Type A and Type B (I) t_1 (day)	Type A and Type B (I) Duration[c] (day)	Type B (II) and Type C t_2 (day)	Type B (II) and Type C Duration[c] (day)	Structure
88	C			>90	0.13-90	2,2',3,3',4,4',5,5'
89[e]						
91[f]						2,2',3,3',4,5,5',6,6'
92[f]						2,2',3,3',4,4',5,6,6'
93[f]						2,2',3,3',4,4',5,5',6

[d]Source: Tanabe et al., 1981

[b]Oral administration of a mixture of Kanechlors 300, 400, 500 and 600 (1:1:1:1)

[c]Period for the calculation of biological half-lives.

[d]Not detected because of the disappearance of PCB peaks <0.13 days after administration.

[e]Not determined.

[f]Degradated in alkaline digestion process.

t_1 = Biological half-lives of Type A PCBs and of initial regression of Type B PCBs.

t_2 = Biological half-lives of Type C PCBs and of subsequent regression of Type B PCBs.

r = Correlation coefficients obtained from linear regressions.

(1:1:1:1) orally administered to immature male Wistar rats (Tanabe et al., 1981). Most congeners exhibited biphasic half-lives (whole body) in which the initial t_1 value was relatively low (~0.13-7 days) for all congeners and the t_2 value was much greater and clearly structure-dependent. A closer examination of individual t_1 and t_2 values demonstrates a remarkable similarity between the results reported for the mixture pharmacokinetics and the data obtained for the studies that utilized individual PCB congeners.

Owing to the accumulation of PCB in adipose tissue, studies have been performed on rats to determine the effects of adipose tissue mass on the pharmacokinetics of 2,2',4,4',5,5'-hexachlorobiphenyl. This specific isomer is metabolized only to a very limited extent and is found in human tissues and milk extracts. In a series of studies (Muhlebach and Bickel, 1981; Wyss et al., 1982; Jondorf et al., 1983), 2,2',4,4',5,5'-hexa-CB was administered to rats at different stages of body fat depletion induced by a dietary restriction paradigm. Up to 75% of the dose was deposited in the fat of rats fed a standard diet whereas adipose-depleted (dietary restricted) rats retained <0.1% of the dose in adipose tissue. As disposition of 2,2',4,4',5,5'-hexa-CB to fat decreased in fat-depleted animals, the disposition to skin increased. Excretion patterns also change whereby a larger proportion of the dose is excreted in fat depleted animals. The magnitude of the increased excretion can be well in excess of a factor of 2-3 times greater than that observed in rats fed a normal diet. Thus, it is apparent that alterations in body fat content can affect the disposition of the 2,2',4,4',5,5'-hexa-CB body burden and the disposition of subsequent doses of this isomer.

Long-term kinetics of 2,2',4,4',5,5'-hexa-CB have been studied in rats maintained at a constant adipose tissue mass (Wyss et al., 1986). Table III-5 indicates that under these conditions, the majority of the body burden of this isomer is relegated to the fat compartment with the skin accumulating the next highest load. There is a striking persistence of this congener, with 49% of the dose still associated with tissue compartments 280 days after dosing. The half-times for specific compartments are given in Table III-6. Levels in tissues generally decline in a triphasic fashion with half-times of the terminal component on the order of 450 days. As seen in Table III-7, only minimal amounts of 2,2',4,4',5,5'-hexa-CB are excreted in urine. Extrapolation to infinite time points predicts that ~83% of the total dose will eventually be excreted in the feces with a half-time of 478 days. Owing to its persistence and extremely long half-time for elimination, this particular congener has a high potential for accumulation within the body.

The pharmacokinetics of PCB mixtures and congeners in several other species including the dog, fish, mink, avian species and swine have been reported (Sparling and Safe, 1980b; Lutz et al., 1984; Sipes et al., 1982a,b; Hansen et al., 1983; Brunn, 1984; Hornshaw et al., 1983; Gruger et al., 1975; Guiney et al., 1979; Guiney and Peterson, 1980). The results are somewhat comparable for all species with long-term accumulation of individual PCBs occurring primarily in adipose tissue. It was apparent that rates of PCB metabolism were important with respect to tissue persistence of individual compounds. Sparling and Safe (1980b) suggested that the degree of ortho-chloro substitution (Cl-2; Cl-6) may contribute to the ultimate

TABLE III-5

Time Course of 2,2',4,4',5,5'-Hexa-CB Tissue Distribution, Elimination, and Recovery (percentage of dose) in Rats with Constant Adipose Tissue Mass[a,b]

Days:	4	7	14	28	42	140	175	280
No. of Rats/ Time Point:	6	6	3	3	6	4	2	4
Blood	0.27	0.24	0.14	0.12	0.09	0.07	0.06	0.06
Liver	1.5	1.1	1.05	0.9	0.75	0.56	0.44	0.45
Lung	0.27	0.30	0.17	0.20	0.10	0.09	0.08	0.07
Muscle	5.4	4.8	4.4	4.0	3.6	3.3	3.15	3.0
Brain	0.13	0.12	0.11	0.12	0.07	0.05	0.05	0.04
Skin	10.1	10.8	15.3	12.5	11.0	8.4	7.9	6.9
Adipose	58.9	63.1	64.4	67.8	58.8	44.4	42.7	38.4
Tissues[c]	76.6	80.9	85.5	86.0	74.5	57.0	54.5	49.0
Urine	0.15	0.21	0.27	0.37	0.48	1.03	1.18	1.49
Feces	3.01	4.0	5.9	9.3	12.4	28.5	32.7	43.0
Excretion[d]	3.2	4.2	6.2	9.7	12.9	29.5	33.9	44.5
Recovery[e]	79.8	85.1	91.7	95.7	88.4	86.5	88.4	93.5

[a]Source: Adapted from Wyss et al., 1986

[b]Single i.v. dose of 0.6 mg/kg bw.

[c]Percentage of dose distributed to all tissues.

[d]Percentage of dose excreted in urine and feces.

[e]Percentage of dose recovered in tissues and excreta.

TABLE III-6

Tissue Kinetics of 2,2',4,4',5,5'-Hexa-CB in Rats with Constant Adipose Tissue Mass[a,b]

Tissue	Half-life for Removal		
	α-Phase	β-Phase	γ-Phase
Blood	0.114	8.4	462
Liver	0.161	9.9	442
Lung	0.182	12.3	433
Muscle		12.1	478
Brain		17.3	449
Skin		13.9	431
Adipose		10.9	456

[a]Source: Adapted from Wyss et al., 1986

[b]Half-lives are given in days.

TABLE III-7

Excretion Kinetics of 2,2',4,4',5,5'-Hexa-CB in Rats with Constant Adipose Tissue Mass[a,b]

Excretion	Component	Decay Rate Constant	Half-life	No. of Time Points	Cumulative Excretion for Infinite Time
		$days^{-1}$	days		% dose
Fecal	I	0.616	1.1	7	2.07
	II	0.012	57.3	36	13.55
	III	0.001	478	16	83.45
					99.07
Urinary	I	0.112	0.95	5	0.15
	II	0.0095	150	30	1.85
					2.00

[a]Source: Adapted from Wyss et al., 1986

[b]Values are means of 4-8 animals/time point.

persistence of PCBs in various species. A mixture of 2,2',4,4',6,6'-, 2,2',4,4',5',6'-, 2,2',4,4',5,5'-, 2',3,4,4',5,5'- and 3,3',4,4',5,5'-hexa-CBs (1:1:1:1) was administered by gastric gavage to rats, guinea pigs, rabbits, Japanese quail and trout, and the concentrations in the fat or whole carcass were determined after 29 days (Table III-8). These isomers are all relatively resistant to metabolism but contain 0-4 ortho chlorine substituents (Cl-2; Cl-6). The total hexa-CB levels in rat, rabbit and guinea pig fatty tissue were 8.27, 6.84 and 4.74 ppm, respectively: whereas 3.02 and 2.15 ppm of the hexa-CBs were detected in the trout and Japanese quail carcasses, respectively. The extent of ortho-chloro substitution markedly affected the levels of the individual hexa-CB isomers retained in the test animals. In the rat, the di-ortho substituted analog was preferentially retained over the other isomers whereas the coplanar most toxic isomer, 3,3',4,4',5,5'-hexa-CB, was present in the lowest concentration. The rabbit and guinea pig preferentially retained the hexa-CBs with 0, 1 and 2 ortho-chloro substituents, the Japanese quail retained only the 3,3',4,4',5,5'-hexa-CB isomer, whereas no striking preferences in hexa-CB isomer retention was observed in the trout. The marked differences in the retention of hexa-CB isomers with 0, 1,2,3 and 4 ortho-chloro substitution by different animal species should be considered in chronic toxicity studies, since the most toxic polychlorinated biphenyls have minimal (1 or 0) ortho-chloro substituents.

The critical or rate limiting event in the elimination of PCBs is metabolism. The major site of metabolism is the hepatic cytochrome P-450 dependent monooxygenase system. Species variation in the intrinsic

TABLE III-8

Hexa-CB Levels in Rabbit, Rat and Guinea Pig Adipose Tissue,
Trout and Japanese Quail Carcasses 29 Days after Administration of the Isomer Mix (1:1:1:1)*

Hexa-CB Isomers	Tissue Levels (ppm)				
	Rabbit Fat (5/group)	Rat Fat (4/group)	Guinea Pig Fat (2/group)	Japanese Quail Carcass (5/group)	Trout Carcass (3/group)
2,2',4,4',6,6'-	0.302±0.056	1.253±0.460	0.120±0.020	ND	0.612±0.148
2,2',4,4',5',6-	0.357±0.077	2.003±0.847	0.074±0.004	ND	0.838±0.174
2,2',4,4',5,5'-	2.043±0.655	3.053±0.855	0.933±0.004	ND	0.559±0.131
2',3,4,4',5,5'-	2.103±0.508	1.433±0.681	2.108±0.230	ND	0.462±0.001
3,3',4,4',5,5'-	2.030±0.495	0.529±0.222	1.500±0.018	0.215±0.018	0.553±0.009

*Source: Sparling and Safe, 1980b

ND - Nondetectable

metabolism of PCBs demonstrates that different species have different basal capacity to metabolize these compounds. This difference in metabolic capacity is reflected ultimately in the elimination half-lives of the PCBs.

Table III-9 summarizes data on the in vitro hepatic metabolism and in vivo metabolic clearance of 2,2',3,3',6,6'-hexa-CB, 4,4'-di-CB, and 2,2',4,4',5,5'-hexa-CB in humans, monkeys, dogs and rats (Schnellmann et al., 1985). Significant species variation was found in the microsomal metabolism of PCBs. For each PCB, the V_{max} values for metabolism in the monkey, dog and rat are consistent with the respective metabolic clearance values generated from in vivo studies. For example, the monkey metabolized 2,2',3,3',6,6'-hexa-CB at a faster rate than 4,4'-di-CB and did not metabolize 2,2',4,4',5,5'-hexa-CB. The in vivo metabolic clearance values indicate that 2,2',3,3',6,6'-hexa-CB was eliminated faster than 4,4'-di-CB, which in turn was eliminated faster than 2,2',4,4',5,5'-hexa-CB. The metabolic clearance of 2,2',4,4',5,5'-hexa-CB in the monkey is <1 mℓ/min and only 18% of a dose of this isomer is excreted over 90 days (Sipes et al., 1982a; Lutz et al., 1984). In general, the findings with the rat were similar to those observed in the monkey. Unlike the rat and monkey, the dog metabolized 2,2',4,4',5,5'-hexa-CB in vitro. This result is consistent with the fact that the dog eliminated 50% of a dose of 2,2',4,4',5,5'-hexa-CB in 8 days, while the monkey and rat were incapable of eliminating 50% of the administered dose during their remaining lifespan (Lutz et al., 1977; Kato et al., 1980; Sipes et al., 1982a). In summary, the kinetic constants for PCB metabolism obtained from the dog, monkey and rat hepatic microsomal preparations were good predictors of in vivo metabolism and clearance for the three PCBs.

TABLE III-9

Metabolism Parameters of Three PCBs in Humans, Monkeys, Dogs and Rats*

Constant	Human	Monkey	Dog	Rat
In Vitro Apparent Km (μM)				
2,2',3,3',6,6'-hexa-CB	8.8	5.2	0.12	2.9
4,4'-di-CB	0.43	0.92	1.3	0.36
2,2',4,4',5,5'-hexa-CB	ND	ND	9.5	ND
In Vitro V_{max} (pmoles/nmoles P-450/min)				
2,2',3,3',6,6'-hexa-CB	19	14	29	16
4,4'-di-CB	4.4	4.3	160	6.4
2,2',4,4',5,5'-hexa-CB	ND	ND	5.8	ND
In Vivo Metabolic Clearance (mℓ/min)				
2,2',3,3',6,6'-hexa-CB	NA	15	180	5
4,4'-di-CB	NA	7	470	2
2,2',4,4',5,5'-hexa-CB	NA	0.67	16	0.045
In Vivo Metabolic Clearance (mℓ/min/kg)				
2,2',3,3',6,6'-hexa-CB	NA	3	15	20
4,4'-di-CB	NA	1.4	39	8
2,2',4,4',5,5'-hexa-CB	NA	0.13	1.3	0.18

*Source: Adapted from Schnellmann et al., 1985

ND = Not detected

NA = Not analyzed

Pharmacokinetic Studies in Humans

In investigations directed at determining which species most accurately predicts the metabolism and disposition of PCBs in humans, the in vitro metabolism of 2,2',3,3',6,6'-hexa-CB, 4,4'-di-CB, and 2,2',4,4',5,5'-hexa-CB was also investigated in human liver microsomes (Schnellmann et al., 1983, 1984). Data in Table III-9 suggest that the human metabolism of PCBs would most closely resemble that of the rat and monkey, but not the dog. There is good agreement between the V_{max} values generated from the human and rat preparations, whether expressed per nmole P-450 or per mg microsomal protein (Schnellmann et al., 1985). Since hepatic cytochrome P-450 concentration are relatively similar in the human and the rat, Schnellmann et al. (1985) concluded that the rat would be a good model for human PCB disposition studies.

In vivo data on the relative persistence of specific PCBs in humans are also consistent with the above in vitro results on the metabolism of PCBs. Jensen and Sundstrom (1974) reported that 2,2',4,4',5,5'-hexa-CB was the PCB congener found in the highest concentration in human adipose tissue, while 2,2',3,3',6,6'-hexa-CB was not detected. Since both compounds are found in commercial PCB mixtures and in the environment, the presence of 2,2',4,4',5,5'-hexa-CB in adipose tissue is apparently related to the resistance of this congener to biotransformation and elimination (Sissons and Welti, 1971; Albro et al., 1981). Other investigators have measured the comparative rates of elimination of individual PCBs from the blood of PCB-poisoned patients in Taiwan (Chen et al., 1982). They found that the blood concentration of 2,2',4,4',5,5'-hexa-CB only decreased 10% over 300-500 days. This suggests that this PCB is not readily eliminated and,

thus, is not metabolized or is only minimally metabolized by humans. Finally, PCB concentrations were measured in the blood and adipose tissue from workers in a capacitor manufacturing facility (Wolff et al., 1982a). The PCBs with unsubstituted 3,4-positions on at least one of the phenyl rings were in lower concentration than PCBs with substitutions in the 2,4- or 3,4-positions on both rings.

Human populations have accumulated PCBs by three major pathways, namely environmental (oral exposure), accidental (oral exposure) and occupational (dermal and inhalation); several papers have reported the identification of PCBs in human tissues by low or high resolution GC analysis (Wasserman et al., 1979; Higuchi, 1976; Cordle et al., 1978; Holdrinet et al., 1977; Safe, 1982; Pellizzari et al., 1985; Hansen et al., 1975; Hansen, 1979; Stalling et al., 1979; Safe et al., 1975b; Jensen and Sundstrom, 1974; Yakushiji et al., 1979). A major problem associated with PCBs in humans has been the unequivocal identification of the individual congeners. Table III-1 summarizes the composition of the major individual PCBs identified in human milk determined by high resolution capillary GC using all 209 PCB isomers and congeners as standards (Safe et al., 1985a). With few exceptions all other studies have been conducted with a limited number of authentic standards. Although there are numerous qualitative differences in the PCB composition of human tissues, it is evident that several compounds, including 2,2',4,4',5- and 2,3',4,4',5-penta-CB, 2,2',4,4',5,5'-, 2,2',3',4,4',5- and 2,3,3',4,4',5-hexa-CB, 2,2',3,4,4',5,5'- and 2,2',3,3',4,4',5-hepta-CB are routinely identified in all human tissues (liver, adipose tissue, serum and milk). The PCB composition of serum or adipose tissue from occupationally-exposed individuals is highly dependent on the point source pollutant (that

is, commercial PCB product). For example the PCB composition of serum or adipose tissue of workers exposed to the lower chlorinated PCB product, Aroclor 1016, is significantly different than observed in Yusho patients and there is bioconcentration of the more persistent lower chlorinated congeners such as 2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2',3,4,4'-tetra-CB and 2,3',4,4',5-penta-CB (Wolff et al., 1982b), which are present in the commercial product. The more familiar higher chlorinated PCB congeners that bioconcentrate from environmental sources are also evident (at relatively lower concentrations) in the gas chromatograms of occupationally-exposed worker's tissue extracts.

Chen et al. (1982) investigated the elimination of individual PCBs from the blood of PCB-poisoned humans in Taiwan. The results indicate that tetra- and pentachlorobiphenyls with adjacent unsubstituted carbon atoms at meta-para positions are rapidly eliminated from the blood of patients, while PCBs with the same degree of chlorination but with adjacent unsubstituted carbon atoms at ortho-meta positions are eliminated more slowly. They calculated terminal half-lives of 2,4,5,3',4'-penta-CB and 2,3,4,3',4'-penta-CB in the blood of exposed humans to be 9.8±5.0 and 6.7±2.5 months (means ± SD), respectively.

Fetal and Neonatal Studies

Several studies (Torok and Weber, 1981; Masuda et al., 1978, 1979; Orberg, 1977; Curley et al., 1973; Baker et al., 1977; Mizunoya et al., 1974; McCormack et al., 1979; Allen and Barsotti, 1976; Iatropoulos et al., 1978; Bailey et al., 1980; Takagi et al., 1976; Ando, 1978; Vodicinik and Lech, 1980; Vodicinik, 1986) clearly demonstrate that PCB mixtures and

individual congeners can cross the placental barrier and accumulate in fetuses. At high-dose levels of PCBs this can result in fetal toxicity. Another major exposure occurs by lactation in which the highly lipophilic PCBs are readily transferred from the parent to the neonate. Most studies indicate that this latter route is the most important route of exposure for the young.

Table III-10 summarizes several studies using laboratory animals, which describe the transfer of PCBs from mothers to fetuses and suckling neonates. The results reported in most of these papers are comparable and only a selected few studies will be discussed in detail.

Vodicinik and Lech (1980) investigated the transfer of 2,2',4,4',5,5'-hexa-CB in pregnant mice to fetuses and nursing offspring. The compound was administered to the mice 2 weeks before mating and a group of virgin mice served as controls. At the day of birth, PCB levels in liver, adipose tissue and kidney were higher in the sacrificed pregnant mice compared with the controls. The PCB levels in the fetuses were minimal (that is, <5 µg/g liver and <1 µg/g carcass) compared with the mother (~27 µg/g liver, >1000 µg/g adipose tissue). Five days postpartum there were dramatic increases in the PCB levels in offspring liver muscle and skin, and after 20 days postpartum almost the entire body burden of the nursing mother was transferred to the offspring (Table III-11).

Masuda et al. (1979) administered a reconstituted mixture of seven PCB congeners (2,4,4'-tri-CB, 2,3',4,5-tetra-CB, 2,2',4,5,5'-penta-CB, 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5-hexa-CB, 2,2',3,4,5,5',6-hepta-CB and

TABLE III-10

Distribution of PCBs to Fetuses and Nursing Young

Species/Strain	Sex/Number	Source of PCBs	Vehicle	Dosage/ Route of Administration	Distribution to Dams Milk or Offspring	Reference
Mice/NMRI	F/NR	[^{14}C]2,4',5' tri-CB [^{14}C] Mixture of PCBs	sesame oil	trace amounts/gavage on days 13, 15, 17 of pregnancy	In dams: fat>mammary gland>liver>kidney> ovary-blood. Fetal: day 18 levels>14, mostly in GI tract and liver at day 18.	Jorok and Weber, 1981
Mice/ddN	F/10-15/ group	2,4,4'-tri-CB; 2,3',4,5-tetra-CB; 2,2',4,5,5'-penta-CB; 2,2',4,4',5,5'-hexa-CB; 2,2',3,4,4',5'-hexa-CB; 2,2',3,4,5,5',6-hepta-CB or 2,2',3,3',4,4',5,5'-octa-CB	diet	0.32 mg/kg diet 0.42 mg/kg diet 0.44 mg/kg diet 0.44 mg/kg/diet 0.16 mg/kg diet 0.23 mg/kg diet	Fetal levels: greater when PCB fed during rather than before pregnancy. In all cases tested, exposure of dams pregestational elevated fetal tissue levels.	Masuda et al., 1979
Mice/ddN	F/7-12/ group	Kanechlor-500	diet	0.01 (control), 0.94, 8.4 or 86 mg/kg diet from days 0-18 of pregnancy or day 0 of pregnancy to 5 weeks postpartum	Fetuses: whole body levels dose-related; at 86 mg/kg diet level fetal adipose tissue PCB >maternal liver PCB concentrations. PCB levels of offspring during lactation ≥100x previous fetal levels.	Masuda et al., 1978
Mice/NMRI	F/21 F/25	2,4',5 tri-CB or 2,2',4,4',5,5'-hexa-CB	peanut oil	0 or 0.05 mg/days for days 5-19 of gestation 0 or 0.05 mg/day for days 1-12 of lactation	Dams: liver hexa-CB>>tri-CB Fetuses: adipose hexa-CB>>tri-CB Dams: liver hexa-CB>>tri-CB Offspring: liver hexa-CB>>tri-CB; stomach contents hexa-CB>>tri-CB	Orberg, 1977
Rat/Sherman	F/6.13/ group	Aroclor 1254	peanut oil	0, 10 or 50 mg/kg bw/day, days 7-15 of gestation	Fetuses: <0.12, 0.63, 1.38 µg/g tissue Milk: <0.75, 20.63, 66.2 µg/g milk 21-day-old weanling males: 0.19, 3.35, 18.24 µg/g liver	Curley et al., 1973
Rat/Wistar	F/5/group	Aroclor 1254	drinking water	6.4 mg/kg bw daily for 9 weeks	Fetal levels: low: ~1 µg/g whole body	Baker et al., 1977
Rat/Wistar-SLC	F/12/group	Kanechlor-400	diet	0, 10, 50 or 250 mg/kg diet during gestation	PCB concentrations in fetal tissue <blood of dams. Marked increase at day 14 of gestation. PCB concentrations in 28-day-old offspring >tissue levels of dams. Tissue levels of 28-day-old pups whose dams received 50 mg/kg: liver> kidney>lung>spleen>heart>brain.	Mizunoya et al., 1974

TABLE III-10 (cont.)

Species/Strain	Sex/Number	Source of PCBs	Vehicle	Dosage/ Route of Administration	Distribution to Dams Milk or Offspring	Reference
Rat/Sprague-Dawley	F/NR	Aroclor 1254	diet	0, 25 or 50 mg/kg diet starting day 8 of gestation - day 14 postpartum	Dam: fat>mammary>kidney>liver>lung Milk: postpartum day 0/293 mg/ml/50 mg/kg; postpartum day 14/32 µg/ml/50 mg/kg	McCormack et al., 1979
Monkey/rhesus	F/16	Aroclor 1248	diet	0, 2.5 or 5.0 mg/kg diet continuously 1.5 years, start 6 months prebreeding	Stillborn male-5.0 mg/kg: lung>pancreas>adrenal>thymus>spleen>muscle>kidney>liver. Male died at 44 days-2.5 mg/kg: bone marrow-lung>thymus>adrenal>pancreas>kidney>spleen.	Allen and Barsotti, 1976
Monkey/rhesus	F/3	Clophen A-30	1% methyl cellulose in water	0 or 16 mg/kg bw/day by gavage 22-29 days	Blood of offspring higher in PCBs than blood of dams. PCB levels in milk 10-20 times that of serum of dam. Higher PCB levels in tissues of infant than dam.	Iatropoulos et al., 1978, Bailey et al., 1980
Rat/JCL-CB	F	Radiolabeled Kanechlor 400	Olive oil	oral administration once a week from day 8-18 of pregnancy	70-56% of dose excreted by dams (skin and placenta-major fetal deposition). Average dam-fetal transfer 28% of dose. Average amount of PCBs transferred by lactation (45 days) - 2% of dose. Nursing rat levels of PCBs lower than dosed pregnant or nonpregnant rats.	Takagi et al., 1976
Rats/Wistar	F	Radiolabeled 2,2',4,4',5,5'-hexa-CB	Olive oil	i.p. administration	Transfer by placenta and lactatum was 2.7 and 39.2%, respectively.	Ando, 1978
Mice/Sprague-Dawley	F	Radiolabeled 2,2',4,4',5,5'-hexa-CB	Corn oil	compound injected i.p. 2 weeks prior to mating	Transplacental transfer of PCB was minimal; after 20 days postpartum, lactation transferred most of the mothers dose to suckling pups.	Vodicnik and Lech, 1980
Mice/ICR	F	Radiolabeled 2,2',4,4'-tetra-CB	Corn oil	i.p. injection of 150 mg/kg on day 15 of gestation	Transplacental transfer ~1% of maternal body burden, 90% of maternal body burden eliminated over a 4-day nursing period.	Vodicnik, 1986

TABLE III-11

Transfer of [^{14}C]Hexa-CB from Mother Mice to Nursing Offspring[a]

Day of Sacrifice	Mothers[b]			Offspring[c]		
	mg Hexa-CB/ Total Carcass	µg Hexa-CB/g Litter	Percentage Total Dose Eliminated[d]	mg Hexa-CB/ Litter	µg Hexa-CB/ Litter	Percentage of Mother's Dose Accumulated
Day 19 pregnancy	0.862	5.12	0			-
Birth	-	-	2.7			-
Day 5 postpartum	0.372	8.59	56.8	0.545	15.31	3.00[e]
Day 10 postpartum	0.167	3.48	80.6	0.810	13.97	94.0
Day 15 postpartum	0.038	0.87	95.6	0.743	11.18	86.2
Day 20 postpartum	0.016	0.37	98.1	0.900	12.50	104.4

[a]Source: Vodicnik and Lech (1980)

[b]Virgin female mice pretreated with 50 mg/kg [^{14}C]2,2',4,4',5,5'-hexa-CB (~1.25 mg/animal) 2 weeks before mating. Each value represents the mean of two carcasses.

[c]Each value represents the mean from the carcasses of two pooled litters.

[d]Represents percentage eliminated from dose remaining in mothers at day 19 of pregnancy.

2,2',3,3',4,4',5,5'-octa-CB) in the diet to adult female mice for 18 days either before or after mating. The results demonstrated that there was transfer of all the PCB congeners to fetuses and offspring and it was apparent that lactation was the predominant route of exposure for the offspring. Not surprisingly, the more readily metabolized 2,4,4'-tri-CB, 2,3',4',5-tetra-CB and 2,2',3,4,5,5',6-hepta-CB were rapidly eliminated from the dams and their offspring. Higher levels of the 2,2',4,5,5'-penta-CB were detected in the offspring (aged 5 weeks) and this was not expected since this compound would also be rapidly metabolized. In contrast the more highly chlorinated 2,2',4,4',5,5'-hexa-CB, 2,2',3',4,4',5-hexa-CB and 2,2',3,3',4,4',5,5'-octa-CB persist in the tissue of both the dams and their offspring. The two hexa-CB isomers also preferentially bioconcentrate in human tissues.

Infant monkeys nursed by PCB-exposed dams rapidly developed signs of PCB-induced intoxication. Female monkeys were fed diets containing 2.5 or 5.0 mg Aroclor 1248/kg starting 6 months before breeding and exposure continued for 18 months (Allen and Barsotti, 1976). One male infant was stillborn and its PCB tissue levels ranged from 99.5 µg/g in lung > pancreas > adrenal > thymus > spleen > muscle > kidney to 2.5 µg/g in liver. All of the surviving infants developed typical facial skin lesions by 2 months of age. Tissue levels of PCBs in a male infant that had died at 44 days of age ranged from 50.8 µg/g in bone marrow ~lung > thymus > adrenal > pancreas > kidney to 0.62 µg/g in liver. Three nursing rhesus monkeys were treated with 16 mg Clophen A-30/kg/bw/day by gavage starting on days 46-127 postpartum and continuing for 22-29 days (Iatropoulos et al., 1978;

Bailey et al., 1980). The youngest infant and her dam became moribund on exposure day 21. Necropsy of the infant revealed mild hepatocellular pathology and dilation of renal tubules containing casts. Levels of PCBs in milk appeared to range from 10-20 times the levels in serum. In general, serum levels of PCBs in infants were about 2 times the levels in their dams. Body fat contained the highest levels (1687 μg/g) > bone marrow > lymph nodes > adrenals > thymus > kidney > spinal cord > liver (80 μg/g). In all tissues except the thymus, infant tissue levels were 1.94-5.47 times the corresponding levels in the moribund dam sacrificed after 22 days of exposure. These studies confirm the importance of lactation as the major source of PCB exposure in neonates.

The importance of lactation as a major route for PCB excretion was demonstrated in a study of a woman occupationally exposed to Kanechlor 300 and 500 in a capacitor factory (Yakushiji et al., 1978). The PCB levels in the tissues and fluids from the mother and child are summarized in Table III-12. Since PCB levels in umbilical tissues, umbilical blood and amniotic fluid were considerably less than measured in mothers blood it was evident that there were some barriers to transplacental exposure to these toxins. Other recent studies confirm this observation (Jacobson et al., 1984; Bush et al., 1984). Since the mother's milk and serum contained unusually high levels of PCBs, the baby was not nursed on her breast milk. Lactation of this individual resulted in the excretion of 200 mg of PCBs in 818 ℓ of breast milk and resulted in an overall 76% decrease in (milk) PCB levels.

TABLE III-12

Levels of PCBs in the Tissues and Fluids from a Mother and Child Occupationally Exposed to Kanechlor 300 and 500*

Sample	Date	Tissue (ppm)	Fluid (ppm)
Placenta	July 1975	-	0.056
Umbilicus tissues	July 1975	-	0.011
Umbilicus blood	July 1975	-	0.016
Mother's blood	July 1975	-	0.057
Amnion fluid	July 1975	-	0.010
Omentum adipose tissue	July 1975	16.1	12.2
Subcutaneous adipose tissue (taken from the mother)	November 1976	4.1	4.0
Baby's blood	November 1975	-	0.003
Baby's blood	November 1976	-	0.004

*Source: Yakushiji et al., 1978

These data clearly illustrate the importance of lactation as the major route of infant PCB exposure and as a major route of depuration for the highly exposed mothers.

Metabolism

As discussed previously in this chapter, the major factor that affects the long-term persistence of individual PCBs in animal tissues is the rate of metabolism of these compounds. It was initially shown by Block and Cornish (1959) that the lowest chlorinated biphenyl, 4-CB, was metabolized to give 4'-chloro-4-biphenylol and its glucuronide as urinary metabolites. Hutzinger et al. (1972) reported that not only 4-CB but several higher chlorinated biphenyls were metabolized to give hydroxylated and dihydroxylated PCB products as determined by MS analysis. These initial results also suggested the rates of metabolite excretion were species-dependent (for example, rats > birds > fish) and dependent on the degree of substrate chlorination since only trace levels of the higher halogenated biphenyl metabolites were detected.

The *in vivo* metabolism of individual PCBs by mammalian, avian and plant species and by microorganisms has been reviewed (Matthews and Dedrick, 1984; Schnellmann et al., 1985; Safe, 1980; Sundstrom et al., 1976a). Numerous studies have focused on delineating the problems associated with PCB metabolism, and these include structure determination of PCB metabolites, evaluation of the effects of the position and number of chloro substituents on the sites, and rates of metabolism and determination of the mechanism of PCB metabolism (that is, metabolic pathways).

Figure III-2 summarizes the structures of PCB metabolites that have been identified using a diversity of substrates and biosystems (Block and Cornish, 1959; Hutzinger et al., 1972; Sundstrom et al., 1976a,b; Hsu et al., 1975; Gardner et al., 1973; Safe et al., 1975a,b, 1976; Norback et al., 1976; Sparling et al., 1980; Melancon and Lech, 1976; Ghiasuddin et al., 1976; Hass et al., 1977; Sipes et al., 1980, 1982a,b; Schnellmann et al., 1983, 1984, Shimada, 1976; Jensen and Jansson, 1976; Mizutani et al., 1978; Bergman et al., 1979, 1982; Mio et al., 1976; Mizutani, 1978; Baake et al., 1982; Brandt et al., 1982; Brandt, 1986; Preston et al., 1984; Lund et al., 1985). Invariably, the phenolic products are the major PCB metabolites although sulfur-containing metabolites (for example, methylsulfones), trans-dihydrodiols, polyhydroxylated PCBs, and their methyl ether derivatives and ring-degraded microbial oxidation products have been identified. The effects of chlorine substitution patterns on the sites of oxidation have not been studied systematically; however, examination of the results in the literature suggest the following:

1. Hydroxylation is favored at the para position in the least chlorinated phenyl ring unless this site is sterically hindered (that is, 3,5-dichloro substitution).

2. In the lower chlorinated biphenyls the para position of both biphenyl rings and carbon atoms that are para to the chloro substituent are all readily hydroxylated (Sparling et al., 1980).

3. The availability of two vicinal unsubstituted carbon atoms (particularly C_5 and C_4 in the biphenyl nucleus) also facilitates oxidative metabolism of the PCB substrate but is not a necessary requirement for metabolism.

4. As the degree of chlorination increases on both phenyl rings the rate of metabolism decreases.

5. The metabolism of specific PCB isomers by different species can result in considerable variations in metabolite distribution.

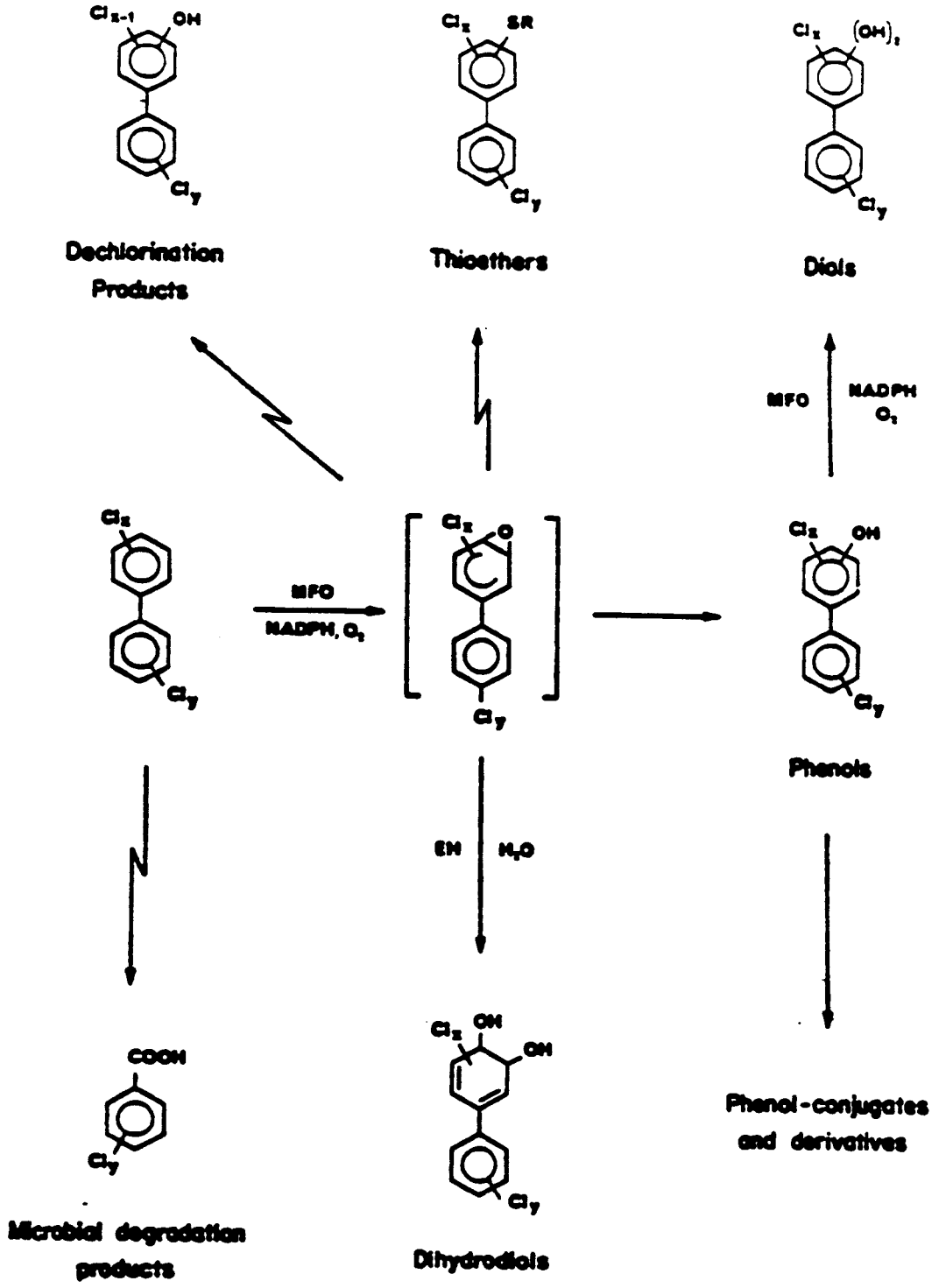


FIGURE III-2

Summary of PCB Metabolism

Source: Safe, 1980

The mechanism of PCB metabolism has been delineated by results obtained from several studies. For example the metabolism of 2,2',5,5'-tetra-CB by a variety of biosystems gave two phenols, 2,2',5,5'-tetrachloro-4-biphenylol and 2,2',5,5'-tetrachloro-3-biphenylol and trans-3,4-dihydro-3,4-dihydroxy-2,2',5,5'-tetrachlorobiphenyl as major metabolites (Hsu et al., 1975; Gardner et al., 1973; Norback et al., 1976; Ghiasuddin et al., 1976). The latter trans-dihydrodiol suggested that the metabolism may involve an arene oxide (Gardner et al., 1973). Arene oxides have been proposed as intermediates in the metabolism of diverse endogenous and exogenous chemicals, and their formation requires molecular oxygen, reduced nicotinamide-adenine dinucleotide (NADPH) and the microsomal monooxygenase enzyme system (Jerina and Daly, 1974). The high reactivity of these intermediates often precludes their detection since arene oxides characteristically hydrate to give trans-dihydrodiols and other rearrangement products. However, using [^{3}H]-2,2',5,5'-tetra-CB and an in vitro microsomal enzyme system, the proposed arene oxide intermediate from 2,2',5,5'-tetra-CB has been identified (Forgae and Allen, 1982).

Arene oxides also spontaneously rearrange to phenols with the concomitant 1,2-migration of substituents (e.g., ^{2}H, ^{3}H, Cl, Br and CH_3) from the site of hydroxylation to the adjacent carbon atom (the NIH shift). The metabolism of 4-chloro[4'-^{2}H]biphenyl (Safe et al., 1975a), 4,4'-dichlorobiphenyl (Safe et al., 1976; Hass et al., 1977; Sipes et al., 1980) and 2,2',4,4',5,5'-hexachlorobiphenyl (Sipes et al., 1982a; Schnellmann et al., 1983; Sundstrom et al., 1976b) all featured the NIH shift of Cl (or

^{2}H) and the results were consistent with metabolism by arene oxide intermediates. Thus, the detailed metabolic studies of selected PCB isomers and congeners suggested that arene oxides play a major role in their metabolism.

Metabolically mediated cytotoxicity, mutagenicity and carcinogenicity have been associated with the in vivo formation of electrophilic species and their subsequent alkylation of critical cellular macromolecules. Arene oxides are potential electrophiles and thus their formation and subsequent cellular reactions can involve the formation of both detoxification products (for example, metabolites, glutathione conjugates, other phase II conjugates), which are excreted, and potentially toxic covalently bound substrate-macromolecular adducts. The in vivo and in vitro formation of PCB-protein, RNA and DNA adducts have been reported in several studies (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Sato, 1978; Stadnicki et al., 1979; Wong et al., 1979; Morales and Matthews, 1979). The in vivo binding of 2,2',4,4',5,5'- and 2,2',3,3',6,6'-hexa-CB to hepatic protein, RNA and DNA in mice has been reported (Morales and Matthews, 1979). Moreover, the in vitro metabolism of numerous PCB isomers and congeners by rabbit, rat, mouse and monkey liver microsomal enzymes results in the formation of hydroxylated metabolites and covalently bound PCB-macromolecular adducts (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Sato, 1978).

In vitro studies using mammalian cells in culture have confirmed DNA damage mediated by PCB congeners and their metabolites. Incubation of 2,2',5,5'-tetra-CB, 2,2',5,5'-tetrachloro-4(3)-biphenylols (4:1 mixture of

the 4 and 3 phenolic products, respectively) and 3,4-dihydro-3,4-epoxy-2,2',5,5'-tetrachloro-biphenyl with L-929 cells was conducted. The DNA was isolated and examined for strand breaks by centrifugation techniques. All the test compounds were capable of inducing single-strand breaks in L-929 cell DNA; however, the arene oxide was clearly the most potent agent (Stadnicki et al., 1979). Another in vitro assay of DNA damage was reported using 4-chlorobiphenyl as a substrate with Chinese hamster ovary cells (Wong et al., 1979). Incubation of the cells with 4-[^{3}H]CB resulted in metabolite formation (that is, hydroxylated products), which was accompanied by binding to protein, RNA and DNA. Moroever, the specific activity of the substrate-DNA fraction was higher than that observed for binding to protein or RNA. In parallel experiments, a DNA repair assay confirmed the DNA damage by a significant increase in the uptake of [^{3}H]dT after incubation of the cells with 4-CB.

The toxicologic significance of PCB metabolism is unknown. However, most studies suggest that the parent hydrocarbon initiates most of the common toxic responses by initial binding to the cytosolic receptor protein (Safe et al., 1982; Safe, 1984; Poland et al., 1979, 1983). The role of metabolism in the genotoxicity of PCBs has not been delineated.

Because of their lipophilic and relatively stable nature, PCBs rapidly bioaccumulate in biota and the tissues of humans. PCBs are effectively absorbed following oral, dermal and inhalation exposure. In most animal species that have been investigated there is an initial uptake of PCBs into the liver and muscle because of high perfusion in the liver and the relatively large muscle volume. Subsequent redistribution of PCBs into adipose

tissue and skin reflects the high affinity of the PCBs for lipophilic tissues. At equilibrium the elimination of PCBs from all tissues will be dependent on the structure-dependent metabolism rates of individual PCB congeners. For example, biological half-lives in the rat range from 0.15 days for 2,2'-di-CB to ~460 days for 2,2',4,4',5,5'-hexa-CB.

Metabolism is apparently the primary rate limiting event regulating the elimination of PCBs from mammalian systems. The in vitro metabolism of PCBs has been investigated in liver microsomes from the human, monkey, dog, and rat. The data suggest that the human metabolism of PCBs would most closely resemble that of the rat. Therefore, the rat should be a good model for predicting the disposition of PCBs in humans.

The position and degree of chlorination substantially influence the rate and extent of PCB metabolism. As the degree of chlorination increases on both phenyl rings the rate of metabolism decreases, though there is also a selectivity with respect to type of substitution for isomers. The availability of two vicinal unsubstituted carbon atoms facilitates metabolism of the PCB substrate but is not a necessary requirement for metabolism. Although phenolic products are the major PCB metabolites, sulfur-containing metabolites, trans-dihydrodiols, polyhydroxylated PCBs and their methyl ether derivatives have been identified. The presence of trans-dihydrodiol metabolites strongly suggests metabolism through an arene oxide intermediate. Arene oxides have been implicated in cellular necrosis, mutagenicity and carcinogenicity; however, the role of metabolism in the genotoxicity of PCBs has not been delineated.

Studies in laboratory animals clearly demonstrate that PCBs can cross the placental barrier and accumulate in the fetus. Another major route of exposure occurs by lactation in which the highly lipophilic PCBs are readily transferred from maternal milk to the neonate. The latter route represents the most important route of PCB exposure for the young.

Preferential structure-dependent bioaccumulation of PCB congeners has been observed in human liver, adipose tissue, serum and milk. 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5'-hexa-CB, 2,2',3,3',4,4',5-hepta-CB and 2,2',3,4,4',5,5'-hepta-CB are major components of both a high molecular weight commercial PCB mixture (Aroclor 1260) and human milk. On the other hand, 2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2,2',4,4',5-penta-CB, 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB are identified as major components of human milk extract, while representing only minor components of Aroclor 1260. Human studies also clearly indicate the importance of lactation as the major route of infant PCB exposure, as well as representing a major route of depuration for highly exposed mothers.

IV. HUMAN EXPOSURE

Humans may be exposed to PCBs from a variety of sources including food, ambient air, occupational settings and consumer products. This section is limited to water, food and ambient air because these media are considered to be sources common to all individuals. Evidence of human exposure to PCBs from finished drinking water is limited. The bulk of the information relates to the years 1984-1986.

Water

United States. The National Organic Monitoring Survey (NOMS) was conducted in 1976 to determine the frequency of occurrence of specific organic chemicals (including PCBs) in finished water supplies of 113 cities nationwide (U.S. EPA, 1977). Data from three phases (referred to as NOMS I, NOMS II and NOMS III) of the study were collected over an 11-month period (March 1976 to January 1977) to reflect any long-term or seasonal variations.

PCBs were not found in groundwater supplies sampled in NOMS I (minimum quantifiable limit = 0.12 µg/ℓ). Only a single finished groundwater sample in each of NOMS II and NOMS III contained detectable levels of PCBs (~6% frequency of occurrence for both phases). Concentrations of 0.1 µg/ℓ were reported for the NOMS II and NOMS III samples (minimum quantifiable limits ranged from 0.1-0.2 µg/ℓ, respectively).

During a groundwater study in the state of New Jersey, Tucker and Burke (1978) examined 163 wells in all nine counties of the state, including public and private drinking water wells, and wells near industrial sites and

landfills. Thirty-two of the 163 wells contained PCBs with concentrations ranging from 0.06-1.27 µg/ℓ. (The minimum reportable concentration was 0.06 µg/ℓ.) The highest concentration reported, 1.27 µg/ℓ, was from a well in Mercer County, NJ. Many of the wells sampled were from highly populated, industrialized areas. The levels of PCBs detected in drinking water from these sources were thus in the very low µg/ℓ range.

PCBs were detected in finished surface water supplies in all three phases of NOMS. In NOMS I, concentrations of two samples observed were 0.13 and 1.4 µg/ℓ (mean = 0.77 µg/ℓ, frequency of occurrence = 2.2%). For NOMS II, two samples contained 0.1 µg/ℓ and one sample had a level of 0.2 µg/ℓ (mean = 0.13 µg/ℓ, frequency of occurrence = 3.3%). Only a single sample in NOMS III contained PCBs at a level of 0.2 µg/ℓ (frequency of occurrence = 1.1%).

PCBs were found in the water of a small upstate New York public water supply system near the heavily polluted section of the Hudson River (Brinkman et al., 1981). The impounded water contained a uniform level of Aroclor 1016 congeners (Dority Reservoir, 70-130 ng/ℓ; New Reservoir, 110-120 ng/ℓ; Distribution system, 69-100 ng/ℓ) while the levels in rain water were much higher (1300 ng/ℓ). Low concentrations of Aroclor 1254 congeners (up to 36 ng/ℓ) were detected in the New Reservoir only. The high levels of PCBs in the Hudson River (360 ng/ℓ) near Port Edwards were thought to be responsible for high impounded water levels. Finished tap water did not show evidence of Aroclor 1254 congeners (<12 ng/ℓ). The median concentration of Aroclor 1016 congeners was 85 ng/ℓ in finished tap water. One sample at the chlorination site was 30% higher in Aroclor 1016 congeners than at a household tap.

The Aroclor 1016 origin was confirmed by identifying at least five specific surrogate congeners by retention time from a possible 19 congeners. The 19 congeners were: 4-Cl-CB/2,2'-Cl_2-CB (also Aroclor 1221); 2,4'-Cl_2-CB (also Aroclor 1221); 2,2',5'-Cl_3-CB; 2,2',4'-Cl_3-CB; 2,2',3'- and 3,2',6'-Cl_3-CB; 4,2',6'-Cl_3-CB; two unidentified Cl_3-CBs; 3,3',5'-Cl_3-CB; 3,2',4'-Cl_3-CB; 2,4,4'-Cl_3-CB (also Aroclor 1221); 2,3',4'-Cl_3-CB; 2,5,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',5'-Cl_4-CB (also Aroclor 1254); 2,3,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',4'-Cl_4-CB (also Aroclor 1254); 2,3,2',3'-Cl_4-CB (also Aroclor 1254); and two unspecified Cl_4-CBs (one of which also arose from Aroclor 1254). Thus, 10 of the 19 congeners were unambiguously from Aroclor 1016, with 6 being resolved specific congeners. In this study, 60 congeners were utilized to identify the possible presence of Aroclors 1221, 1016, 1254 and 1260. Each peak chosen provided an independent estimate of the quantity of the Aroclor using the appropriate response factor for each congener. The concentration of the Aroclor was calculated as the average of the concentrations by each of the five chosen peaks. Representative samples were confirmed by GC/MS. The detection limit was 50 pg, equivalent to a 12 ng/ℓ (12 ppt) concentration in 2 ℓ of water subjected to the analysis technique.

In raw tap water in the Waterford, NY treatment plant, which also has the Hudson River as its source, mean PCB levels in 1976 were 0.12 µg/ℓ (range: 0.05-0.24) (Schroeder and Barnes, 1983). The average efficiency of PCB removal was 80-90% at high and low flows with levels in the treated drinking water seldom exceeding 100 ng/ℓ.

PCB measurements in water samples from various rivers at several different U.S. geographical locations have indicated their detection at low ppb levels (Interdepartmental Task Force, 1972), for example, in the Great Miami River, OH (5.7 ppb), Pestigo River, WI (0.31-0.38 ppb), Oconto River, WI (0.16-0.45 ppb), Milwaukee River (0.02-2.07 ppb), Lake Michigan (0.013 ppb), South Florida (<0.02 ppb), Escambia River and Bay, FL (<0.1 ppb), Green Bay, WI (0.04-0.07 ppb).

PCBs in the Hudson River were first detected in 1969, but it was not until 1975 that a problem was deemed to exist (Brown et al., 1985). In 1975, two capacitor-manufacturing facilities at Fort Edwards and Hudson Falls were identified as the major sources of PCB pollution. It was estimated that 14 kg PCB/day had been discharged over a 30-year period, mostly as Aroclors 1016 and 1242. The discharges were decreased to 1 g/day by 1977, and the 306 km section of the riverbed from Hudson Falls through New York Harbor was left as the major site of PCB contamination. Contaminated sediments removed from the river as part of maintenance dredging were deposited in several upland disposal sites during 1974-1977. By 1978, the Hudson River system was estimated to contain the following PCB budget: riverbanks, 63,500 kg; upper river, 134,000 kg; lower river, 91,000 kg. Fish, aquatic macroinvertebrates and river/sediment water have been analyzed for PCBs since 1977 and zooplankton between 1978 and 1981. Since 1982, only the upper river has been sampled with emphasis on high flow events such as the spring melting of snow. Comparison of the relative concentrations of Aroclors 1016 and 1254 is suggestive of a decline in less chlorinated congeners over time as reflected also in biological samples. The geometric mean in waters collected at Stillwater and Schuylerville from May to

September each year declined from 0.68 µg/ℓ in 1977 to 0.11 µg/ℓ in 1982. PCB transport declined below river flows of 400 m^3/second. During low flow conditions, most of the PCB penetrates a 0.45 µm filter whereas this is not so at high flow. Also, the less chlorinated congeners are present in greater proportions in the filtrate than in the nonfilterable residue. At high flow, the more chlorinated congeners dominate in whole-water samples. In the late 1970s, waters from the tidal Hudson contained generally 0.1-0.2 µg/ℓ as dissolved PCBs; in 1982, the range was reported as 0.05-0.10 µg/ℓ. Particle size and organic content appear to control PCB content in the Hudson River.

Bush et al. (1985a) identified the PCB congeners in Hudson River water sampled on July 6 and August 15, 1983 at Roger's Island, Thompson's Island and Stillwater (Table IV-1). The respective total PCB concentrations in July were 100, 532 and 266 µg/ℓ, respectively; in August, the concentrations were 331, 586 and 243 ng/ℓ, respectively, mostly as Aroclor 1221, 1242, 1254 and 1260. A specific congener analysis is presented in Table IV-1 for the three sites. The levels primarily reflected dissolved PCBs since very little sediment was present in all samples. A surprising feature of the results was that half of the transport appeared to be caused by only three low chlorinated PCB congeners (2-, 2,2'- and 2,6-PCB). The levels of more chlorinated Aroclors did not vary greatly from site to site, but those of Aroclors 1221 and 1242 did.

Baker et al. (1985) reported that resuspension events in midsummer in Western Lake Superior waters resulted in a 50% increase in PCB residues in the period May to October, 1983. The seasonal cycling of PCB congeners at 12 sampling sites was strongly dependent on their degree of chlorination

TABLE IV-1

Mean Water Concentration (ng/ℓ) of Chlorinated Biphenyl Congeners in Hudson River Water at Roger's Island (RI), Thompson's Island (TI) and Stillwater (ST) in 1983

Congener	Aroclor	July			August		
		RI	TI	ST	RI	TI	ST
2	1221	0.5[b]	145[b]	5.5[c]	38	20	2.6
2,2'	21/42	2.8[b]	147[b]	73[c]	4[b]	44[b]	37
2,6	21/42	3	150[c]	73[c]	4	50	40
2,3'	21/42	0.6[b]	3.6[b]	1.1[c]	ND[b]	0.5[b]	ND
2,4'	21/42	1.2[b]	33[b]	17[c]	0.8[b]	9.7[b]	8.9
2,2',5'	21/42	2.0[b]	14[b]	4.9[c]	2.1	4.7	ND
2,2',4'	1242	3.1	11	8	2.6[b]	6.4[b]	5.6
2,2',3'+3,2',6'	1242	0.95[b]	6.2[b]	4.3	0.6[b]	2.1[b]	2.2
4,2',6'	1242	1.0	3.3	2.3	1.0[b]	6.0[b]	1.9
4,4'	1242	5.1	17	15	1.6[b]	5.5[b]	6.7
2,2',4',6'	21/42	ND	10	13	1.8	3.6	2.1
3,2',5	1242	0.6[b]	1.1[b]	2.6[c]	0.4	1.6	1.5
2,4,2',6'	1242	0.8[b]	7.5[b]	6.7	0.5	15	3.8
3,2',4'	1242	2.5[b]	13[b]	9.7	1.8	11	2.4
3,2',3',+4,2',4'	1242	3.3	0.1	5.8	5.8	6.7	10
4,2',3'	1242	2.2	5.0	3.2	1.0[b]	2.6[b]	3.1
2,5,2',5'	42/54	2.3[b]	10[b]	7.0	2.9[b]	6.3[b]	7.4
2,4,2',5'	42/54	2.0[b]	8.1[b]	6.4	1.5	2.3	2.2
2,3,2',5'	42/54	2.1	1.6	3.3	3.5[b]	9.5[b]	11
2,4,2',4'	42/54	1.2[b]	7.4[b]	4.9	0.9	4.5	1.6
Cl_4C	54/60	2.2	6.8	4.9	2.2	3.9	3.9
Cl_4D	54/60	2.6	9.2	6.1	2.7	4.8	5.3
2,3,2',3',6	54/60	0.5	1.0	0.8	ND	3.6	0.7
2,5,3',4'	54/60	2.0	3.7	2.6	1.2	5.9	3.5
2,4,3',4'	54/60	1.2	2.7	1.7[c]	1.5	2.7	1.7
2,5,2',4',5'	54/60	1.0	1.9	3.1	0.6	3.7	0.1

TABLE IV-1 (cont.)

Congener	Aroclor	July			August		
		RI	TI	ST	RI	TI	ST
2,4,2',4',5'	54/60	1.2	2.9[b]	5.7[b]	14	45	6
2,3,2',4',5'	54/60	1.0	1.0	1.9	1.6	1.6	0.6
2,5,2',3',4	54/60	0.4	0.9	1.1	8.0	2.9	1.8
2,4,2',3',4'	1254	1.6	1.5	1.6	2.6	4.4	1.3
2,3,2',3',4'	54/60	2.4	2.5	2.6	0.7[d]	5.5	2.0
2,5,2',3',5',6'	54/60	0.6	0.5	1.9	0.3	0.7	0.4
2,3,2',3',5',6'	54/60	ND	ND	0.2	3.3	6.7	0.0
2,3,4,2',3',6'	54/60	0.2	0.7	0.9	1.3	2.5	0.9
3,4,3',4'	1254	0.8	0.7	0.7	3.5	28	2.0
2,3,6,2',3',4',6'	54/60	0.5	0.6	0.7	1.8	2.3	2.3
2,4,5,2',4',5'	54/60	ND	ND	ND	0.9	1.2	0.3
2,3,4,2',4',5'	54/60	2.8	1.9	0.4	2.3	2.2	1.0
3,4,2'3',4',6'	54/60	1.6	1.6	0.5	2.8	1.7	0.3
2,3,4,2',3',4'	54/60	1.7	1.4	1.0	1.0	0.8	0.04
2,3,6,2',3',4',5',6	54/60	ND	ND	ND	120	85	50
3,4,2',3',4',5'	54/60	9.4	9.4	11	0.2	0.2	ND
2,3,4,5,2',3',5',6'	1260	0.03	0.5	0.3	0.2	0.4	0.1
Total PCB		100	532	266	331	586	243

[a]Source: Bush et al., 1985a

[b]Probability that sites identical <0.005

ND <0.01 ng/ℓ

with the heavier chlorinated congeners lost from the water column (range 0.33-0.77 ng PCBs/ℓ) with a half-time of 17-28 days at two sites. Total PCB concentrations (range 0.57-1.1 ng PCB/ℓ) in the benthic nepheloid layer were maintained over the summer by transport of lighter chlorinated congeners from the underlying sediments. Though atmospheric and riverine inputs to the Great Lakes have decreased in recent years (water concentration ranges were 0.5-2.0 ng/ℓ in 1978; 3.2-3.4 in 1979; 0.4-2.1 in 1980), the seasonal processes of lake mixing and sediment resuspension do increase PCB and other residues. The soluble PCBs in this study were sorbed by XAD-2 resin and analyzed by capillary GC with ^{63}Ni electron capture detection after Soxhlet extraction, sulfuric acid treatment, and Florisil chromatography (recoveries of Aroclor 1254 and 1242 were 85%). In the 1983 samples, Aroclor 1242 made up ~70% of the sediment residues and 90% in the dissolved phase. Resuspended particles were estimated to contain concentrations between 100 and 300 ng/g, and were enriched in Aroclor 1254 relative to Aroclor 1242 in general. The lighter chlorinated PCB congeners migrated from the pore waters of surficial sediments to the overlying benthic nepheloid layer at an approximate rate of 27 ng/m²/day during stratification.

Capel et al. (1985) have reported also on the concentrations of PCB congeners in a Lake Erie sediment at a depth of 8-20 cm. The congener levels were in ng/g: Cl_2, 2.18; Cl_3, 13.13; Cl_4, 32.06; Cl_5, 33.2; Cl_6, 26.69; Cl_7, 14.33; Cl_8, 1.68. The sum was 123.2 ng total PCB/g. This was compatible with a composition of 24, 42 and 34% Aroclors 1242, 1254 and 1260 at a r^2 of 0.91, as calculated using least squares multiple regression. The same technique applied to Lake Superior water samples taken in 1979 showed an Aroclor 1242 composition of between 37 and 56% for concentrations between 0.5 and 8.5 ng/ℓ using a 50 peak analysis. In Lake

Superior sediments taken in 1982, a similar analysis showed an Aroclor 1242 composition which varied between 15 and 21% (the rest being Aroclor 1254) at Aroclor 1242 levels between 1.5 and 1.9 ng/g sediment.

In a laboratory experiment (Vitkus et al., 1985), 208 mg of applied Aroclor 1254 in wastewater influent was diluted to a biochemical oxygen demand (BOD) of 200 ppm so that the Aroclor 1254 concentration was 1 ppm. After treatment with a lab-scale, fixed biomass for up to 17 weeks, 54% of the PCB was recovered in effluent plus biomass. At 1 ppb levels, all of the Aroclor was recovered in the effluent plus biomass. Volatilization (30-39% of that applied) also accounted for substantial loss of the Aroclor at the 1 ppm level. The chemical oxygen demand (COD) and BOD removal even at 1 ppm Aroclor 1254 remained between 80 and 100% after week 3. There was no toxicity to the biomass even at exposure levels of up to 100 ppm for 2 days. The U.S. EPA has estimated that industrial and publically-owned waste treatment facility effluents are responsible for an annual discharge of 110.08×10^3 kg of PCBs into U.S. waters, and this has resulted in PCB levels of 100-3000 ng/ℓ in waters and 2.0-160 µg/kg in sediment. The sedimentation process in wastewater treatment plants primarily removes settleable particles that contain high levels of adsorbed PCBs (Garcia-Gutierrez et al., 1982; McIntyre et al., 1981).

PCBs (Aroclor 1260) have been detected in rainfall, street particulates, run-off and basin soils (4/11 samples) of the Fresno Metropolitan Flood Control District, California, which relies on aquifer recharge basins for stormwater retention (Salo et al., 1986).

Table IV-2 summarizes the PCB content of bulk deposition (rain, snow, fog, dew and cloud water) as contained in a review by Mazurek and Simoneit (1985). Villeneuve and Cattini (1986) have also detected Aroclor and specific PCB congeners in rain (both particulate bound and dissolved) sampled in the western Mediterranean. Dry deposition of Aroclor 1254 (18.2 ng in 12 days), and 2,2',4,5'-Cl_4-CB (78.6 ng in 12 days) was also detected. PCBs have been found in precipitation from all over the world in urban and rural areas. Long-range aerial transport of PCBs has thus been demonstrated. The more chlorinated Aroclors tended to be associated with particulates but the less chlorinated congeners predominated in the dissolved aqueous phase. Drinking water fed from rainwater may therefore contain PCBs.

Voudrias et al. (1986) detected hydroxychlorinated biphenyls as a result of chlorination or chloroamination of phenol adsorbed on granular activated carbon. Since hydroxychlorinated PCBs are <u>in vivo</u> metabolites of PCBs, analysis of these hydroxychlorinated biphenyls quantitates both chlorination effects and any partial metabolism of PCBs. High levels of trichloro-hydroxybiphenyls were also present after chlorination of phenol adsorbed on granular activated carbon.

Villeneuve and Cattini (1986) have also detected Aroclor and specific PCB congeners in rain (both particulate bound and dissolved) sampled in the western Mediterranean. Dry deposition of Aroclor 1254 (18.2 ng in 12 days), and 2,2',4,5'-Cl_4-PCB (78.6 ng in 12 days) was also detected.

Table IV-2. PCBs in Rain and Snow Around the World

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Total	0.1 g/m^2-day-10^7	Bulk deposit; unfiltered	Bulk collector - glass sheet coated with mineral oil	Event basis; 2/71	Suburban La Jolla, CA, USA
	n.d. 130 ppt	Bulk deposit; unfiltered	Unknown	Variable weekly monthly periods: 7/74-11/74	Chesapeake MD, USA
	50-230 ppt[b]	Snow; unfiltered	Unknown	Event basis; 1974-1976	Remote, urban Lake Superior, USA
	97.5-229 ppt	Snow; unfiltered	Unknown	Event basis; 1974-1976	Remote, urban Lake Michigan USA
	21 ng/l[b]	Rain; unfiltered	Bulk collector - stainless steel w/glass reservoir	Event basis; 5/76 - 11/76	Rural Great Lakes, Canada
	29 ng/l[b]	Snow; unfiltered	Bulk collector - aluminum sheet w/ manual packing into containers	Event basis; winter 1975-76	Rural Great Lakes, Canada
	21-28 ng/l[b]	Rain; unfiltered	Bulk collector - stainless steel funnel w/glass reservoir	Event basis; 5/76-11/76 5/77-11/77	Rural Great Lakes, Canada
	29 ng/l[b]	Snow; unfiltered	Manual collection bulk sample	Accumulated snowpack; fall thru winter, 1975-76	Rural Great Lakes, Canada
	14-138 ng/l[b]	Rain, snow; aqueous, particulate; wet only	(1) Bulk collector - galvanized steel funnel with particulate filter and adsorbant cartridge ; in situ extraction & (2) Auto. wet-only collector (HASL)	Event basis; 1975-1978	Rural, urban Lakes Huron & Superior, USA
	9-158 g/km^2 yr[b]	Bulk deposit; unfiltered	Bulk collector - metal cylinder	Monthly samples 1975-1978	Rural, urban Lakes Huron & Superior, USA

PCB	Concentration	Sample Type	Sample	Collection Period	Location
	Unknown	Rain	Unknown	Unknown	Unknown
	10-100 ng/l	Rain; unfiltered	Unknown	5/75-12/75	Rural Ontario Canada
	1-61 ng/l	Rain; aqueous; wet only	Auto. wet-only collector - Teflon coated stainless steel funnel with adsorbant cartridge; in situ extraction	Event basis; 5/81-8/81	Urban, rural Ontario, Canada
	0.3-4.1 ppt	Rain; snow; particulate	Bulk collector - aluminum 50-l can	Event basis; 1973-1976	Rural, urban Norway; network
	<1.0-6.7 ppt	Rain; snow; aqueous	Bulk collector - aluminum 50-l can	Event basis; 1973-1976	Rural, urban Norway; network
	620-10,510 ng/m^2-month[b]	Bulk deposit; unfiltered	Bulk collector - nylon net impregnated w/silicone oil	2-3 month period; 1970-71	Rural southern Sweden
	1400 ng/m^2 -month[b]	Snow; unfiltered	Unknown	1972	Urban, suburban Uppsala, Sweden
	5 g/gx10^{14}	Snow; unfiltered	Bulk collection - manual trimming of ice blocks with melting into glass containers	Accumulated 5-10 yr snowpack; sampled 1969	Remote Halley Bay, Antarctica
	160-1000 pg/l	Snowpack; unfiltered	Manual collection with polyethylene containers	Accumulated snowpack 1980 era; collected 5/81	Remote Japanese, Antarctica
	220 pg/l	Snowpack; unfiltered	Manual collection with polyethylene containers	Accumulated snowpack 1960 era; collected 5/81	Remote Japanese Antarctica

Table IV-2 (cont.)

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Total	Unknown	Rain; unfiltered	Unknown	Event basis	Urban Lake Zurich, Switzerland
	178–6010 ng/m^2–100 days	Rain; aqueous	Bulk collector - aluminum funnel w/ adsorbent cartridge; in situ extraction	3-mo. period; 6/75 - 5/76	East coast United Kingdom; network
Aroclor 1016	1300 ng/l	Bulk deposit; unfiltered	Automatic Wong Sampler	Weekly collection or 30-day composite sample	Urban Fort Edward, NY USA
Aroclor 1242	39–57 ng/l[b,c]	Rain; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in situ extraction	Event basis; 7/75–1/77	Rural, urban Lake Michigan USA
	16–31/ng/l[b,c]	Rain; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75–1/77	Rural, urban Lake Michigan USA
	41 ng/l/[bc]	Snow; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75–1/77	Rural, urban Lake Michigan USA
	33 ng/l[b,c]	Snow; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75–1/77	Rural, urban Lake Michigan USA
	<0.6 ng/l[b]	Rain; unfiltered	Bulk collector - Stainless steel funnel with glass reservoir	Event basis; 4/79–8/79	Remote Enewetak Atoll, Pac. Ocean
Aroclor 1254	<3–24 ng/kg rain	Rain; unfiltered	Bulk collector - stainless steel bowl	Event basis spring/fall 1977–1979	Coastal SC, USA

Table IV-2 (cont.)

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Aroclor 1254	35-49 ng/l[b,c]	Rain; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis 7/75-1/77	Rural, urban Lake Michigan USA
	30-46 ng/l[b,c]	Rain; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	24 ng/l[b,c]	Snow; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	76 ng/l[b,c]	Snow; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis; 7/75 - 1/77	Rural, urban Lake Michigan USA
	<1-27 ng/kg rain	Bulk deposit; unfiltered	Bulk collector - stainless steel funnel w/glass bottle reservoir	Variable 1-3 week periods; 1/976-1978	Semi-rural coastal SC USA
	<1-27 ng/kg rain	Bulk deposit; ulfiltered	Bulk collector - stainless steel funnel w/glass bottle reservoir	Continuous collection; spring 1976 to spring 1978	Coastal suburban SC USA
Aroclor 1260	14-26 ng/l[b,c]	Rain; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75 - 1/77	Rural, urban Lake Michigan USA
	8-23 ng/l[b,c]	Rain; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in-situ extraction	Event basis 7/75-1/77	Rural, urban Lake Michigan USA

Table IV-2 (cont.)

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Aroclor 1260	11 ng/l[b,c]	Snow; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis 7/75-1/77	Rural, urban Lake Michigan
	24 ng/l[b,c]	Snow; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis; 7/75- 1/77	Rural, urban Lake Michigan USA
Poly-chlorinated terphenyl (PCT)	Unknown	Rain	Unknown	Unknown	Unknown

[a]Source: Mazurek and Simoneit, 1985
[b]Mean concentration

Other Countries. PCBs at concentrations of 10-100 ng/ℓ have been detected in tap water from Kyoto, Japan (Panel on Hazardous Trace Substances, 1972) and 0.33 ng/ℓ in a Swedish tap water sample (Ahling and Jensen, 1970).

PCB levels in River Nile water in Egypt were decreased (Aly and Badawy, 1986) by coagulation with Nalco (0.5 mg/ℓ)/aluminum sulfate (50 mg/ℓ) to the extent of 19-41% for Aroclors 1221, 1232, 1242, 1248, 1254 and 1260. If ferric chloride was used instead of aluminum sulfate, the removal percentage was 27-34% for these Aroclors. Aluminum sulfate did not remove Aroclor 1248 efficiently (19% removal). The chlorine content of Aroclor 1221 only was increased by conventional chlorination methodology; the chlorine contents of the other Aroclors were not affected by chlorination. Levels of Aroclors in the canal water and wastewaters, near the River Nile, have also been reported (Badawy and Aly, 1986).

The PCB pollution of waters of the National Park of Donona in Spain (Baluja et al., 1985) and of the River Po and Adige in Italy (Galassi and Provini, 1981) have been reported.

The levels of PCBs in water have probably been underestimated since less chlorinated PCBs will preferentially solubilize so that the PCB congener composition in water can be greatly different from that of Aroclor standards. Specific congener analysis is essential as discussed in Chapter II.

Food

Dietary PCB intake has been reported for adults, as well as infants and toddlers, in the Food and Drug Administration's (FDA) Market Basket Studies

for fiscal year 1979 (FDA, 1982a,b). The relative daily intakes of PCBs are presented for FY74 through FY79 in Table IV-3. There is no apparent trend in intake levels over the years for which information was obtained. Total dietary intake of PCBs for adults in FY79 was 0.0133 µg/kg/day (FDA, 1982a). [This includes an estimated 0.0053 µg/kg/day from dairy products, 0.0075 µg/kg/day from meat, fish and poultry, and 0.0005 µg/kg/day from oils and fats.]

No PCBs were detected for infant and toddler dietary studies by FDA in FY79 (FDA, 1982b). Total dietary intakes of PCBs for infants and toddlers in FY78 (as reported in FDA, 1982b) were 11.3 and 98.5 ng/kg/day, respectively. Information on the individual food groups, which included the total intake values, was not obtained. The FDA calculations assume that the average infant weighs 8.2 kg (6-month-old) and the average toddler (2-year-old) weighs 13.7 kg. No comparisons of intakes of PCBs by geographic region were presented in the FDA Market Basket Studies.

Bioaccumulation of PCBs in fish and other aquatic life is a major route of exposure to humans.

PCB Residues in Aquatic Life of the United States and Canada. The PCB pollution in the Hudson River in the United States has been discussed (Brown et al., 1985). The monitoring of PCB levels in fish in 1977 showed that a PCB contamination problem existed (the levels were well above the then FDA temporary tolerance level of 5.0 ppm). Since 1977, not only fish but net-spinning caddis fly larvae (Trichoptera:Hydropsychidae) have been monitored from June through September. Zooplankton (e.g., Gammarus, Neomysis, Leptodera and Crangon) have also been monitored. Levels are higher in the

TABLE IV-3

Estimated Dietary Intake of PCBs for Adults, Infants and Toddlers[a]
(μg/kg/day)

	Adult	Infant	Toddler
FY79	0.0133	ND	ND
FY78	0.0269	0.0113	0.0985
FY77	0.0164	0.0253	0.0301
FY76	T[b]	T	ND
FY75	T[b]	T	T
FY74	0.0056	--	--

[a]Source: FDA, 1982a,b

[b]In the FDA report that lists the intakes (FDA, 1980a,b), values for the adult in FY75 and FY76 were reported as 0.0000 μg/kg/day. These values indicate that only trace amounts of PCBs were detected in the market basket studies.

ND = Not detected

T = Trace

-- = Data not obtained

upper river than those in the lower river and have been steadily declining ever since remedial actions have been completed in 1977. Mean total PCB concentrations in fillets from largemouth bass (Micropterus salmoides) collected near Stillwater declined from 145.3 µg/g in 1977 to 10.2 µg/g in 1981; at Catskill in the estuary, the residues decreased from 29.5 µg/g in 1977 to <1.0 µg/g in 1981. PCB concentrations in median striped bass (Morone saxatilis) declined from 9.9 µg/g in 1978 to 2.6 µg/g in 1982. During the same period, the fish showing levels below the FDA temporary tolerance level increased from 11-75%. In 1983, only 10% of the fish were below the current FDA limit of 2.0 ppm.

A strong correlation between PCB and lipid concentrations was observed for all Hudson River resident species but not for anadromous (river-spawning) species. For example, mean lipid-based PCB concentrations in yearling pumpkinseed (Lepomis gibbosus) declined from 1079 µg/g in 1979 to 36 µg/g in 1982. Similarly, mean lipid based PCB concentrations in brown bullhead (Ictalurus nebulosus), goldfish (Carassius auratus), and largemouth bass (Micropterus salmoides) declined from 2.51, 6.76 and 6.01 mg/g to 0.428, 0.310 and 1.000 mg/g, respectively. Between 1978 and 1981, a progressive decline in PCB levels also generally occurred in zooplankton, especially in Gammarus spp. In samples of resident and anadromous fish, the pattern of decline in total PCB concentration is dominated by the decrease in Aroclor 1016. For example, in Gammarus spp, the mean was 1.5 ppm in 1979 and 0.76 ppm in 1980. During 1977-1982 in the summer, the water PCB concentrations correlated well with the PCB concentrations in yearling pumpkinseed collected in the fall at Stillwater. Though less correlated, the PCB levels in other fish species and in macroinvertebrates are still correlated in the upper Hudson River.

More recent work has implicated PCB contaminated fungi like Fusarium oxysporum as a route of exposure (mostly in the gut) responsible for high PCB levels in Gammarus tigrinus in the Hudson River (Pinkney et al., 1985). After a period of 144 hours, 57% of the accumulated ^{14}C-Aroclor 1254 was eliminated in in vitro experiments. Gammarus is a major component of the diet of striped bass (Morone saxatilis) and Atlantic tomcod (Microgadus tomcod), and also eats microzooplankton, algae and detritus. After exposure to 7 ng ^{14}C-Aroclor 1254/g for 24 hours, the apparent distribution coefficients at 24 and 48 hours were 1.3×10^{3} and 1.14×10^{3}, respectively. Maximum accumulation occurred between 9 and 24 hours.

The presence of 74 specific PCB congeners was detected (Bush et al., 1985a,b) in caddisfly larvae from three sites in the Hudson River, Roger's Island, Thompson's Island and Stillwater (Table IV-4). The data reveal that selective uptake of different congeners by the various species occurred. Hydropsyche leonardi appears the most representative species for PCB exposure (Table IV-5) since the bioaccumulation factors appeared to be constant at each distinct site. However, the factors were different at different sites. PCBs in striped bass (Morone saxatilis) have been reported by White et al. (1985). PCB levels in standard fillets (µg/g net weight) were assessed using peak-to-peak summation of representative congeners: 40.0-44.9 cm length, 1.1-5.8 ppm (13 fish); 45.0-49.9 cm length, 1.3-21.3 ppm (18 fish); 50-56 cm, 1.2-40.3 ppm (19 fish). It is possible that the bioaccumulation of PCB congeners depends on bioaccumulation along the food pathway as well as at the PCB-in-water/fish level.

Lake trout ranging in age from 6-12 years from Cayuga Lake in Central New York were examined in 1978 (Wszolek et al., 1979). The levels of PCBs

TABLE IV-4

Chlorinated Biphenyl Congener Concentration (µg/g net weight)

in Caddisfly Larvae taken from the Hudson River[a]

Congener	Roger's Island				Thompson's Island						Stillwater	
	H. leo.		Chemo(g)		H. leo.		P. gut.		Chemo(g)		P. gut.	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
2	.08	.05	.07	.04	.6	.2	0.3	0.1	.3	.04	.004	.002
2,2'	.03	.01	.05	.01	3.	.8	.2	.09	.8	.04	.1	.01
2,3'	.03	.01	.06	.01	.06	.02	.01	.008	.07	.002	.07	.002
2,4'	.04	.008	.06	.01	.5	.2	.05	.02	.3	.01	.01	.002
2,2',5'	.02	.01	.5	.1	1.2	.2	.1	.05	.6	.03	.08	.004
2,2',4'	.06	.03	.1	.03	.7	.1	.05	.02	.3	.07	.03	.001
2,2',3'+3,2',6'	.04	.02	.1	.03	0.	0.	0.	0.	0.	0.	0.	0.
4,2',6'	.1	.06	.4	.1	2.0	.4	.1	.04	.9	.02	.08	.004
4,4'	.06	.03	.09	.03	.3	.07	.2	.02	.1	.05	.3	.009
2,2',4',6'	.1	.04	.1	.06	1.1	.2	.06	.02	.4	.03	.03	.004
3,2',5'	.06	.02	.1	.02	1.0	1.0	0.	0.	0.	0.	.05	.05
3,2',4'	.1	.1	0.	0.	1.6	.07	.4	6.0	.8	.03	.7	.2
3,2',3'+4,2',4'	.2	.1	.8	.1	.7	.03	.09	.05	.8	.1	.06	.03
4,2',3'	.4	.2	.7	.2	2.6	.4	.2	.08	1.3	.05	.1	.03
2,5,2',5'	1.2	.5	2.3	.5	7.4	.9	.7	.1	3.1	.1	.5	.04
2,4,2',5'	.5	.2	1.0	.2	1.8	.2	.2	.04	.8	.06	.1	.01
2,3,2',5'	1.1	.5	2.3	.5	12.	1.6	1.7	.07	3.5	.1	1.2	.2
2,4,2',4'	.3	.1	.7	.1	1.6	.2	.1	.02	.6	.03	.1	.01
CL4C	.5	.2	1.4	.3	2.5	.4	.1	.05	1.2	.03	.08	.01
CL4D	.6	.2	1.8	.4	3.7	.6	.3	.06	2.0	.06	.2	.06
2,3,2',3',6'	.07	.03	.2	.04	.5	.02	.05	.02	.4	.03	.02	.003
2,5,3',4'	.8	.3	1.6	.3	2.6	.1	.4	.03	1.2	.03	.2	.02
2,4,3',4'	.5	.2	1.1	.2	1.6	.2	.5	.05	.5	.01	.1	.02
2,5,2',4',5'	.2	.06	.3	.07	.9	.2	.1	.01	.6	.005	.07	.01
2,4,2',4',5'	.2	.06	.3	.06	.5	.2	.2	.02	.5	.006	.08	.04
2,3,2',4',5'	.1	.06	.3	.06	.6	.09	.1	.005	.4	.009	.07	.01
2,5,2',3',4'	.3	.1	.6	.1	1.3	.3	.1	.02	.5	.1	.08	.02
2,4,2',3',4'	.2	.8	.4	.9	1.4	.2	.2	.02	.7	.004	.2	.03
2,3,2',3',4'	.3	.1	.7	.1	1.8	.3	.2	.005	1.3	.02	.1	.01
2,5,2',3',5',6'	.01	.005	.02	.008	.3	.05	.02	.003	.2	.01	.01	.003
2,3,2',3',5',6'	.003	.003	.01	.004	.03	.004	0.	0.	.1	.1	.004	.002
2,3,4,2',3',6'	.05	.008	.1	.03	.4	.1	.06	.01	.4	.003	.04	.01
3,4,3',4'	0.	0.	.004	.002	.06	.06	0.	0.	.002	.002	.01	.006
2,3,6,2',3',4',6'	.2	.07	.4	.08	1.0	.01	.2	.03	.7	.1	.2	.02
2,4,5,2',4',5'	0.	0.	0.	0.	.3	.3	0.	0.	0.	0.	.3	.3
2,3,4,2',4',5'	.2	.05	.3	.06	.6	.2	.1	.02	.5	.05	.1	.006
3,4,2',3',4',6'	.03	.006	.04	.008	.1	.03	.03	.006	.2	0.1	.02	.002
2,3,4,2',3',4'	.03	.02	.02	.0 03	.2	.01	.04	.005	0.3	.04	.03	.008
3,4,2',3',4',5'	.02	.01	.05	.007	.1	.03	.004	.002	0.1	.001	.002	.002
2,3,4,5,2',3',5',6'	.02	.007	.02	.002	.09	.006	.01	.006	0.1	0.1	.008	.00002
Total	9.6	4.	22.	5.	66.	12.	8.	.7	31.	1.	6.0	3.

H. leo = Hydropsyche leonardi; Chemo(g) = Chemetopsyche green phase; P. gut = pycnopsyche guttifer;

[a]Source: Bush et al., 1985a

TABLE IV-5

Bioaccumulation Factors[a] of Macroinvertebrate Species in the Hudson River[d]

Species[1] Congener	July								August			
	Roger's Island		Thompson's Island			Stillwater			Roger's Island	Thompson's Island		Stillwater
	H. leo.	Chemo(g)	H. leo.	P. gut.	Chemo(g)	Chemo(b)	P. gut.	Macron.	H. leo.	H. leo.	Macron.	Macron.
2	178	151	4	2	2	1	7	14	0	3	2	3
2,2'	11	19	19	2	6	2	7	1	6	1	15	10
2,2',4'	64	136	114	9	54	20	8	49	64	143	72	130
2,2',4',6'	164	348	273	14	97	40	12	105	101	73	216	281
3,2'3'+4,2',4'	70	256	92	11	101	47	10	62	22	34	126	55
2,5,2',5'	509	992	719	64	307	133	72	276	167	682	328	425
2,3,2',5'	516	1100	2600	382	761	368	382	1030	142	678	401	515
2,3,2',3',6'	139	370	538	56	398	188	33	187	ND	54	77	286
2,5,2',4',5'	167	336	484	54	325	173	22	85	153	168	92	1290
2,3,2',4',5'	135	282	617	109	378	219	38	63	47	302	193	332
2,3,5,2',4',5'	150	313	1000	85	903	531	25	157	ND	ND	ND	ND
2,4,5,2',3',5',6'	3	6	18	2	152	63	10	26	50	ND	ND	449
2,4,5,2',3',4',5',6'	103	24	363	83	316	201	9	39	23	55	53	63
3,4,5,2',3',4',5'	ND	ND	178	8	221	92	;	26	2	117	67	6
Total	92	209	98	11	46	23	17	62	34	92	72	162
Standard Error	39	48	17	1	2	4	1	16	2	---	---	15
N	3	3	3	3	3	3	3	3	4	1	1	5

[a]Concentration in macroinvertebrates/mean concentration in water x 10^{-3}

[1]H. leo. - Hydropsyche leonardi; Chemo(g) - Chimarra green phase; P. gut - Pycnopsyche guttifer; Chemo(b) - Chimarra brown phase; Macron.. - Macrongma carolina

[d]Source: Bush et al., 1985a

in the flesh of the 12 year-old fish were ~13 ppm relative to wet weight, about the same levels as in aged trout taken from the same lake in 1970. The PCB resembled Aroclor 1254 but contained a higher proportion of more highly chlorinated isomers (higher Cl_6- and lower Cl_4-PCBs). The PCB accumulation in the flesh but not in the liver increased with fish age (3 fish/age): 6 years, 4.1-4.8 ppm; 7 years, 5.2-6.1 ppm; 8 years, 7.4-8.8 ppm; 9 years, 7.5-11.7 ppm; 10 years, 9.3-11.6 ppm; 12 years, 12.8-13.5 ppm (2 fish).

Fish are not the only edible animal known to accumulate PCBs from the Hudson River drainage area. PCBs have been measured in the subcutaneous fat and breast muscle of 55 waterfowl collected in New York State along the Hudson River and near Long Island during 1981 and 1982 (Kim et al., 1985). Waterfowl have relatively large amounts of fat, so it is possible that the FDA tolerance level for domestic poultry (3.0 µg/g) might be exceeded. Fifty-five waterfowl were examined for maximum PCB residues in terms of µg/g wet weight: 11 Canada geese (Branta canadensis) 0.63-15 (subcutaneous fat), 0.05-0.33 (breast muscle), and 0.08 (1 liver); 13 mallards (Anas platyrhynchos) 0.34-14 (subcutaneous fat), 0.07-1.1 (breast muscle), and 0.23 (1 liver); 18 black ducks (Anas rubripes) 0.59-20 (subcutaneous fat), 0.05-0.69 (breast muscle), and 0.16-0.29 (2 liver); 1 green-winged teal (Anas carolinensis) 0.81 (subcutaneous fat) and 0.27 (breast muscle); 1 hooded merganser (Lophodytes cacullatus) 124 (subcutaneous fat) and 6.3 (breast muscle); 1 shoveler (Anas clypeata) 8.8 (subcutaneous fat), 0.30 (breast muscle), and 0.21 (liver); 5 canvasback (Aythya valisineria) 0.98-13 (subcutaneous fat) and 0.11-0.66 (breast muscle); and 4 woodduck (Aix spousa) 0.64-9.0 (subcutaneous fat) and 0.08-0.12 (breast muscle). Levels in general were lower than in 1979 and 1980 samples. Sex and age were not

factors. This confirms widespread PCB contamination in the birds' migration region and it points out the possibility of humans ingesting PCBs while consuming game birds.

PCBs in 10 mussels (Mytilus edulis), each from 10 sites in Long Island Sound, CO, have also been reported (Greig and Sennefelder, 1985). The mean maximum PCB levels ranged from 0.049-0.115 ppm as wet weight. These are below the 5 ppm limit set by FDA for PCBs in fish and shellfish.

The maximum PCB residues in 547 finfish from the Chesapeake Bay and its tributaries during 1976-1980 have also been reported (Eisenberg and Topping, 1985). The concentrations in flesh were as follows (in ppm): in 1976, not detected to 0.98 (145); in 1977, 0.030-0.51 (40); in 1978, 0.06-4.64 (51); in 1979, 0.01-1.60 (98); and in 1980, 0.003-1.45 (24). There was clear evidence of accumulation in fish roe and perhaps in the gonads of specific fish species.

Snapping turtles (Chelydra serpentina) from the contaminated Hackensack Meadowlands of New Jersey and an "uncontaminated" area in Maryland have been analyzed for evidence of PCB residues (Albers et al., 1986). At the contaminated site, mean maximum PCB levels in visceral fat were (in terms of ppm lipid) 291±305 (8 males), 34±16 (3 females), and 23±11 (8 males from freshwater). In the "uncontaminated site," the concentrations were 41±37 (7 males) and 36±81 (6 females).

Table IV-6 summarizes PCB residue data for freshwater fish tissues (Schmitt et al., 1985). Residues in freshwater fish (obtained by GC/MS) appear to be declining steadily from the data of 107 stations operated by

TABLE IV-6

PCB Residues in Freshwater Fish in the United States[a,b]

PCB Type	Sample Site/Years		Geometric Mean of PCB Concentration	
			Wet Weight (ppm)	Lipid Weight (ppm)
Aroclor 1248	107 U.S. stations (freshwater)	76/77	0.14	0.6
		78/79	0.14	0.8
		80/81	0.11	0.8
Aroclor 1254	107 U.S. stations (freshwater)	76/77	0.48	4.3
		78/79	0.46	5.0
		80/81	0.24	2.1
Aroclor 1260	107 U.S. stations (freshwater)	76/77	0.37	3.4
		78/79	0.37	3.6
		80/81	0.25	2.6
Total PCBs	107 U.S. stations (freshwater)	76/77	0.88	8.3
		78/79	0.85	9.6
		80/81	0.53	5.4

[a]Source: Schmitt et al., 1985

[b]Between 1976 and 1981, 935 samples were taken representing 62 taxa; in 1980 and 1981, 315 samples were taken representing 48 taxa.

the U.S. Fish and Wildlife Service on key rivers of the United States; in the years 1976-1981 continuous data have been obtained for 97 of these stations. PCBs have been reported at 94% of the stations since 1976. Although levels for Aroclors 1254 and 1260 decreased in 1980 and 1981, residues for Aroclor 1248 remained the same. In 1980 and 1981, the highest PCB concentrations (>2 µg/g net weight) were in the Northeast (Hudson, Merrimack, Connecticut and Delaware Rivers); Lakes Michigan, Huron, Erie and Ontario; Lake City, Minnesota; the Ohio River System and in the Cape Fear River, North Carolina. Aroclor 1260 was the most widespread Aroclor, unlike in 1978 and 1979 when Aroclor 1254 was more widespread. However, this could be caused by the change from packed column GC technology to capillary-GC in 1980 and 1981. The Aroclor 1248 levels indicated either recent inputs of this Aroclor or the degradation of more persistent Aroclors. Total PCB levels proved to be more reliable than the levels of specific Aroclors in intercollaboratory studies.

Composite fish samples were collected during a separate monitoring program in 1980 and 1981 from Great Lakes harbors and tributary mouths and analyzed for PCBs by GC and GC/MS methods (DeVault, 1985). The Sheboygan River in Wisconsin was still severely contaminated (63-98 mg total PCB/kg wet weight as compared with 10-750 mg/kg in 1978), mostly as Aroclors 1248 and 1254. Moderate PCB pollution (<5 ppm wet weight) was also found in the Ashtabula River (OH), the Milwaukee River (WI), the Kinnickkinnic River, and the Fox River above and below DePere (still about the same level, 2-21 mg total PCB/kg wet weight, as measured in 1978). Low levels of PCBs (0.40-0.66 mg total PCB/kg net weight) were found in Chequamegon Bay in Lake Superior. PCB levels have also been reported in fish (<0.30 mg total PCB/kg wet weight) from the San Joaquin Valley in California in 1981 (Saiki and

Schmitt, 1986), from the Atchafalaya River basin in Louisiana in 1981 (Winger and Andreasen, 1985) and from Lake Verret, Plaquemire-Brule and East Franklin in Louisiana in 1978 and 1979 (Dowd et al., 1985).

Few PCB levels in salt water fish have been reported for U.S. waters. Uptake of ^{14}C-2,2',4,5,5'-Cl_5-CB by adapted juvenile Atlantic salmon (Salmo salar) is ~3-fold more efficient from freshwater than from seawater (Tulp et al., 1979). The generality of this finding still remains to be proven.

Countries Outside of the United States and Canada. PCBs were first detected in 1967 in fish and wildlife in Great Britain and the Netherlands. PCBs have been found in fish caught in and near Finland in 1982 (Vuorinen et al., 1985), and Norway during 1972-1982 (Skare et al., 1985). Game animals in Spain in 1982-1983 (Hernandez et al., 1985), in West Germany (Brunn et al., 1985) and in Sweden (Villeneuve et al., 1985) have been shown to contain high PCB levels. Birds and animals eating earthworms contaminated with PCBs will accumulate PCBs (Diercxsens, et al., 1985).

Air

Information on the potential inhalation exposure to PCBs is sparse. Even though PCBs exhibit low vapor pressures they have been detected in ambient air, in indoor air and in occupational environments. Samples of ambient air collected using an ethylene-glycol impinger sampler in suburban locations in Florida, Mississippi and Colorado in 1975 contained PCBs at all locations (Kutz and Strassman, 1975).

PCBs were detected in effluents from combustion of coal/refuse at Ames, IA at levels of 2.0-10.0 ng/m³ (Harkov, 1986). Murphy et al. (1985) have also detected PCBs in incinerator emissions after burning municipal refuse [40±45 (n=5), and 360 ng/m³] and sewage sludge [2000 ng/m³ (n=2); and 430 ng/m³ (n=2)], mostly as Aroclors 1248 and 1254. The PCB content in sanitary landfill gases ranged from 37-390 ng/m³ (7 samples). Bidleman et al. (1986) separated ambient airborne PCBs into particulate and vapor phases. The levels were 1.5, 0.45, 9.3 and 0.067 ng total PCB/m³ at Columbia, SC; Denver, CO; New Bedford, MA (landfill); and Stockholm, Sweden, respectively. The PCB was identified as Aroclor 1254. The fraction of particulate/vapor components depended on the ambient temperature. In the highly contaminated Hudson River basin, Purple Loosestrife (Lythrum salicaria) absorbed PCBs from ambient air containing a PCB concentration of 141 ng/m³ (Bush et al., 1986). When the ambient air level was low, a contaminated plant emitted the most volatile PCB congeners (e.g., 2-chloro- and 2,2'-dichloro-biphenyl). Specific PCB congeners also were absorbed from PCB-contaminated soil by the plants, and this was the major source of plant PCB. Levels between 1.6 and 15 ng/m³ of 31 specific congeners were found in ambient air. Cash crops such as broad bean, bean, tomato and cucumber can accumulate PCBs from PCB-contaminated soils, and probably also from airborne PCB (Bacci and Gaggi, 1985).

The potential presence of PCBs in indoor air appears to be greater than outdoor air (Benoit et al., 1984; Oatman and Roy, 1986). Air, whether in commercial, industrial or residential buildings, can contain levels of PCBs at least 1 order of magnitude higher than outdoor levels. The average level of PCBs (as Aroclor 1242 plus 1254) found outside of an industrial research building was <0.02 µg/m³, while the level inside was 5 times higher,

0.10 μg/m³. Inside laboratories the level was 10 times higher than ambient, averaging 0.21 μg/m³. Comparing outside to inside air of homes on the same day, the levels were 0.004 μg/m³ and 0.31 μg/m³, respectively. In a room containing a burned-out light ballast, PCB levels in air were 50 times higher than normal (11.6 vs. 0.2 μg/m³) for that room and remained elevated for several months afterward. Airborne PCB levels in nine homes ranged from 39-580 ng/m³ with the higher levels occurring in kitchens with pre-1972 fluorescent lighting. Another source of PCB emissions such as video display terminals (VDT) has been reported (Benoit et al., 1984; Digermes and Astrup, 1982) in the foreign literature. Levels ranging from 46-81 ng/m³ were found in offices containing VDTs, whereas the outside air levels were 0.5-1 ng/m³. In three buildings with PCB transformers in Minnesota (Oatman and Roy, 1986) the air levels of Aroclor 1242 and 1254 ranged from 192-881 ng/m³. Surface levels ranged from 0.05-1.47 μg/100 cm². Four buildings without PCB transformers contained air levels ranging from 78-384 ng/m³, and surface levels of 0.05-1.00 μg/100 cm². In another building where improper incineration conditions for Askarel had been used, PCB air levels in 31 buildings ranged from 0.14-3.2 μg/m³ (53 samples) with surface levels ranging from <0.01-4 mg/m² (Thompson et al., 1986).

Since most people spend 16-17 hours/day in buildings (Chapin, 1974), the potential exposure contribution from PCBs in indoor air becomes important relative to outdoors. Because there are few data on PCB levels in indoor air, the total exposure and fractional contribution from indoor air to exposure for humans remains difficult to assess.

Large exposures in the occupational environment have occurred (NIOSH, 1977, 1986). Air levels of Aroclor 1242 have ranged as high as 2.2 mg/m³ (Ouw et al., 1976). NIOSH has documented many occupational exposures to PCBs in its NIOSHTIC data base during PCB production, handling, foundry work (decachlorobiphenyl is used as an investment casting wax), railroad building and maintenance, capacitor and transformer manufacturing and maintenance, and handling of older types of carbonless copy paper (3.4% PCB content).

In 1976, a NIOSH evaluation of the Monsanto manufacturing facility revealed PCB levels (Aroclors 1016, 1242 and 1254) in the breathing zone ranging from 20-86 µg/m³. At two capacitor manufacturing facilities in 1977 breathing zone levels ranged from 24-1260 µg/m³. Plasma levels of PCBs in workers in a U.S. capacitor manufacturing facility in 1976 ranged from 0.03-850 ng/mℓ plasma (Wolff et al., 1982a). Personnel in a Massachusetts machine shop company (Christiani et al., 1986) showed PCB serum levels of 2.0-20 ppb (office males), 3.0-97 ppb (production males) and 1.0-8.0 ppb (office females) in year 1. In year 2, the levels were 4.8-13.0 ppb (office males), 3.1-65 ppb (production males), and 2.0-15.0 ppb (office females). The PCB levels exposing Italian electrical workers between 1949 and 1965 varied between 48 and 275 µg/m³, with blood PCB levels between 41 and 1319 µg/kg of blood. These levels were correlated with adverse effects in the liver and chloracne (Maroni et al., 1981a,b). Similar effects were also observed in three cohorts of Japanese workers (Takamatsu et al., 1985).

Another source of large exposure to PCBs is during and after PCB fires (e.g., Stockholm, 1978, 1981; Binghamton, New York, 1981; Surahanmar,

Sweden, 1982; Imatra, Finland, 1982; Hallstahammar, Sweden, 1982; in a Swedish locomotive, 1982; Skovda, Sweden, 1982 and Kisa, Sweden, 1983).

Other Exposures

In addition to the occupational exposures and the large exposures characteristic of PCB fires and point-source environmental pollution, the Yusho and Yu-Cheng incidents in Japan (1968) and Taiwan (1979), respectively, have also caused large PCB exposures by ingestion of contaminated rice oil (Hsu et al., 1985; Yoshimura and Hayabuchi, 1985; Chen et al., 1985; Miyata et al., 1985; Kashimoto et al., 1985; Hara, 1985). In Japan, the rice oil samples contained 151-968 ppm Kanechlor 400/500; Yu Cheng oil contained between 22 and 113 ppm (Miyata et al., 1985). The congener contents are known along with the PCQ and PCDF levels. The health effects are dealt with in Chapter VI.

PCB residues as Aroclor 1260 in Louisiana showed PCBs in 1980 from 8 donors to range between 0.59 and 2.33 ppm lipid, and in 1984 from 10 donors to range between 0.65 and 1.96 ppm lipid (Holt et al., 1986). These were among the highest concentrations and occurrences reported by previous U.S. EPA National Human Monitoring Programs. Residues in the breast tissue of females tended to be high. Two hexachlorobiphenyl congeners were determined on autopsy in tissues from seven people who had resided on the Texas Gulf Coast (Ansari et al., 1986). The levels for 2,2',4,4',5,5'-Cl_6-CB in the anterior abdominal wall ranged from 98-276 ppb adipose tissue, <5-251 ppb in the axillary fossae, and 109-231 ppb in the omentum; the levels for 2,2',3,4,4',5 Cl_6-CB in the anterior wall ranged from 211-1625 ppb, <5-1166 in the axillae, and 221-1161 ppb in the omentum. Since fat contents ranged between 7.5 and 20% among the different tissues examined, only fat

from the anterior abdominal wall was analyzed in 109 cadavers. The levels increased with age: 0-4 years., 22±12 and 67±13 ppb (n=3) of 2,2',4,4',5,5'-Cl_6-PCB and 2,2',3,4,4',5'-Cl_6-PCB, respectively; 4-9 years, 30±10 and 77±25 (n=2); 10-19 years, 212±131 and 19±19 (n=3); 20-29 years, 82±17 and 146±29 (n=15); 30-39 years, 163±61 and 253±61 (n=12); 40-49 years, 136±41 and 340±110 (n=15); 50-59 years, 154±24 and 586±130 (n=16); 60-69 years, 153±28 and 296±56 (n=24); 70-79 years, 128±17 and 296±73 (n=14); and 80-89 years, 198±97 and 641±372 (n=5). There were no gender differences in the 60-69 year age group. Safe has found the burden of PCBs in human fat to range between 500 and 1500 ppb (Safe, 1984). Kimbrough (1985) in a review has asserted that mean blood PCB levels in the U.S. population are ~5-7 ng/mL with adipose tissue and human milk levels being 100-200 times higher with PCBs tending to accumulate with increasing age and increasing fat content of tissues. Wolff et al. (1986) has reported that the PCB pattern in serum for people exposed through the food chain is different from that characteristic of "directly exposed persons," which tends to resemble Aroclor 1260, using specific congener markers. Similar PCB residue data in fat and serum samples have been reported from Israel (Pines et al., 1986), Denmark (Unger et al., 1984); Italy (Focardi et al., 1986) and in Japan (Ando et al., 1986).

Human milk samples in the United States can contain high levels of PCBs (Bush et al., 1985b; Safe, 1986). In the highly contaminated Hudson River area (Bush et al., 1986), whole milk total PCB from 40 samples based on specific congener analysis was 26.5±2.5 ng/g (standard error) with the corresponding maternal blood levels being 3.5±0.1 ng/g (standard error). The major congeners in 74 samples of milk were 2,2',4,4',5,5'-hexa-CB (12%); 2,2',3,3',5,6-hexa-CB (9.4%); 2,2',3',4,4',5-hexa-CB (7.8%); and 2,3',4',5-

tetra-CB (6.6%). The corresponding percentages in maternal blood were 8.8, 8.07 and not detected, respectively. While the milk/blood ratio for specific congeners was between 3.5 and 10 for most congeners, the ratio for 2,2,,3',4,4',5-hexa-CB was >7500, and 2,3,3',4,4',5-hexa-CB, 20. Inhalation exposure in the Lake Ontario and the Hudson River areas may also contribute to maternal exposure (2.8±0.5 ng PCB/m³ (n=6) at Oswego, NY). Safe et al. (1985a) quantitated 80 specific congeners of Aroclor 1260 in a human milk sample and found the 2,4,4'-tri-CB; 2,4,4',5-tetra-CB; 2,2',4,4',5-penta-CB; 2,3',4,4',5-penta-CB; 2,2',3,4,4',5'-hexa-CB; 2,2',4,4',5,5'-hexa-CB; 2,2',3,3',4,4',5'-hepta-CB; and 2,2',3,4,4',5,5'-hepta-CB congeners predominated, unlike in the original formulation.

Similar results (noncorrespondence of abundant congeners in human milk compared with the exposing PCB) have been found in recent studies from Yugoslavia (Krauthacker et al., 1986), Israel (Weisenberg et al., 1985) and Japan (Yakushji et al., 1978; Ando et al., 1985).

Estimated United States Exposure

Table IV-7 presents estimates of the total amount of PCBs potentially received by an adult U.S. male from ambient air, food and drinking water. Seven separate exposure levels for drinking water and three levels for air and food (representing a probable range of exposure levels based on the data presented in the Exposure Estimation section) are shown in the table. The actual contribution of air exposure is not precisely known. Indoor air levels may play an important role in exposure with preliminary findings indicating levels of up to 0.580 µg/m³ in normal settings such as residential homes. Occupational sources and PCB fires may also contribute to the total exposure. The data presented represent possible exposures

TABLE IV-7

Estimated Intake of PCBs from the U.S. Environment by Adult Males

Drinking Water (µg/l)	Total Intake in µg/kg/day (% from drinking water)								
Food:	0.005			0.01			0.03		
Air:	0.002	0.02	0.20	0.002	0.02	0.20	0.002	0.02	0.20
0	0.007* (0)	0.025 (0)	0.205 (0)	0.012 (0)	0.03 (0)	0.21 (0)	0.032 (0)	0.05 (0)	0.23 (0)
0.05	0.008 (17)	0.026 (5)	0.206 (0.1)	0.013 (10)	0.031 (5)	0.211 (0.1)	0.033 (4)	0.051 (3)	0.231 (1)
0.10	0.010 (29)	0.028 (10)	0.208 (1)	0.015 (19)	0.033 (9)	0.213 (1)	0.035 (8)	0.053 (5)	0.233 (1)
0.20	0.013 (45)	0.031 (19)	0.211 (3)	0.018 (32)	0.036 (16)	0.216 (3)	0.038 (15)	0.056 (10)	0.236 (2)
0.50	0.018 (78)	0.039 (36)	0.219 (6)	0.026 (54)	0.044 (32)	0.224 (6)	0.046 (30)	0.064 (22)	0.244 (6)
1.00	0.036 (81)	0.054 (54)	0.234 (12)	0.040 (69)	0.059 (49)	0.239 (12)	0.061 (47)	0.079 (37)	0.259 (11)
1.40	0.047 (85)	0.065 (62)	0.245 (16)	0.052 (77)	0.070 (57)	0.250 (16)	0.072 (56)	0.090 (44)	0.27 (15)

Intake Assumptions:	Water	Air	Food
	0.05 µg/l : 0.0014 µg/kg/day	0.002 µg/kg/day	0.005 µg/kg/day
	0.1 : 0.0029	0.02	0.01
	0.2 : 0.0057	0.2	0.03
	0.5 : 0.014		
	1.0 : 0.029		
	1.4 : 0.04		

*Sum of air, food and water intake

based on the occurrence data and the estimated intakes. The values presented in Table IV-7 for air and food levels of PCBs, as well as the values for drinking water levels, represent a range from the values found in the PCB monitoring data (see Drinking Water, Air and Food Sections). The intake from ambient air may be 0.05 µg/kg/day assuming 0.20 µg PCB/m^3 and time-activities of 16 hours indoors. Assuming the intermediate food intake of 0.01 µg/kg/day and the intake of 0.02 µg/kg/day from air to be representative, drinking water would be the predominant source of PCB exposure in the adult male when drinking water levels exceed 1.0 µg/ℓ. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the current data but it is likely that persons in the Hudson River Valley, the Great Lakes Region (except for Lake Superior), the Ohio Valley, the upper Mississippi, and the Cape Fear River in North Carolina have a higher potential for PCB exposures than others.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for PCBs by route of exposure. Eschenroeder et al. (1986) have estimated the possible exposures and the resultant health risk after PCB spills. Since PCBs tend to penetrate down only into the first 2 cm of soil, plants and vegetables with shallow root systems will be predisposed to PCB contamination. As preferential volatilization of the less chlorinated congeners also occurs, the more chlorinated congeners will bioaccumulate.

Summary

The major exposure routes to humans are through food and drinking water, and by inhalation. Dermal exposure is also important in occupational expo-

sures, for swimmers in polluted waters and in cleaning up PCB spills or in hazardous waste sites containing PCBs. In all cases, total PCB levels must be based on specific congener analysis or direct perchlorination rather than in terms of Aroclors because the congener patterns in environmental media and biological tissues usually do not match those in Aroclor fluids unless massive contamination has occurred (typical of spills and some occupational situations). Thus, predictive models based on specific congener data must also be utilized.

The less chlorinated congeners predominate in air samples from known contaminated areas and in water and wet deposition samples with temperature and the amount of sediment in river and water samples being important co-variables. In contrast, the more highly chlorinated isomers with substituents at the 2,4,5- or 2',4',5'-positions tend to bioaccumulate in some crop vegetables, game animals, fish and in human tissue samples. PCBs in contaminated soils can be absorbed by plants and vegetables with shallow-root systems to PCB contamination, although volatilization in this situation is also favored; erosion of such soils will also cause contamination of sediments. The more chlorinated congeners dominate in soils and sediments and the resident biota (cash crops, vegetables, fish, aquatic life). The absolute levels in any situation depend on which of the competing processes dominates as estimated in Table IV-7.

V. HEALTH EFFECTS IN ANIMALS

Commercial PCB mixtures vary in PCB isomer and congener composition, and impurities. In general, PCB mixtures produce low to moderate acute toxicity in mammalian species, but produce pronounced subacute and chronic toxicity. In contrast, invertebrates exhibit greater acute toxicity to PCBs (LC_{50}s <1 mg/ℓ) (NAS, 1979). In addition, as reported for other halogenated aromatic hydrocarbons, PCBs exhibit significant interspecies variability in toxicity. In considering the health effects of PCBs in animals, it is important to consider the isomer and congener composition of the PCBs, potential impurities, the length of exposure and the species under investigation.

Acute Toxicity

Representative toxicity data following a single exposure to PCBs are summarized in Table V-1. Single oral dose LD_{50}s of commercial PCB mixtures in rats ranged from 1.01-11.3 g/kg bw (see Table V-1). The data do not establish a consistent relationship between commercial PCB formulations and reported LD_{50}s. Some of the variability in reported LD_{50}s for specific PCB mixtures has been related to differences in the observation period, strain and solute concentrations. There appears to be no significant sex differences in the acute toxicity for the PCB mixtures studied; however, Aroclor 1254 was found to be slightly more toxic to immature than mature rats (Linder et al, 1974; Grant and Phillips 1974).

TABLE V-1

Acute toxicity of PCBs
(single exposure)

Species/ Strain	Sex/No.	Source of PCB	Route	LD_{50}	Comments	Reference
Guinea pig/ Hartley	NR	3,4,5-sym. hexa-CB	oral	1.39 μmol/kg bw (0.5 mg/kg)	Single dose Half of the animals died within 30 days (LD_{50})	McConnell and McKinney, 1978
Guinea pig/ NR	NR/8	NR; ~42% Cl	oral	NR	Two 69 mg doses 7 days apart Mortality 11-29 days; centrilobular liver necrosis and fatty infiltration	Miller, 1944
Rat/Wistar	M/42	Aroclor 1254	oral	1.3 g/kg bw (30 days old)	Single doses Immature seemed more susceptible than older rats; sex did not seem to to be a factor; majority died within 3 days	Grant and Phillips, 1974
	F/42			1.4 g/kg bw (30 days old)		
	M/42			1.4 g/kg bw (60 days old)		
	F/42			1.4 g/kg bw (60 days old)		
	M/42			2.0 g/kg bw (120 days old)		
	F/42			2.5 g/kg bw (120 days old)		
Rat/Sherman	F/50-80	Aroclor 1254	i.v.	358 mg/kg bw	Adult; single dose; death in 5-110 min; dyspnea, depression, salivation, diarrhea	Linder et al., 1974
	NR/50-80	Aroclor 1254	oral	4-10 g/kg bw	Adults, single dose	
		Aroclor 1260	oral			
	M/50-80	Aroclor 1254	oral	1.295 g/kg bw	Weanlings, single dose: diarrhea, depression, salivation, death 1-3 days	
	M/50-80	Aroclor 1260	oral	1.315 g/kg bw	Weanlings: diarrhea, depression, salivation, death 1-7 days	
Rat/Sprague-Dawley	M/NR	Aroclor 1242	gavage	4.25 g/kg bw	14-day LD_{50}	Bruckner et al., 1973; Kimbrough et al., 1978
Rat/Wistar	M/NR	Kanechlor-400	oral	1.30 ml/kg bw		Kimbrough et al., 1978
	F/NR	Kanechlor-400	oral	1.14 ml/kg bw		
	M/NR	Kanechlor-300	oral	1.15 g/kg bw		
	F/NR	Kanechlor-300	oral	1.05 g/kg bw		

TABLE V-1 (cont.)

Species/ Strain	Sex/No.	Source of PCB	Route	LD_{50}	Comments	Reference
Rat/NR	NR	Aroclor 1221	oral	3.98 g/kg bw	Toxicity apparently decreasing with increasing chlorine substitution	Fishbein, 1974; Nelson et al., 1972
		Aroclor 1232	oral	4.47 g/kg bw		
		Aroclor 1242	oral	8.65 g/kg bw		
		Aroclor 1248	oral	11 g/kg bw		
		Aroclor 1260	oral	10 g/kg bw		
		Aroclor 1262	oral	11.3 g/kg bw		
		Aroclor 1268	oral	10.9 g/kg bw		
Rat/Sherman	F/NR	Aroclor 1221	oral	4.0 g/kg bw		Nelson et al., 1972
		Aroclor 1262	oral	11.3 g/kg bw		
Rat/Osborne-Mendel	M/NR	Aroclor 1254	oral	1.01 g/kg bw	Single observation period	Garthoff et al., 1981
	M/NR	Aroclor 1254	oral	1.53 g/kg bw	5 multiple doses 2 times/week	
	M/NR	Aroclor 1254	oral	1.99 g/kg bw	5 multiple doses 1 time/week	
Rabbit/NR		Aroclor 1221	dermal	2.000-3.169 g/kg bw		Nelson et al., 1972
		Aroclor 1232	dermal	1.26-2.0 g/kg bw		
		Aroclor 1242	dermal	0.794-1.269 g/kg bw		
		Aroclor 1248	dermal	0.794-1.269 g/kg bw		
		Aroclor 1260	dermal	1.26-2.0 g/kg bw		
		Aroclor 1262	dermal	1.26-3.16 g/kg bw		
		Aroclor 1268	dermal	2.5 g/kg bw		
Rabbits	NR	NR	NR	8-11 g/kg bw		Peakall, 1975
Mice/CFI	M/NR	Kanechlor 400	oral	1.875 mL/kg bw		Kimbrough et al., 1978
Mice/CFI	F/NR	Kanechlor 400	oral	1.57 mL/kg bw		
Mice/dd	F/NR	2',4' di-CB	oral	7.86 g/kg bw	Data reviewed suggest increased toxicity in mice with greater chlorine substitution	Kimbrough et al., 1978
Mice/DVI	NR	tri-CB	oral	3.06-4.25 g/kg bw		
Mice/DVI	NR	2,4,3',4'-tetra-CB	i.p.	2.15 g/kg bw		
Mice/CFI	NR	2,3,4,3',4'-penta-CB	i.p.	0.65 g/kg bw		

TABLE V-1 (cont.)

Species/ Strain	Sex/No.	Source of PCB	Route	LD_{50}	Comments	Reference
Mice/CBA	NR	Aroclor 1254	i.p.	880 mg/kg bw	5-day observation period	Lewin et al., 1972
Mice/ALAS	NR	Aroclor 1254	i.p.	1200 mg/kg bw	5-day observation period	
Mice/BALB/CJ	NR	Aroclor 1254	i.p.	1080 mg/kg bw	5-day observation period	
Mice/CSF	NR	Aroclor 1254	i.p.	1000 mg/kg bw	5-day observation period	
Peromyscens maniculatus*	NR	Aroclor 1254	i.p.	970 mg/kg bw	5-day observation period	
Mink/Pastel	NR/81	Aroclor 1221, 1242, 1254	gavage	500-4000 mg/kg bw	Single doses	Aulerich and Ringer, 1977

*Field mouse

NR = Not reported

LD_{50} values from dermal application of commercial PCB mixtures in rabbits ranged from 0.794-3.169 g/kg (see Table V-1). There was no association of degree of toxicity with chlorine content. In addition, the data suggest that PCBs are readily absorbed following dermal exposure, although no comparative data are available on toxicity in rabbits following oral exposure. Several reviews (Peakall, 1972; Nelson et al., 1972; Fishbein, 1974; Kimbrough, 1974; NIOSH, 1977; Kimbrough et al., 1978; McConnell, 1980a) report both LD_{50} data and a further discussion of the acute toxic effects of PCBs.

As mentioned previously, the toxicity of PCB mixtures can vary because of a number of factors, including the content of specific congeners and isomers. Kimbrough et al. (1978) reported increased toxicity in mice exposed to PCB congeners containing greater chlorine substitution. The structural requirements for biological activity (AHH induction) and toxicity of this class of compounds has been recently reviewed (Poland and Knutson, 1982). One of the structure requirements for AHH induction, and apparently toxicity, is an unsubstituted carbon atom in the ortho position. These PCB congeners produce biologic and toxic activities related to that produced by chlorinated dibenzodioxins and dibenzofurans. 3,3',4,4'-tetra-CB and 3,3',4,4',5,5'-hexa-CB (Biocca et al., 1976; McKinney, 1976) and 3,3',4,4',5-penta-CB (Safe, 1984) are highly toxic. The 3,3',4,4'-tetra-CB is found in commercial PCB mixtures (Albro and Parker, 1979).

Subchronic Toxicity

Multiple exposure studies are summarized by species and route of exposure in Tables V-2 to V-5. As with acute toxicity, attention must be given to the type of PCB, species, and the route of exposure employed in

TABLE V-2

Acute, Short-term and Subchronic Toxicity of Orally Administered PCBs to Rats

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	F/56	200-300 g	Aroclor 1254/diet	0-900 ppm for 10 days	≥300 ppm: weight loss. Decreased placental protein, glycogen; partial anorexia.	Spencer, 1982
Sprague-Dawley	M/18	250-300 g	Aroclor 1254/corn oil	50 mg/kg bw for 7 days	Increased acid phosphatase in testicular interstitial cells.	Dikshith et al., 1975
Holtzman	F/25	sexually mature	Aroclor 1254/peanut oil	0 64 mg/kg day for 7 days	64 mg/kg/day: increased liver weight.	Sager, 1983
Fischer	M/42	weanlings	Aroclor 1254/diet	0, 71, 179, 357, 429, 700, 1400 ppm for 14 days	Depressed rate of gain, food intake; increased liver weight.	Carter and Mercer, 1983
Sprague-Dawley	M/12-18	200-250 g/ 7 weeks	Aroclor 1254/mineral oil	0, 0.05, 0.25, 0.5 g/kg bw daily for 21 days	≥0.05 g/kg bw/day: decreased rate of gain to frank weight loss; depressed feed intake; depressed water intake; depressed body temperature.	Komives, 1979; Komives and Alayoku, 1980
Wistar	F/40	1 year	Aroclor 1254/corn oil	0, 12.5, 25.0, 50, 100, 400, 800 mg/kg bw daily for 7 days	≥400 mg/kg: mortality; ≥100 mg/kg: increased liver fat percent ($p<0.05$). All doses: increased liver weight ($p<0.05$).	Grant and Phillips, 1974
Wistar	M-F/144	30, 60 or 120 days	Aroclor 1254/corn oil	0, 5, 10, 20 mg/kg bw/day for 7 days	All doses: increased liver weights, increased aniline hydroxylase activity.	Grant and Phillips, 1974
Long-Evans	M/125, F/25	5 weeks	2,5,2',5'-tetra-CB/ corn oil	0, 0.5, 1.0, 1.5, 2.0 g/kg bw, single dose	≥1.0 g/kg: heavy mortality; thymic hemorrhage; atrophy; liver and kidney enlargement; splenic and lymph node regression.	Allen et al., 1975
Hooded	M/NR	180-200 g	Aroclor 1254/diet	250 ppm for 14 days	Increased thyroid activity.	Bastomsky, 1974
Sprague Dawley	F/6	200-250 g	^{14}C-labeled 2,5,2',5'-tetra-CB/ corn oil	0, 1.7 g/kg bw, single dose	Intracellular vacuolization; vesiculation, fragmentation of RER, enlarged, varified cytoplasm; altered mitochondrial conformation; AlPase inhibition.	Lin et al., 1979
Sprague-Dawley	F/24, M/24	300 g	Phenoclor DP6/diet	0, 100 ppm for 8 days	Decreased phenobarbital sleeping time, increased liver weight and protein content; males more greatly affected than females.	Marbonne, 1979

TABLE V-2 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	M,f/48	adult and 35 days	Phenoclor DP6/diet	13 ppm adult 24 ppm young for 8 days	Liver weight elevated equally in both sexes; elevated liver protein and fat more noticeable in adults.	Narbonne, 1979
Fischer	M/50	34 days	Aroclor 1254/diet	0, 20 ppm for 1, 2, 4, 8, or 14 days	Hepatomegaly by day 4.	Carter, 1983
CD	f/3/ group		4 mono-CB/ cottonseed oil	30 mg/kg bw/day on days 8, 11, 13, 15, 18 of pregnancy	Elevated intestinal monoamine oxidase, serum sorbitol dehydrogenase and alkaline phosphatase.	Wolden et al., 1982
Long-Evans	M/12	130 g	Aroclor 1248/diet	0 or 100 ppm for 4 weeks	Hepatomegaly (4.46% of bw), obvious increase in SER.	Allen et al., 1975
			2,5,2',5'-tetra-CB		Hepatomegaly (3.38% of bw), less obvious increase in SER.	
Wistar	M,f/38	NR	Aroclor 1254/diet	1000 ppm for 14 or 30 days	At ≥14 days, 30-72% reduction in rate of gain; at 30 days, 29% reduction in food intake; no change in liver weight. Altered cholesterol, fatty acid synthesis.	Kling et al., 1978
Osborne-Mendel	M/6/ group	8 weeks	Aroclor 1254/diet	0, 5, 50, 500 ppm for 4 weeks	≥5 ppm: enlarged thyroid, reduced follicle size, follicular lumen reduced, papillary projections and cytoplasmic projections, diluted RER.	Collins and Capen, 1980b
Gunn	M/12/ group	300-400 g	Aroclor 1254/diet	500 ppm for 42 days	Thyroid follicular cells more columnar, diluted RER, vacuolated mitochondria.	Collins and Capen, 1980a
Osborne-Mendel	M/NR	8 weeks	Aroclor 1254/diet	0, 50, 500 ppm for 4 or 12 weeks	≥50 ppm, by 4 weeks: enlarged thyroid, follicular cells more columnar, vacuoled cytoplasm, papillary projections, cytoplasmic processes. Dilated RER, Golgi apparatus more prominent, larger number of enlarged lysosomes. Reduced serum thyroxin; after 35-week recovery period thyroids resemble those of controls, serum thyroxin normal.	Collins et al., 1977

TABLE V-2 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	M/40	100-130 g	Kanechlor 500/diet	100 ppm for 4 weeks	No effect on food intake, water intake, urinary volume. Slightly enlarged brain, spleen and liver. Hematologic values unchanged. Serum protein, cholesterol, cholinesterase elevated; serum triglyceride reduced.	Oishi et al., 1978
Holtzman	M/6-16/ groups	250 g	Aroclor 1254/diet	0, 5, 50 or 500 ppm for 2, 3 or 5 weeks	500 ppm: weight loss. ≥5 ppm: hepatomegaly. 500 ppm: slightly increased size of kidney, testes; decreased adipose. 50-500 ppm: liver - increased content of fat; decreased protein, RNA, DNA. 50-500 ppm: blood - glucose reduced, BUN, cholesterol, protein increased. 5 ppm: aminopyrine demethylase activity increased. 50-500 ppm: p-nitrobenzoate reductase, pentobarbital hydroxylase activity increased.	Garthoff et al., 1977
Sprague-Dawley	M/10/ group	weanlings	Aroclor 1254 or 1260/ diet	0 or 20 ppm for 28 days	No effect on food intake, weight gain or liver size. Moderate liver lobular pattern with periportal perinuclear halos and perivenous cytoplasmic ballooning; anisokaryosis, moderate fatty liver degenerations. Thyroid changes (see Collins et al., 1977). Reduced SGOT; induced mixed function oxidases.	Chu et al., 1977
Wistar/ Neuherberg	M/10/ group	100 g	Clophen A-50/olive oil	0, 2, 10, 50, 150 or 250 mg/kg bw, twice weekly for 6 weeks	≥50 mg/kg: decreased bw; slightly increased food intake; increased liver weight. ≥150 mg/kg: elevated SGOT, SGPT. ≥50 mg/kg: increased serum bilirubin, protein, triglycerides; increased urinary porphyrin precursors. >2 mg/kg: increased serum cholesterol; hepatic coagulation focal necrosis, PMN infiltration, fatty degeneration, enlarged (functional) nucleoli.	Baumann et al., 1983
NR	M/10	6 months	"PCBs-1221"/ethyl alcohol	250 mg/l in drinking water for 10 weeks	Elevated plasma corticosterone; hyperactivity of zona fasciculata of adrenal cortex.	Wasserman et al., 1973

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	M/NR	100 g	Aroclor 1248, 1254 or 1260/diet	0 or 1000 ppm up to 6 weeks	Reduced rate of gain: Aroclor 1248 > 1254 > 1260. Moderate elevation of Hb, PCV. Relative neutrophilia, lymphocytopenia. Enlarged liver, decreased thymus, fatty liver degenerations, cystic areas and focal necrosis with infiltration of inflammatory cells. ER proliferation, vesiculation of RER, increased number of lysozymes. Increased hepatic protein, RNA, phospholipid; decreased DNA, cholesterol. Induction of N-demethylase, nitroreductase.	Allen and Abrahamson, 1973
Wistar	F/8	112-130 g	Phenoclor DD6/diet	2000 ppm up to 56 days	>3 weeks, UV fluorescence of incisors, small intestine (porphyria). Hepatic enlargement with centrilobular degeneration. Splenic degeneration with disappearance of white pulp, reduction in red pulp, evidence of siderosis.	Vos and Koeman, 1970
Sprague-Dawley	M,F/4/group	NR	Clophen A-50/olive oil	0 or 100 mg/kg bw 1 time/week for 7 weeks	M: Increased liver percent of bw from 2.6-3.3%. Presence of ATPase deficient islands. F: Increased liver percent of bw from 2.9-3.6%. Greater presence of ATPase deficient islands.	Deml and Oesterle, 1982
Holtzman	M/30	NR	Aroclor 1254/diet	0, 5, 50, 500 ppm for 5 weeks	≥50 ppm: hepatomegaly, fatty degeneration, hepatocellular hypertrophy and cytoplasmic vacuolization. ≥5 ppm: enlarged SER; decreased number of mitochondria, lysosomes; increased Golgi apparatus. ≥50 ppm: Golgi apparatus decreased.	Kasza et al., 1978b
Holtzman	M/30	NR	Aroclor 1254/diet	0, 5, 50 or 500 ppm for 5 weeks	≥5 ppm: enlarged thyroid, reduction in follicular size, hyperplastic cells with papillae and cytoplasmic processes extending into lumenal colloid; follicular cells more columnar, mitochondria vacuolated with disrupted cristae, accumulation of colloid, increased number of lysosomes.	Kasza et al., 1978a

NR = Not reported

TABLE V-3

Acute, Short-term and Subchronic Toxicity of Orally-Administered PCBs to Mice

Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
NMRI	F/116	sexually mature	2,4',5-tri-CB	peanut oil	0, 0.05, 0.5 mg/day	0.50 mg/day: increased cytochrome P-450	Orberg, 1978
NMRI	F/108	sexually mature	2,2',4,4',5,5'-hexa-CB	peanut oil	0, 0.05, 0.5 mg/day for 6 days	≥0.05 mg/day: increased cytochrome P-450 ($p<0.005$). 0.5 mg/day: hepatomegaly	
NMRI	F/45	sexually mature	Clophen A-60	peanut oil	0 or 0.025 mg/mouse daily for 62 days	Increased ($p<0.0005$) length of estrus cycle	Orberg and Kihlstrom, 1973
CD-1	M/6/group	19-24 g	Aroclor 1254	Emulphor: saline(1:8)	0, 10, 30, 100, 250 or 500 mg/kg bw, single dose	500 mg/kg: depression of spontaneous locomotor activity for <8 hours	Rosin and Martin, 1981
CD-1	F/NR	60-90 days	3,3',4,4',5,5'-hexa-CB	cottonseed oil	0-16 mg/kg/day for 10 days	≥8 mg/kg/day: decreased weight gain, lethargy, vaginal bleeding of pregnant females	Marks et al., 1981
CBH	F/10/group	12 weeks	2,2',4,4',5,5'-hexa-CB	peanut oil	0, 0.5 mg/day for 7 or 13 days	Increased liver weights; reduced sensitivity to stressful stimuli (moving)	Mattsson et al., 1981
ICR	M/5/group	adult	Aroclor 1254	diet	0, 62.5, 250, 1000 or 4000 ppm for 14 days	4000 ppm: total mortality by day 7. 1000 ppm: death of 3/5 by day 15. 250 ppm: hepatomegaly, depressed food intake, decreased pentobarbital sleeping time. 62.5 ppm: elevated serum corticosterone.	Sanders et al., 1974
CD-1	M/9/group	25-29 g	Aroclor 1254	Emulphor: saline(1:8)	0, 30 or 100 mg/kg bw/day for 14 days	Prolonged pentobarbital-induced sleep time at both doses.	Rosin and Martin, 1983
Swiss Albino	M/10/group	23-47 g	2,4,5,2',4',5'-hexa-CB	peanut oil	0, 200, 500, 1000 mg/kg bw/day for 28 days	No significant effect on body weight, food or water intake, fecal or urinary output. 1000 mg/kg: decreased kidney weight; 500 mg/kg: increased liver weight. Brain, testes, spleen; no change. PCV: no change. Hepatocytes: enlarged cytoplasm and nuclei; fatty infiltration, reduced glycogen, increased SER; 200 mg/kg: increased lysosomes, mitochondria, RER. No deficits in neuromuscular coordination.	Carter and Cameron, 1977

TABLE V-3 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
						Lowest exposure (ppm) to cause:	
						Enlarged Liver / Reduced Spleen Thymus Wt. / Increased Testis Weight	Blocca et al 1981
C57Bl/6J	M/5/group	18-20 g, 5 weeks	3,4,5-sym. hexa CB... 2,4,6-sym. hexa-CB... 2,4,5-sym. hexa-CB... 2,3,6-sym. hexa-CB...	diet	0, 0.3, 1, 3, 10 or 30 ppm diet for 28 days 0, 10, 30, 100 or 300 ppm diet for 28 days	...0.3 / 10 / 10 ...100 / 300 / NR ... 30 / 300 / NR ... NR / NR / NR 300 ppm Diet / Levels in Adipose / Levels in Liver 3,4,5- / 6912 / 1344 2,4,6- / 4329 / 1022 2,4,5- / 3923 / 637 2,3,6- / 280 / 52 30 ppm 3,4,5-hexa-CB depressed serum protein, caused UV fluorescence of liver, teeth, sternum. Liver: 1.0 ppm 3,4,5-hexa-CB caused liver microabscesses to severe fatty degeneration and necrosis at 30 ppm. Other isomers: same lesions at 300 ppm. Thymus: 3.0 ppm 3,4,5-hexa-CB caused moderate to marked involution at 30 ppm; 300 ppm 2,4,6-hexa CB caused marked involution; 300 ppm 2,3,6 hexa CB caused slight involution. Spleen: 3.0 30 ppm 3,4,5-hexa-CB, 300 ppm 2,4,6 hexa CB caused moderate depletion of lymphocytes. 3,4,5-hexa-CB: enlarged spermatagonia. 2,4,6 hexa-CB: cardiomyopathy and passive congestion of liver, lung.	
BALB/CJ	M/~13/group	18-20 g	Aroclor 1242	diet	0 or 167 ppm for 6 weeks	Increased ($p<0.05$) mortality caused by *Salmonella typhosa* endotoxin at 6 weeks. Increased ($p<0.05$) mortality caused by *Plasmodium berghei* at 3 weeks. Hepatocytic hypertrophy; no histological alteration of lymphoid tissues.	Loose et al., 1978b

Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
BALB/CJ	M/~15/group	18-20 g	Aroclor 1242	diet	167 ppm for 6 weeks	>2 fold reduction in primary and secondary splenic plaque forming cells in response to sheep RBC, decreased serum immunoglobulin. Decreased memory cell function and serum IgA when immunized with sheep RBC 3 weeks before 6 week exposure to Aroclor 1242.	Loose et al., 1978a
			Aroclor 1016 or 1242	diet	167 ppm for 6 weeks	Increased ($p<0.05$) mortality caused by S. typhosa endotoxin. (No difference between Aroclor 1016 or 1242.) Increased ($p<0.05$) mortality caused by P. berghei at 3 weeks. (No difference between Aroclor 1016 or 1242.) No histopathological changes in lung, thymus, mesenteric lymph nodes, spleen. Histopathological exam of liver revealed hepatocytic hyperplasia.	
C57Bl/6	M/NR	18-20 g	Aroclor 1016	diet	167 ppm for 3 weeks	Splenic cells from treated mice injected into neonates elicited greater graft vs. host response, indicating Aroclor 1016 may activate donor lymphocytes.	Silkworth and Loose, 1978
Outbred albino	f/7/group	4-6 weeks	Aroclor 1248	diet	0, 50, 100, 500, 1000 ppm for 3-5 weeks	PCB residues (ppm adiposa) 1.1, 109, 399, 1330, 3760 respectively at 3 weeks. No decreased food intake or other signs of toxicity except usual hepatocellular alterations.	Thomas and Hinsdill, 1978
	f/7/group				0, 1000 ppm for 5 weeks	At 4+ days postinoculation with live Salmonella typhimurium, treated mice had greater numbers of live organisms in liver and blood.	
	f/7/group				0, 100 or 1000 ppm for 5 weeks	Apparently dose-related increase in mortality due to S. typhimurium endotoxin.	
CL/ICR	f/25/group	sexually mature	Kanechlor 500	diet	0 or 500 ppm for ~42 days	Depressed feed intake, hepatomegaly	Ianimura et al., 1980

NR = Not reported

TABLE V-4

Acute, Short-term and Subchronic Toxicity of PCBs Administered by Routes Other than Oral

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
s.c.	Guinea pig/ NR	NR/54	NR	NR; 42% Cl	None	69-690 mg, single dose	Local injection necrosis to fibrous encapsulation. Hepatic: centrilobular necrosis, atrophy; fatty infiltration, splenic lymphoid hyperplasia, pulmonary congestion, mortality.	Miller, 1944
s.c.	Guinea pig/ NR	NR/10	NR	NR; ~42% Cl	Mineral oil	345 mg, single dose	As above; complete mortality 13 days; pulmonary congestion more severe	
s.c.	Rat/NR	NR/30	NR	NR; ~42% Cl	None	69 or 690 mg, single dose	Fatty liver degeneration; splenic hypertrophy; local injection fibrous encapsulation	
s.c.	Rabbit/NR	NR/3	NR	NR; ~42% Cl	None	690 or 1380 mg, single dose	Death in 14-72 days (as above, except liver contained fine droplets of fat).	
		NR/3	NR	NR; ~42% Cl	Mineral oil	345 or 690 mg, single dose	Death in 42-360 days (as above, except liver contained fine droplets of fat).	
Dermal	Guinea pig/ NR	NR/11	NR	NR; ~42% Cl	None	34.5 mg/day for 11 days	Death within 21 days. (Dermal epithelial destruction. Lesions in internal organs as above.)	
		NR/16	NR	NR; ~42% Cl	Mineral oil	3.5-17 mg/day for 7 or 15 days		
s.c.	Mice/ddY	F/NR	7-8 weeks	Kanechlor 500	95% ethanol	0-10 mg/day for 10 days	Killed 2 days after last dose: Mortality ≥4 mg/day	Watanabe and Sugahara, 1981
i.p.	Rat/NR	M/NR	NR	Aroclor 1254	NR	100 mg/kg/ day for 6 days	Aminolevulinic acid (ALA) synthetase activity increased, ALA dehydratase activity decreased, microsomal heme and cytochrome P 450 increased	
Inhalation	Rat/NR	M/5, F/5	NR	Decachloro-biphenyl	NA	2.54 g/m³ for 6 hours	Blinking and sneezing, reversible; 14-day observation, no effects on appetite or growth. Gross pathology, no lesions.	Berczy et al., 1974

TABLE V 4 (cont.)

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
Inhalation	Rat/NR	NR/4		Solvol	NA	10 g/m³ for 3 hours	All uncoordinated, comatose, dead in 24 hours. Hepatic necrosis, fatty infiltration, renal tubules cloudy swelling. Heart and spleen congested, splenic necrosis.	Rozanova, 1943
Inhalation	Rat/NR	NR/3		Solvol	NA	0.5 g/m³ for 11 exposures	1 death, necropsy similar to above, signs less marked. Hyperplasia of Kupfer cells.	
i.p.	Rat/Wistar Woodlyn	M/7	young	pure mono-, di-, tetra-, hexa-, octa-CBs pure mono-, di-, tetra-isomers of PCBs		50 mg/kg bw daily for 3 days 100 mg/kg bw daily for 7 days	Hepatocytic proliferation of SER, changes in RER, focal necrosis, cytoplasmic vacuolization. More pronounced hepatic changes; fatty infiltration, centrilobular necrosis, biliary proliferation.	Hansell and Ecobichon, 1974
i.p.	Rat/Wistar	M/NR	young	Aroclor 1016, 1221, 1232, 1242, 1248, 1254, 1260	Peanut oil	50 mg/kg/ day for 3 days	Induction of many hepatic enzymes.	Ecobichon, 1975
i.p.	Rat/Long-Evans	M/NR	3 weeks	Aroclor 1254 or 27 purified isomers	Corn oil	500 µmol/kg bw 1 time	Increased liver weight, decreased thymic weight; induction of various cytochrome P-450s	Parkinson, et al., 1983a
i.p.	Rat/Sprague-Dawley	M/24	adult	Aroclor 1254	Corn oil	Control, corn oil, or 1 g/kg bw	"Typical" liver lesions; no effect on plasma corticosterone	Dunn et al., 1983
i.p.	Rat/Sprague-Dawley	M/NR	150-200 g	Aroclor 1254	Ringer's solution	0, 25, 50 mg/kg	Hepatomegaly, elevated cytochrome P 450, various hepatic enzyme systems induced or inhibited.	Hinton et al., 1978
i.p.	Rat/Sprague-Dawley	M/NR	100-120 g	Aroclor 1254	NR	100 mg/kg/day for 6 days	Elevated ALA synthetase, microsomal heme, cytochrome P-450. Depressed ALA dehydration.	Alvares and Kappas, 1979
						100 mg/kg once weekly for 6 weeks	Elevated total porphyrins, microsomal heme, cytochrome P-450. Depressed ALA dehydration, ferrochelatase.	

TABLE V-4 (cont.)

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
i.p.	Rat/Sprague-Dawley	M/13	NR	Aroclor 1242	Peanut oil	100 mg/kg bw twice weekly for 6 weeks, once weekly for an additional 4 weeks	Body weight loss, hepatic midzonal sudanophilic vacuolization, focal necrosis, dilation of renal tubules with proteinaceous casts. Decreased PCV, RBC, hemoglobin, neutrophils. Increased serum iron, decreased corticosteroids and blood glucose. Increased urinary protein sugar, coproporphyrin.	Bruckner et al., 1974b
i.p.	Rat/Sprague Dawley	M/24	200-300 g	Aroclor 1242	Peanut oil	0, 1, 5, 25, 50 or 100 mg/kg bw,	Elevated hydroxylation, N-demethylation, cytochrome P-450	Bruckner et al., 1974b
		M/6/treated group, 3/ control group	NR	Aroclor 1242	Peanut oil	single dose 0 or 100 mg/kg bw, single dose	Examinations of microsomal enzyme induction at 1, 5, 10, 20, 40 days post treatment indicated maximum induction at 5 days, some residual induction at 20 days. Hydroxylation most dramatically elevated.	
i.p.	Rat/Wistar	M/120	250 g	Clophen A-50	Corn oil	0 or 100 mg/kg bw, single dose 4 weeks observation	Cytochrome P-450 increased 3- to 4-fold, maximum in 1 week. NADPH activity doubled, P-nitroanisole O-demethylase induced 6- to 7-fold; ~4-fold after 1 month. AHH activity increased 3-fold, down to normal ~1 month. Microsomal epoxide hydratase increased 2.5 fold at 1 week, persisted at least 4 weeks. Glutathione S-transferase increased at 1 day remained at these levels. Microsomal UDP glucuronosyltransferase activity increased 2.5 fold in 1 week, persisted 4 weeks.	Parkki et al., 1977
i.p.	Mice/BALB/CJ	NR/4-10/ group	NR	Aroclor 1242	Corn oil	1000 mg/kg bw single dose	Splenomegaly: significant by day 6, peak by day 9, gone by day 13. Cellularity: significant reduction in lymphocytes days 6-10.	Carter and Clancey, 1980

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
Dermal	Rabbit/New Zealand White	f/16	2500 3050 g/5 months	Phenoclor DP6 Clophen A 60 Aroclor 1260	Isopropanol	118 mg/day, 5 days/week for 38 days (27 applications)	All PCBs: Gradual weight loss, mortality beginning at day 10, erythemia and thickening of skin, subcutaneous edema, ascites, UV fluorescence. Fecal coproporphyrin and protoporphyrin elevated. Hematology: leukopenia. Apparent hepatomegaly, kidney enlargement. Liver: centrilobular degeneration, focal hydropic degeneration, focal necrosis, centrilobular hepatocytic atrophy (more pronounced in Clophen, least in Aroclor group), periportal fibrosis. Kidney: hydropic degeneration of convoluted tubules, pyknotic nuclei, rhexis and lysis of tubular epithelial, cells, tubular dilatation with casts of necrotic cells.	Vos and Beems, 1971
Dermal	Rabbit/New Zealand White	f/12	2.5-2.9 kg/3.5 months	2,4,5,2',4',5'-hexa-CB Aroclor 1260	Isopropanol	120 mg/day, 5 days/week for 4 weeks (20 applications)	Dermal: erythema, wrinkling, hyperkeratosis, reduced hair regrowth; more severe in Aroclor 1260 group. Fecal coproporphyrin elevated in both treatment groups with UV fluorescence. Hepatomegaly, elevated SGPT, SGOT in 2,4,5-hexa-CB group. Dermal sections: epidermal follicular hyperplasia; follicular plugging more in Aroclor 1260 group. Moderate thymic atrophy in both PCB groups. Liver lesions similar to previous study (Vos and Beems, 1971), more severe in 2,4,5-hexa-CB group; SER proliferation, RER dilation and degranulations, picnotic nuclei.	Vos and Notenboom Ram, 1972

NR - Not reported

TABLE V 5

Acute, Short-term and Subchronic Toxicity of Orally-Administered PCBs to Other Species

Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
Monkey/ rhesus	M/1	9.2 kg/ adult	2,5,2',5'-tetra-CB	corn oil	0.18 mg/kg bw	Moderate proliferation of SER, slight decrease of liver DNA, increase in cytochrome P-450.	Allen et al., 1975
Rabbit/ New Zealand White	F/20, M/20	NR	Aroclor 1221, Aroclor 1242 Aroclor 1254	corn oil	0 or 300 mg 1 time weekly for 14 weeks	Aroclor 1242, 1254: elevated SGOT, SGPT. Aroclor 1254: slight transient increase in serum cholesterol, reduced rate of gain, severe hepatomegaly, uterine atrophy. No differences in hematologic parameters, BUN, serum protein fractions. Histopathology, Aroclor 1254: vacuolated and granular enlarged hepatocytes, centrilobular necrosis and fibrosis. Ballooned RER. Lesions less obvious in Aroclor 1242-exposed, absent in Aroclor 1221-exposed.	Koller and Zinkl, 1973
Rabbit/NR	F/16	adult	Aroclor 1254	corn oil	0, 1.0, 10, 12.5, 25, 50 mg/kg bw daily for 28 days	No effect on total number of fetuses, number of viable fetuses, number of resorption sites or number of abortions at doses of 1.0 or 10 mg/kg bw/day. Liver weights in the dams were signifi cantly increased at the 10 mg/kg bw/day dose. Effects on fetal viability as well as other maternal effects were seen at doses of 12.5 or greater.	Villeneuve et al., 1971a,b
Rabbit/New Zealand White	M/7/group	~2 kg	Aroclor 1254	diet	0, 3.7, 20.0, 45.8, 170 ppm diet for 8 weeks: 0.18, 0.92, 2.1 or 6.54 mg/kg bw/day, respectively	No effect on feed consumption, growth rate, visceral pathology except hepato megaly which was statistically signifi cant (p=0.05) at the highest two doses. No effect on hematologic parameters. No consistent immunological response (hemolysis or hemagglutination titers) to sheep RBC. Gamma globulin reduced at all levels. No effect on dermal tuberculin reaction. Splenic and thymic reductions in gamma globulin-producing cells, dose-related.	Street and Sharma, 1975
Guinea pig/ Dunbar/ Hartley	F/5-19/ group	500 600 g/ 8-10 weeks	Clophen A50 2,4,5,2',4',5'-hexa CB	peanut oil	25 or 100 mg. total doses over 55 days	"All seemed unaffected by the treatment." Clophen A-50: Increased cytochrome P 450	Brunstroem et al., 1982

TABLE V-5 (cont.)

Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
Guinea pig/ NR	M/40	3-4 weeks/ ~225 g	Clophen A60	diet	0, 10, 50, 250 ppm for 4 weeks	250 ppm: 80% mortality; cachexia, lymphoid atrophy, liver damage, hepatomegaly ≥50 ppm. ≥10 ppm: dose related reduction in hemagglutination titers and tetanus antitoxin producing cells in popliteal lymph nodes following tetanus toxoid immunization.	Vos and van Genderen, 1973
	f/40	3-4 weeks/ ~225 g	Clophen A60	diet	0, 10, 50 ppm for 6 weeks	50 mg/kg Clophen: Increased liver weight.	
	f/40	3-4 weeks/ ~225 g	Aroclor 1260	diet	50 ppm for 6 weeks	Significant reduction of tetanus antitoxin titers, circulating leukocytes and lymphocytes and thymus atrophy with both PCBs, 50 ppm. 100% mortality at 250 ppm. Reduced tuberculin skin reaction, thymus atrophy, leukopenia at 50 ppm level.	Vos and van Genderen, 1973
	f/30		Clophen A60	diet	0, 50, 250 ppm for 7 weeks		
Guinea pig/ albino	f/36	~220 g/ 4 weeks	Aroclor 1260	diet	0, 10, 50 ppm for 8 weeks	50 ppm: reduced rate gain, hepatomegaly, reduced weight of kidney, adrenals. 10 ppm: splenic atrophy; reduced popliteal lymph node, gamma-globulin-producing cells.	Vos and de Roij, 1972
Pig/ Yorkshire	NR/11	14 days	Aroclor 1254	condensed milk added to diet	0, 12.5, 25, 50, 100 mg/kg bw up to 35 days	All levels: partial anorexia, reduced weight gain, diarrhea (melena or blood at ≥50 mg/kg), abdominal distension, gastritis, colitis, enlarged thyroid, thymic and splenic atrophy, liver and kidney enlargement.	Miniats et al., 1978
Monkey/ rhesus	f/12	5.6 kg/7-10 years	Aroclor 1248	diet	0, 25 ppm for 2 months; total intake of 260-450 mg	Alopecia; edema of lips, eyelids, face; pustules involving hair follicles; pruritis; necropsy of the animal consuming 450 mg: severe weight loss, subcutaneous edema, acute hyperplastic gastritis with focal hemorrhage, ulceration. Liver: focal necrosis, enlarged hepatocytes, lipid accumulation. Hypocellularity of bone marrow.	Allen et al., 1974b

TABLE V-5 (cont.)

Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
Monkey/ rhesus	M/1	9.2 kg/adult	2,5,2',5' tetra CB	corn oil	0 or 18 mg/kg bw, single dose	"No obvious clinical effects." No change in hematology. Levels (14 days) of tetra CB: adiposa, 135; adrenals, 33; lung and heart, 9; liver and skin, 4; thyroid, 2 µg/g tissue. Microscopically, all tissues normal. Hepatic ultrastructive: proliferation of SER, elevated cytochrome P 450.	Allen et al., 1975
Monkey/ rhesus	NR	adult	Aroclor 1248	diet	100 or 300 ppm for 2-3 months	Gradual weight loss, alopecia lacrimations, conjunctival congestion, facial edema, comedones, large intrafollicular keratin cysts. Hematology: gradual decrease in PCV, Hb; lymphocytopenia and concomitant neutrophilia. Reduced serum proteins, lipids, cholesterol, triglycerides. Thickened gastric mucosa with mucin-filled cysts, moderately invasive gastric hyperplasia. Two-fold hepatomegaly, enlarged hepatocytes with increased SER; decreased liver DNA, RNA, increased MFO.	Allen, 1975
Monkey/ rhesus	M/2 F/2	2.8-3.6 kg	2,5,4'-trICB	diet	5 ppm for 84 days (historic controls)	Most organs: increased blood volume. Increased relative liver, brain weight (males). Microscopically, venous congestion in many tissues. Adrenals: hemorrhages and cellular changes in zona fasciculata. Renal cortical and medulary degeneration, tubal colloid. Liver: congestion, fatty infiltrations. CNS: parenchymal and mesenchymal degeneration, macrozlial proliferation, gliosis, swelling of Purkinje cells.	Iatropoulos et al., 1977

NR = Not reported

these studies. Various routes of administration of PCB to many species have produced similar signs and symptoms of toxicity. Some species, such as the guinea pig, appear to be more sensitive to the effects of PCBs (Vos and van Genderen, 1973). In the following section, the pathological effects of short-term PCB exposure will be described. The studies discussed in the following sections are also summarized in Tables V-2 to V-5.

Hepatic System. The majority of the toxicity studies have evaluated the effects of PCBs on the liver. Grant and Phillips (1974) administered Aroclor 1254 by gavage to male and female Wistar rats. In both sexes, 5 mg/kg bw/day for 7 days significantly increased liver weights.

Longer exposure to PCBs produced hepatoxicity. Allen and Abrahamson (1973) fed diets containing up to 1000 mg Aroclor 1248, 1254 or 1262/kg diet to male Sprague-Dawley rats for 6 weeks. Liver weights at the end of 6 weeks were increased >3-fold; the livers from the Aroclor 1262-exposed rats were most enlarged and livers from Aroclor 1248-exposed rats were least enlarged. More recently, Baumann et al. (1983) reported that male Wistar/ Neuherberg rats treated with 2-250 mg/kg of Clophen A-50 by gavage twice weekly for 6 weeks exhibited liver damage at levels as low as 2 mg/kg bw. Liver damage was characterized by increased liver size, congestion, fatty degeneration and focal necrosis. Lin et al. (1979) did not report increased liver size, but found considerable ultrastructural damage (intracellular vacuolization fragmentation of RER, altered mitochondrial conformation) in 200-500 g female Sprague-Dawley rats that were treated by gavage with single doses of 1.7 g 2,2',5,5'-tetra-CB/kg bw.

Additional hepatic alterations were described by Kasza et al. (1978b). Four-week-old male Holtzman rats received 0, 5, 50 or 500 mg Aroclor 1254/kg in the diet for 5 weeks. The animals experienced hepatic alterations consistent with those previously described in this section. Additionally, a dose-related increase in the number of liposomes, as well as lipid droplets and an increase in the number of Golgi apparatus at the 5 ppm exposure level and a modest reduction in Golgi apparatus in the 50 and 500 ppm exposed groups. Laminated cytoplasmic inclusions or membrane whorls were seen in hepatocytes from rats exposed to 500 ppm. The observations from this study indicate that a blockage occurred in the mechanism by which hepatocytes discharge lipids.

PCBs have been used widely to induce hepatic enzymes, often in studies with other chemicals. In these studies, large doses of PCBs are often given by i.p. injection or gavage to obtain maximal enzyme induction.

The rapidity in which certain hepatic enzyme activities are induced and their persistence in the induced form was demonstrated in a study by Parkki et al. (1977). A one-time i.p. administration of 100 mg Clophen A-50/kg bw to male Wistar rats elicited profound biochemical changes in the liver. Cytochrome P-450 levels increased 3- to 4-fold with a maximum achieved in 1 week. NADPH cytochrome c reductase activity doubled, and p-nitroanisole-o-demethylase activity increased 6- to 7-fold and declined to ~4 times normal activity at the end of the 4-week observation period. AHH activity increased 3-fold initially and had returned to normal by the end of 4 weeks. Microsomal epoxide hydratase activity had increased 2.5-fold at 1 week and persisted at this level. Glutathione-S-transferase activity had increased by 1 day and remained elevated for 4 weeks.

Similar evidence for rapid onset of enzyme induction was demonstrated in Sprague-Dawley rats fed diets containing Aroclor 1248, 1254 or 1260 for 6 weeks. This treatment resulted in many enzymes systems being induced after 1 week of exposure to all of the Aroclors tested. Microsomal nitroreductase activity increased initially and declined to near normal values by the second week. Activity continued to decline except in livers from Aroclor 1260-exposed rats. N-demethylase activity persisted at high levels throughout the 6-week period, whereas, AHH, glucose 6-phosphatase and esterase activities decreased during the study. An increase in the amount of endoplasmic reticulum correlated with the occurrence of enzyme induction with this phenomenon. By 6 weeks, degenerative changes such as vesiculation of the endoplasmic reticulum, dissolution of membranous whorls and accumulation of numerous lipid droplets had occurred. This degeneration was accompanied by a decrease in hepatic enzyme activities (Allen and Abrahamson, 1973).

Few studies have been designed to define minimum effective oral doses required to induce hepatic enzyme activities. Chu et al. (1977) reported induction of MFO activity in male weanling rats exposed to 20 mg Aroclor 1254 or Aroclor 1260/kg in the diet for 28 days. Similarly, Garthoff et al. (1977) reported that 5 ppm of Aroclor 1254 in the diet for 3 weeks resulted in induction of hepatic aminopyrine demethylase activity; exposure at the same dose for 5 weeks produced a significant increase in liver weight in male Holtzman rats.

Effects on the livers of mice are strikingly similar to those observed in rats (Carter and Cameron, 1977; Orberg, 1978; Sanders et al., 1974; Loose et al., 1978a,b). Levels of 0.3-1.0 ppm of 3,3',4,4',5,5'-hexa-CB diet for 28 days resulted in liver enlargement; fatty degeneration and formation of

microabscesses were found at doses ≥1.0 ppm of diet (Biocca et al., 1981). This study used groups of five C57Bl/6J male mice to test the relative potency of four symmetrical isomers of hexa-CB. The other isomers tested elicited similar responses at the 30-300 ppm diet level. Mattson et al. (1981) observed hepatomegaly in groups of female CBA mice that were exposed to 2,2',4,4',5,5'-hexa-CB in peanut oil at levels of 0.5 mg/mouse/ day for 7 days. Higher levels of commercially available PCB products are necessary to elicit these hepatic responses. Loose et al. (1978b) exposed groups of male/BALB/CJ mice to a diet containing 167 ppm Aroclor 1242 for 6 weeks to demonstrate hepatocytic hypertrophy. Sanders et al. (1974) demonstrated hepatomegaly in groups of five adult male ICR mice exposed to dietary levels of 250 ppm Aroclor 1254 for 14 days.

Other species have demonstrated variable alterations in hepatic parameters upon exposure to PCBs. Oral administration of levels as low as 3.7 ppm Aroclor 1254 in the diet (0.18 mg/kg bw/day) for 8 weeks to male New Zealand rabbits failed to produced hepatomegaly (Street and Sharma, 1975). Guinea pigs treated with a 250 mg Clophen A-60/kg diet for 4-7 weeks experienced hepatomegaly with "liver damage" (Vos and van Genderen, 1973).

Skin -- Only one study was found that implicated PCBs (Aroclor 1254) in dermatitis in rats (Zinkl, 1977). Alopecia and a crusty dermatitis with serum ooze developed first on the ears, then the dorsum of the nose, tail and feet of female CD rats after 10 weeks of exposure to 100 ppm Aroclor 1254 diet.

Signs of toxicity in monkeys acutely exposed to PCBs closely parallel those reported in other species with a few notable exceptions. Frequently,

the first obvious sign of PCB intoxication is the development of facial lesions. Facial and palpebral edema followed by alopecia and development of comedones was reported in female rhesus monkeys exposed to 25 ppm Aroclor 1248 in the diet for 2 months (Allen et al., 1974b; Allen, 1975). Total Aroclor 1248 intake was calculated on the basis of known food intake to be 260 mg. Within 1 month, all the PCB-exposed animals suffered from alopecia, subcutaneous edema, purulent ocular discharge and acneform lesions. These signs progressed to generalized subcutaneous edema, pruritus and alopecia. As described in more detail in the Chronic and Subchronic Toxicity Section, chronic low level toxicity studies by McNulty et al. (1980) resulted in lesions identical to those reported for rhesus monkeys fed higher doses of Aroclor 1248.

Immune System -- Immunotoxicity of PCBs appears to be dependent upon the expression of the aromatic hydrocarbon (Ah) receptor and on the ability of the PCB to bind to the receptor. As stated previously the receptor binding affinity of PCBs is dependent on the molecular conformation that is determined by the chlorine substitution pattern. Two tetra-CBs, 3,3',4,4' and 2,2',4,4', were found to have different enzyme inducing capabilities as well as differing potentials to induce immunotoxicity; that is, 3,3'4,4'-tetra-CB was immunotoxic while 2,2',4,4'-tetra-CB was not. In addition, this immunotoxicity appears to be dependent upon the presence of the Ah locus in the test animal studied (Silkworth and Grabstein, 1982; Silkworth et al., 1984).

Mice have been used as a model to demonstrate the effects of PCBs on suppression of the immune system. Loose et al. (1978a,b) demonstrated immunosuppression as measured by increased mortality to Salmonella typhosa

endotoxin and Plasmodium berghei in groups of male BALB/CJ mice that were treated with 167 ppm Aroclor 1016 or 1242 in the diet for 6 weeks. These treatments did not result in histologically-demonstrable lesions in thymus, spleen or mesenteric lymph nodes. Thomas and Hinsdill (1978) demonstrated decreased mortality of S. typhimurium in groups of outbred female mice that were given 1000 ppm Aroclor 1248 in the diet for 5 weeks and an apparent dose-related increase in mortality caused by S. typhimurium endotoxin at levels of 100 and 1000 mg/kg diet.

Male C57Bl/6J mice exposed to one of four symmetrical hexa-CB isomers exhibited thymic involution especially with 3,3',4,4',5,5'-hexa-CB. Concentrations of 3.0 ppm in the diet for 28 days caused moderate depletion of splenic lymphocytes (Biocca et al., 1981).

The guinea pig demonstrated immunosuppression resulting from a 4- to 7-week exposure of groups of female albino guinea pigs to 50 ppm of Clophen A-60 or Aroclor 1260 in the diet (Vos and de Roij, 1972; Vos and van Genderen, 1973). In this same laboratory, guinea pigs were exposed to ≤250 ppm of Clophen A-60 in the diet for 4-7 weeks experienced atrophy of lymphoid tissue and reduction in tetanus antitoxin titers following injection with tetanus toxoid (Vos and van Genderen, 1973). However, recently Brunstroem et al. (1982) reported that all animals "seemed unaffected by the treatment" in a study that exposed pregnant females to total Clophen A-50 or 2,2',4,4',5,5'-hexa-CB amounts of 100 mg over a 55-day period.

Dermal applications of 120 mg of either 2,2',4,4',5,5'-hexa-CB or Aroclor 1260, 5 times weekly for 4 weeks resulted in moderate thymic atrophy in rabbits (Vos and Notenboom-Ram, 1972), the most severe of which was pro-

duced by the hexa-CB. These results indicate that both PCBs had potential for cell mediated immunosuppression.

PCBs have been shown to cause splenic, thymic and lymph node regression in rats (Allen et al., 1975; Allen and Abrahamson, 1973; Parkinson et al., 1983a). Slight splenic enlargement was reported for some workers after occupational exposure to PCBs (Miller, 1944; Oishi et al., 1978; Carter and Clancey, 1980).

Endocrine System -- The thyroid has been implicated as a site of PCB toxicity and thyroid dysfunction as the cause of many of the PCB symptoms. The first study to report thyroid toxicity was conducted using young male Osborne-Mendel rats (Collins et al., 1977). In another study, Kasza et al. (1978a) reported that 4-week-old Holtzman rats fed diets containing 5, 50 or 500 ppm of PCBs diet for 5 weeks produced ultrastructural changes at the lowest dietary PCB level. Aroclor 1254 at levels as low as 5 ppm in the diet for 4 weeks has been shown to cause considerable change in the microscopic and ultrastructural appearance of the thyroid gland in groups of six male 8-week-old Osborne-Mendel rats (Collins and Capen, 1980b). The investigators noted that Aroclor 1254 interfered with thyroid function and reduced thyroxine.

Reproductive System -- PCBs have been implicated in reproductive system dysfunctions in a variety of experimental situations (see Reproductive and Developmental Toxicity Section). Dietary administration of 300 ppm Aroclor 1254 in the diet for 10 days to female Holtzman rats (Spencer, 1982) has been associated with decreased levels of placental protein and glycogen content. Gavage treatment of male Sprague-Dawley rats (250-300 g) with 50

mg Aroclor 1254/kg bw for 7 days resulted in increased acid phosphatase activity in testicular interstitial cells (Dikshith et al., 1975). These studies indicate that PCBs may indirectly hasten steroid catabolism (Spencer, 1982).

Gastrointestinal System -- Development of gastritis progressing to a moderately invasive gastric hyperplasia in the individuals were described in the rhesus monkeys after consuming ~260 mg Aroclor 1248 over 2 months (Allen et al., 1974b) and in six male monkeys exposed for 3 months to a diet containing 300 mg Aroclor 1248 diet (Allen and Norback, 1973). Upon necropsy, edematous thickening of the stomach wall accompanied by glandular hyperplasia was observed. Glandular cells accumulated mucus, resulting in the formation of large, mucus containing cysts. Alterations of the glandular epithelial cells and their nuclei accompanied by inflammatory processes and invasion of the muscularis were observed.

Urinary System -- Rabbits exposed to PCBs responded in a manner similar to other species (Villeneuve et al., 1971a,b) with the exception that dermal application of any of three commercially available PCB products resulted in severe renal damage (Vos and Beems, 1971). Applied at 118 mg, 5 times weekly for 27 applications (38 days), Phenoclor DP6, Clophen A-60 and Aroclor 1260 all resulted in hydropic degeneration of convoluted tubules, destruction of tubular epithelial cells with resultant tubular dilatation and proteinaceous casts. No mention of such lesions was made in a subsequent study by this laboratory using a total of 20 such applications (Vos and Notenboom-Ram, 1972).

Other Observations -- Many reports have indicated that the nutritional status of animals may be altered with PCB treatment. Daily gavage with 0.05 g Aroclor 1254/kg bw to groups of male Sprague-Dawley rats (weighing 200-250 g) for 21 days resulted in depressed food and water intake, depressed body temperature and reduced rate of weight gain or absolute weight loss (Komives, 1979; Komives and Alayoku, 1980). Similar results were obtained by Kling et al. (1978) and Garthoff et al. (1977) using similar doses of Aroclor 1254 in the diet. Other workers (Chu et al., 1977) however, reported that exposure of male Sprague-Dawley weanling rats to 20 mg Aroclor 1254 or Aroclor 1260/kg diet for 28 days did not reduce feed intake or rate of weight gain. Similarly, Oishi et al. (1978) reported that a 100 mg Kanechlor 500/kg diet failed to reduce feed or water intake in rats.

Depressed food intake and rate of weight gain and lethargy were reported in mice treated with PCBs (Tanimura et al., 1980; Sanders et al., 1974). A dose as low as 8 mg of 3,3',4,4',5,5'-hexa-CB/kg bw/day given by gavage for 10 days to pregnant CD-1 mice also caused the above-described effects (Marks et al., 1981). Dietary exposure of male ICR mice to 250 ppm Aroclor 1254 in the diet for 14 days also resulted in depressed food intake (Sanders et al., 1974). Carter and Cameron (1977), however, observed no effect on body weight or food or water intake in groups of male Swiss albino mice that were exposed by gavage to 1000 mg of 2,4,5,2',4',5'-hexa-CB/kg bw daily for 28 days.

In general, blood and urine chemistries appeared to be affected by oral administration of various PCB products (Oishi et al., 1978; Baumann et al. 1983). Blood levels of glucose were reduced and blood levels of urea nitrogen, cholesterol and protein were increased by 50 ppm Aroclor 1254 in

the diet fed for 2 weeks to groups of male 250 g Holtzman rats (Garthoff et al., 1977). Baumann et al. (1983) found increased levels of urinary porphyrin and porphyrin precursors in groups of ten 100 g male Wistar/Neuherberg rats following treatment by gavage with 50 mg Clophen A-50/kg bw for 6 weeks.

Iatropoulos et al. (1977) exposed male and female rhesus monkeys to 5 ppm of 2,4',5-tri-CB diet for 84 days. No mention of total PCB intake was made. They reported a generalized increased blood volume of many tissues apparently resulting from dilation of arterioles, capillaries and veins. Hemorrhages and cellular changes in the adrenal cortex were observed. Parenchymal and mesenchymal degeneration in the brain was also reported.

Chronic Toxicity

Chronic toxicity studies discussed in this section include those >90 days in duration. These studies are summarized in Tables V-6 to V-9.

In contrast to acute toxicity induced by commercial mixtures of PCBs, chronic studies clearly indicate differences in the relative toxicity of the commercial PCB mixtures. A 14-week oral exposure (300 mg, once a week) study evaluated the relative toxicity of Aroclor 1221, 1242 and 1254 in rabbits and found that Aroclor 1254 was the most toxic and that Aroclor 1221 was the least toxic of the products tested (Koller and Zinkl, 1973). Similarly, male BALB/CJ mice fed diets containing Aroclors 1221, 1242 or 1254 resulted in the determination that Aroclor 1254 was more toxic than Aroclors 1242 and 1221 (Koller, 1977).

TABLE V 6

Effects of Chronic Oral Exposure of Rats to PCBs

Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
F344	M,F/191	Aroclor 1254	diet	0, 25, 50, 100 ppm for 2 years	2 years	Reduced body weight. Stomach: "intestinal" metaplasia, dose related; adenocarcinoma of glandular stomach.	Morgan et al., 1981
Sherman	F/400	Aroclor 1260	diet	0 or 100 ppm for 21 months	21 months	No effect on food intake; reduced body weight. Elevated tan liver nodules (170/184), hepatocellular carcinoma (26/184). Other areas: hepatic disruption.	Kimbrough et al., 1975
Wistar	M/290	Kanechlor 300, Kanechlor 400 or Kanechlor 500	diet	0, 500 or 1000 ppm for 27-52 weeks	1 year	Heavy mortality. Hepatomegaly, oval cell and bile duct proliferation, fatty liver infiltration. Cholangiofibrosis at 1000 ppm level of all three Kanechlors, nodular hyperplasia. Depressed final body weight.	Ito et al., 1974
Sprague-Dawley	M/6/group	Aroclor 1242	diet	0, 5 or 25 ppm for 2, 4 or 6 months	2, 4 or 6 months	Elevated hepatic microsomal enzyme activity, lipid content. Elevated urinary coproporphyrin levels. Present after 2 months at 5 ppm.	Bruckner et al., 1974a
Sprague-Dawley	M/96	Aroclor 1248, Aroclor 1254 or Aroclor 1262	diet	0 or 100 ppm for 52 weeks	65 weeks	Increased hepatic protein, RNA and lipid; decreased DNA. Increased microsomal total protein and cytochrome P-450. Induced N-demethylase nitroreductase. Inhibited glucose 6-phosphatase.	Allen and Abrahamson, 1979
CD	F/300	Aroclor 1254	diet	0, 10, 30 or 100 ppm for up to 20 weeks	20 weeks	Serum cholesterol, beta globulin increased, gamma globulin decreased (dose-related). ≥30 ppm: Reduced rate of gain, hepatomegaly, cardiomegaly (dose-related). ≥10 ppm: Hepatic porphyrinic fluorescence. ≥10 ppm: Erythema, crustiness, hyperkeratosis, perikeratosis on ears, dorsum of nose and feet, tail.	Zinkl, 1977
Donryu	M/15, F/15	Kanechlor 400	diet	total intake 450-1500 ppm over 159-560 days	560 days	All treated rats: fatty liver degeneration. Females 1200-1500 mg: multiple adenomatous nodules. All rats >700 mg: hepatomegaly. Lung and intracranoid abscesses suggested impaired resistance to infection.	Kimura and Baba, 1973

TABLE V-6 (cont.)

Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
Sprague Dawley	f/6/group	Aroclor 1242	diet	0, 75 or 150 ppm for 8 or 36 weeks	36 weeks	Both levels: massive venous engorgement of liver with characteristic darkening; marked focal neurosis and regeneration, enlarged hepatocytes; many mitoses and multinucleate cells, accumulation of pigment adjacent to veins, heaviest in Kupfer cells; accumulation of lipid droplets in cytoplasm, some with areas suggestive of lipid-cholesterol complexes; marked SER proliferation; deposits of iron; granular degeneration of mitochondria; many hepatocytes contained whorl-like membranous bodies.	Jonsson et al., 1981
Sherman	M/10, f/10 per group	Aroclor 1254	diet	0, 20, 100, 500 ppm for 8 months	8 months	Mortality (3/20) and reduced rate of gain at 500 ppm. Hepatomegaly, enlarged hepatocytes with foamy cytoplasm-containing inclusions at ≥20 ppm. Adenofibrosis and pigment accumulation at ≥100 ppm.	Kimbrough et al., 1972
	M/10, f/10 per group	Aroclor 1260	diet	0, 20, 100, 500, 1000 ppm for 8 months	8 months	Mortality 1/10, 2/10, 8/10 of females in 100, 500, 1000 ppm groups. Decreased rate of gain at ≥500 ppm. Hepatomegaly, male and female at ≥20 ppm, discolored livers with UV fluorescence, enlarged hepatocytes with foamy cytoplasm-containing inclusions. Increased lipid content at ≥100 ppm. Pigment accumulations at 500 ppm. Adenofibrosis at ≥100 ppm.	
Sprague-Dawley	M/96	Aroclor 1248, Aroclor 1254 or Aroclor 1262	diet	0 or 100 ppm for 52 weeks	65 weeks	Normal appetites, appearance, weight gain, Hb, PCV, WBC, serum protein, A/G ratios. Elevated serum total lipids, cholesterol. Total lipid and triglyceride spiked very high peaks on Aroclor 1254 (only) at 52 weeks. Cholesterol levels persisted at 65 weeks (13 weeks off exposure). Triglyceride levels fell less than controls by 65 weeks. Hepatomegaly: focal degeneration and necrosis by 13 weeks.	Allen et al., 1976

TABLE V-7

Effects of Chronic Oral Exposure of Mice to PCBs

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	References
Mice/dd	M/114	Kanechlor 300, Kanechlor 400 or Kanechlor 500	diet	0, 100, 250 or 500 ppm for 32 weeks	32 weeks	Hepatomegaly in all treatment groups. No effect on final body weight. Oval cell formation and bile duct proliferation at mid- and high dose levels of Kanechlor 400 and Kanechlor 500. Hepatocellular hypertrophy in all exposed groups except low-dose Kanechlor 300. Amyloidosis in all exposed groups except high-dose Kanechlor 400 and Kanechlor 500 groups; greater incidence associated with lower doses of lower-chlorinated Kanechlors.	Ito et al., 1973
BALB/CJ	M/25/group	Aroclor 1221, Aroclor 1242 or Aroclor 1254	diet	0, 3.75, 37.5 or 375 ppm for 6 months	9 months	375 ppm Aroclor 1242 and all Aroclor 1254 exposed groups: significant ($p<0.01$) increase in liver weight after 6 months. Significant ($p<0.01$) decrease in liver weight of 375 ppm Aroclor 1242 and 37.5 ppm Aroclor 1254-exposed groups after 3-month recovery period. Aroclor 1254: 375 ppm: mortality and severe hepatopathology; 37.5 ppm: mild hepatopathology; 3.75 ppm: no liver lesions. Aroclor 1242: 375 ppm: moderate hepatopathology. Aroclor 1221: no liver lesions.	Koller, 1977
Swiss Albino	F/63	Aroclor 1254	diet	200 ppm for 23 weeks	23 weeks	Thickening and erythemia of pinna of the ear; changes in microvasculature.	Bell, 1983
BALB/CJ	M/200	Aroclor 1254	diet	0 or 300 ppm for 6 or 11 months	11 months	Both 11- and 6 month exposure: Hepatomegaly, hepatomas, liver degeneration and elevated porphyrin.	Kimbrough and Linder, 1974
ddN	F/60	"CBP"	olive or rice bran oil	0, 0.5% V/V CBP in olive oil or 1600 mg/kg CBP in bran oil for 13, 17, 22 or 26 weeks	26 weeks	Both exposed groups: slight weight loss, reduced activity; eczematous and ulcerative skin lesions, hepatomegaly and hepatopathology.	Nishizumi, 1970

TABLE V 8

Effects of Chronic Exposure of Monkeys to PCBs

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	F/24 M/NR	Aroclor 1248	diet	0, 2.5 or 5.0 ppm for ~18 months	~39.6 months	Males (5.0 ppm level only): moderate erythema and periorbital edema. Females: more severe skin lesions (alopecia, acne); extreme weight loss, irregular menstrual cycle length, depressed serum progesterone. Considerable improvement after 1 year recovery period.	Barsotti and Allen, 1975
Rhesus	F/30	Aroclor 1248	diet	0, 2.5 or 5.0 ppm	~16 months total intake	Skin lesions as above; 15% weight loss in females. Normal hematograms. After 6 months: serum total lipids reduced, shift in A/G ratio, elevated SGPT. Menstrual cycles lengthened. Serum progesterone and estradiol reduced. After 12 months, serum cholesterol and triglyceride reduced.	Barsotti, et al., 1976; Allen et al., 1979b;
	M/10	Aroclor 1248	diet	0 or 5.0 ppm for ~16 months	90 or 180 ppm by females in 6 months		
	F/8/group	Aroclor 1248	diet	0.5 or 1.0 ppm 3 times weekly for ~16.6 months	~16.6 months total intake ~8 or 16 mg after 7 months	No irregularities in menstrual cycle, or serum estradiol, progesterone or reproduction success. Infants smaller, skin hyperpigmentated.	
	F/24	Aroclor 1016	diet	0.025, 0.25 or 1.0 ppm	NR	No abnormalities of clinical, gross or reproductive parameters in adults. 1.0 ppm: Infants born in the 1.0 ppm group were significantly smaller than controls.	Barsotti and van Miller, 1984
Rhesus	NR/1	Aroclor 1248	transplacental or mother's milk	Mothers exposed to PCBs 6 months before to gestation through gestation and 3 4 months of nursing	Up to infant age of 24 months	Significantly increased locomotor behavior (hyperactivity). Significantly retarded learning ability.	Bowman et al., 1978, 1981
		Aroclor 1248	transplacental or mother's milk	Mothers removed from exposure to PCBs for 22-84 weeks before conception		Mothers exposed to >2.5 mg/kg: hyperactivity.	

TABLE V-8 (cont.)

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	M/3/group	3,4,3',4'- or 2,5,2',5'-tetra-CB	diet	3 ppm (days 1 22) reduced to 1 ppm (days 23 49) reduced to 0.3 ppm (from day 50). For one animal elevated to 1 ppm (from day 104)	Up to 215 days	Mortality of all three by day 215 in 3,4,3',4' tetra CB exposed groups: emaciation, skin lesions, nail bed hyperplasia, loss of nails, thymus atrophy, gastric lesions as described (Allen, 1975). 2,5,2',5'-tetra CB: no signs of toxicity, no gross or histologic lesions.	McNulty et al., 1980
		Control					
	M/4-5/group	3,4,3',4'- or 2,5,2',5'-tetra-CB	diet	1 ppm for 38 days or 133 days, then control diet	~190 days	1 death: necropsy findings as above. Others: squamous metaplasm of sebaceous glands.	
		Aroclor 1242		1 ppm for 133 days 5 mg/kg additional 2 months		No evidence of toxicity.	
Rhesus	M/6	Aroclor 1242	diet	0, 3, 10, 30 or 100 ppm diet	Up to 245 days	All PCB-exposed monkeys: palpebral swelling, erythemia; weight loss, rough hair coat, reduced Hb, leukocytosis. Mortality of 4/6 by day 245. Gastric lesions: hypertrophic gastric mucosa consisting of elongated hyperplastic glands, destruction of parietal and zymogenic cells. Only specific region along greater curvature affected.	Becker et al., 1979
Cynomolgus	F/4	Aroclor 1254	corn oil, gelatin, apple juice	0, 100, 100 or 400 mg/kg bw/day, 3 days/week	Up to 238 days	Lost fingernails, fetal toxicity. Substantially reduced antibody production to SRBC antigen.	Truelove et al., 1982
Cyno molgus	F/1	P-KC-400[a] Y-PCB[b]	olive oil in banana	5 mg/monkey/day 5 or 10 mg/monkey/day	20 weeks	Death of 10 mg Y-PCB-dosed monkeys by 8 weeks. Weight loss of P KC 400 and 5 mg Y PCB-dosed monkeys. Y PCB-dosed: alopecia, acne, hyperpigmentation, periorbital edema. All treatments: reduced antibody production to SRBC. Histopathology Y-PCB: enlarged hepatocytes with enlarged SER, focal necrosis, bile duct proliferation. Dilated renal tubules with casts, epithelial vacuoles. Meibomian cysts, skin hyperkeratosis. Histopathology P KC 400 and PY PCB: lesions in liver, kidney as above, but more mild. Periorbital skin: no lesions.	Hori et al., 1982
		PY-PCB[c]		5 mg/monkey/day			
		control		NA			
				All above treatments given 6 days/week			

TABLE V 8 (cont.)

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	M/6	"PCB"	salad oil in banana	0 or 0.5 mg/kg bw (79.2-253.6 mg)	Up to 5 months	Symptoms of all treated animals similar: 17.3% weight loss, partial alopecia, palpebral edema, acneform eruptions, squamous metaplasia of meibomian glands.	Ohnishi and Kohno, 1979
	F/6	"PCB with PCDF"	diet	2.5 ppm bw PCDF			

[a]P-KC-400 - Kanechlor 400 with PCDFs removed

[b]Y-PCB was prepared from Kanechlor 400, contained ~400 ppm PCDFs

[c]PY-PCB - Y-PCB with PCDFs removed

NA - Not available

TABLE V 9

Effects of Chronic Oral Exposure of Other Species to PCBs

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	References
Mink/ Pastel	M,F/105	Aroclor 1242	diet	0, 5, 10, 20 or 40 ppm	8 months	Aroclor 1242 at 5 or 10 ppm: complete reproductive failure. Mortality of all mink on ≥20 ppm.	Bleavins et al., 1980
		Aroclor 1016	diet	0 or 20 ppm		Aroclor 1016 (20 ppm): death of 3/12 (25%) of females. Necropsy: emaciation, complete absence of body fat, gastric ulceration, reproductive performances reduced.	
Mink/NR	F/3 or 8/ group	Aroclor 1016, Aroclor 1221, Aroclor 1242 or Aroclor 1254	diet	0 or 2 ppm	10 months	Aroclor 1254: interference with reproduction. All Aroclors tested: no significant differences in body weight gain, hemoglobin, PCV. Aroclor 1016 (200 ppm): no effect on reproductive parameters, kit growth, and adult and kit mortality.	Aulerich and Ringer, 1977

NR - Not reported

It is readily apparent that the toxicity of PCB congeners is dependent on the degree and positioning of chlorine on the biphenyl molecule. From a 5 week exposure study Biocca et al. (1981) determined the toxic potential of various hexachlorinated biphenyl isomers in mice and ranked them relative to their toxic potency: 3,4,5-sym-hexa-CB >> 2,4,6-sym-hexa-CB > 2,4,5-sym-hexa-CB > 2,3,6-sym-hexa-CB. Biocca et al. (1981) also reported the same ranking for the relative persistence of the hexa-CB isomers, with 3,4,5-sym-hexa-CB having the highest levels in adipose tissue and liver. Another example of a structure-toxicity relationship for PCBs is reported in the study by McNulty et al. (1980). Administration of a diet containing 0.3-3.0 ppm 3,3',4,4'-tetra-CB caused chloracne, weight loss and death in rhesus monkeys in 1-6 months, while similar feeding of 2,2',5,5'-tetra-CB produced no clinical or pathologic lesions. Toxicity appears to be related to the ability of the congener to bind to a receptor and initiate subsequent genetic expression resulting in pleiotrophic responses (Poland and Knutson, 1982).

Species differences in sensitivity to PCB toxicity have been identified in chronic exposure studies. The monkey appears to be more sensitive to PCBs than rodents. Sprague-Dawley rats did not exhibit excessive mortality when exposed to 100 ppm dietary levels of Aroclor 1248 for 65 weeks; however, rhesus monkeys fed diets containing 25, 5 and 2.5 ppm produced morbidity and mortality after consuming these diets for 2 months and $\leq$18 months, respectively (Allen and Abrahamson, 1979; Allen et al., 1974b; Barsotti et al., 1976). In addition, the mink appears to be one of the more susceptible species to PCB toxicity. Studies have shown that as little as 2 ppm Aroclor 1254 in the diet for 10 months resulted in complete reproductive failure (Aulerich and Ringer, 1977). A subsequent study indicated that the mink was

more sensitive to both Aroclor 1016 and 1242 than the genetically similar ferret (Bleavins et al., 1980). The reason for the apparent large variation in species sensitivity to PCBs has not been elucidated but cannot be fully accounted for by a difference in the rate of PCB metabolism.

Although many responses reported in animals exposed to PCBs are highly species-specific, there is a similarity in the toxic responses produced by PCBs and other halogenated aromatic hydrocarbons (HAHs) (Poland and Knutson, 1982).

Hepatic System -- As with acute and subchronic exposure to PCBs, chronic exposure commonly produced hepatoxicity. Several reviews mentioned at the beginning of this section are recommended for a general discussion of PCB-induced hepatotoxicity. Hepatomegaly has been reported in male rats and to a lesser extent in the livers of female rats exposed to 20, 100, 500 or 1000 ppm Aroclor 1260 in the diet or 20, 100 or 500 ppm Aroclor 1254 in the diet for 8 months (Kimbrough et al., 1972). Grossly, the livers were soft and discolored and nodules were seen in a number of livers. Sprague-Dawley rats fed diets containing 100 ppm Aroclors 1248, 1254 or 1262 in the diet for 52 weeks were reported to have livers as much as 3 times the normal size. In addition, focal degeneration and necrosis were evident (Allen et al., 1976; Allen and Abrahamson, 1979). Discoloration from congestion was also noted in livers of rats treated with 75 or 150 ppm of Aroclor 1242 in the diet for 36 weeks (Jonsson et al., 1981).

Two studies using rats, one employing dietary incorporation of Aroclor 1260 or 1254 (Kimbrough et al., 1972) and the other Aroclor 1242 (Jonsson et al., 1981) described the microscopic and ultramicroscopic changes that

occurred with dietary exposure to these commercial PCB mixtures. Both studies confirmed that the enlargement in livers of PCB-exposed animals was in part due to hypertrophy of individual hepatocytes. Other findings included focal necrosis, hepatocytic regeneration, mitoses and multinucleate cells, cytoplasmic vacuolization and iron deposits in perivascular macrophages, Kupfer cells and hepatocytes.

Ito et al. (1973) exposed male dd mice for 32 weeks to 100, 250 or 500 ppm Kanechlor 300, 400 or 500 in the diet. They reported hepatomegaly, oval cell formation and bile duct proliferation with increasing incidence apparently related to the degree of chlorination of the Kanechlors. Amyloidosis occurred with a greater incidence when smaller doses of less heavily chlorinated Kanechlors were fed in the diet. Kimbrough and Linder (1974) reported hepatopathology in male BALB/CJ mice fed 300 ppm Aroclor 1254 in the diet for 6 or 11 months but made no mention of amyloidosis.

Exposure of animals to pure PCB congeners elicited similar signs of hepatotoxicity. The 2,4,5,2',4',5'-hexa-CB; 2,4,6,2',4',6'-hexa-CB; 2,3,5,2',3',5'-hexa-CB and 2,3,4,5,2',3',4',5'-octa-CB congeners produced alterations in rat livers detectable by conventional histopathological procedures; these included hepatocytes with vacuolated cytoplasm and focal necrosis (Hansell and Ecobichon, 1974).

Hypertrophy of individual hepatocytes has been shown to be due to an increase in the smooth endoplasmic reticulum (Allen and Abrahamson, 1973; Hansell and Ecobichon, 1974; Jonsson et al., 1981; Kimbrough et al., 1972). Lipid-containing vacuoles were also observed in these studies with concentrically arranged membranes surrounding the lipid-containing vacuoles.

Koller and Zinkl (1973) administered 0 or 300 mg Aroclor 1221, 1242 or 1254 by stomach tube, once weekly for 14 weeks, to New Zealand White rabbits and reported similar ultrastructural alterations in livers from Aroclor 1254-treated and to a lesser extent from Aroclor 1242-treated animals. Livers from Aroclor 1221-exposed animals did not differ from those of controls.

Porphyria, evidenced by UV fluorescence, occurred frequently in PCB-treated rats. Fluorescence was most pronounced in the liver, with occasional fluorescence of bone, serum or urine or both (Kimbrough et al., 1972).

Persistent biochemical alterations including elevations of N-demethylase and nitroreductase activities and reduction in glucose 6-phosphatase activity were demonstrated in male Sprague-Dawley rats exposed to diets containing up to 100 ppm Aroclor 1248, 1254 or 1262 for 1 year (Allen and Abrahamson, 1979). Partial (70%) hepatectomy was performed periodically throughout the exposure. At the end of 52 weeks, animals were put on a control diet for 13 weeks before being killed for final examination. Ratios of hepatic protein/DNA and RNA/DNA remained elevated throughout the 52-week exposure period to any of the three Aroclors tested. Levels returned to near control levels by 65 weeks. Liver lipids increased throughout the 52-week exposure period but had decreased toward control levels after 13 weeks on a control diet. Aroclor 1248 produced the highest lipid content following 52 weeks of exposure, while exposure to Aroclor 1262 had the least effect.

Skin -- Skin lesions are a species-specific symptom of PCB exposure. Skin lesions were first reported in mice exposed to 1 mg of an unidentified "CPB" (Nishizumi, 1970). The lesions were eczematous and ulcerative about

the head and muzzle. Another study (Bell, 1983) reported initial lesions consisting of thickening and erythema of the pinna in mice exposed to a 200 ppm Aroclor 1254 diet.

As in the case with acute exposure to PCBs, monkeys exhibit skin lesions when exposed chronically to PCBs. Male rhesus monkeys exposed to 3, 10, 30 or 100 ppm Aroclor 1242 diet for up to 245 days exhibited palpebral swelling and erythema. Similar toxicity was observed in male and female rhesus monkeys fed diets containing 2.5 and 5.0 ppm Aroclor 1248 for 18 months. The females had more severe skin lesions such as alopecia and chloracne (Barsotti et al. 1976).

These same lesions, however, were produced in animals exposed to PCBs devoid of PCDFs. When rhesus monkeys were exposed to 3,3',4,4'-tetra-CB (PCDFs <1 ppm) in the diet, large-scale mortality followed. The skin lesions consisted of squamous metaplasia of sebaceous glands and cystic formation in the eyelids. Nail beds were hyperkeratotic leading to shortening or loss of nails (McNulty et al., 1980). In this same report, other monkeys exposed to 3,3',4,4'-tetra-CB were allowed to recover from PCB exposure for 76 days at which time the animals exhibited normal regeneration of the skin. In a study with cynomolgus monkeys, Hori et al. (1982) found that PCBs devoid of PCDFs did not produce typical skin lesions.

Immune System -- Chronic studies using rhesus monkeys have indicated an apparent effect of PCBs on the immune system. McNulty et al. (1980) found that 3,3',4,4'-tetra-CB produced thymus regression. In another non-human primate study utilizing PCB mixtures with or without PCDFs, Hori et al. (1982) found that all compounds tested depressed immunocompetency as

evaluated by titers developed against sheep red blood cells. There appeared to be no difference in immunotoxicity between PCBs with or without PCDFs.

Gastrointestinal System -- Rats exposed to 0, 25, 50 or 100 ppm of Aroclor 1254 of diet for 2 years developed intestinal metaplasia or adenocarcinoma at the incidences of 3/47 (6.4%), 5/48 (10.4%), 8/48 (16.7%) and 17/48 (35.4%) in the control, low-, medium- and high-dose groups, respectively. There appeared to be no differences in incidence between sexes, and incidence appeared to be dose-related (Morgan et al. 1981).

Nonhuman primates were susceptible to gastric lesions upon PCB exposure. Becker et al. (1979) exposed male rhesus monkeys to 0, 3, 10, 30 or 100 ppm Aroclor 1242 in the diet for up to 245 days. Gastric lesions in exposed subjects included hypertrophic gastric mucosa consisting of elongated hyperplastic glands with destruction of parietal and zymogenic cells. In a study employing 3,3',4,4'-tetra-CB in the diet of rhesus monkeys, McNulty et al. (1980) found at necropsy that the gastric mucosa was severely disrupted, and large mucus cysts and loss of parietal and zymogenic cells developed.

Urinary System -- Few reports exist on the urinary system as a target for PCB toxicity. One study in nonhuman primates that employed PCB mixtures with or without PCDFs found that kidneys were enlarged because of dilated renal tubules. The tubular epithelial cells were enlarged and vacuolated. Kidney tubules contained casts. These microscopic changes were present in all experimental animals studied (Hori et al., 1982).

Other Observations -- A large number of observations and determinations have been recorded in animals exposed to PCBs including gross changes,

alterations in body weights, hematologic, urinalysis and clinical chemistry parameters.

Male Sprague-Dawley rats were fed diets containing 100 ppm Aroclor 1248, 1254 or 1262 for 52 weeks (Allen et al., 1976; Allen and Abrahamson, 1979). Observations continued for 13 weeks following treatment. Appearance, appetite and weight gain were normal in all rats throughout the study. Hematologic parameters and serum protein and albumin/globulin ratio remained normal. Total serum lipids and cholesterol remained elevated throughout the 52-week experimental period and serum cholesterol remained elevated 13 weeks after exposure was terminated. Serum triglycerides from all treatment groups ranged from 20-40% below control levels.

Morgan et al. (1981) reported on the toxicity of feeding diets containing Aroclor 1254 to male and female F344 rats for 2 years. Rats were exposed to levels of 0, 25, 50 or 100 ppm of Aroclor 1254 in the diet. Mortality occurred in 8 and 33, 17 and 21, 42 and 17, and 54 and 29% of the males and females, respectively, in these respective groups. Mean final body weight of all treatment groups were lower than the body weight of the control groups with the exception of the low-dose group males. Beginning at 72 weeks for the high-dose group and 104 weeks for the medium-dose group rats, alopecia, facial edema, exophthalamos, cyanosis and amber colored urine became noticeable.

Long-term studies in nonhuman primates have provided information on a variety of alterations in clinical parameters. Clinical determinations in rhesus monkeys (Barsotti et al., 1976; Allen et al., 1979a; Barsotti, 1981) after 16 months of exposure to 2.5 and 5.0 ppm Aroclor 1248 in the diet

indicated normal hematograms. Six months of exposure resulted in reduced total lipids, elevated SGPT, and a shift in the albumin/globulin ratio. Serum cholesterol and triglyceride were also reduced after 12 months of exposure.

In another laboratory, Becker et al. (1979) exposed six male rhesus monkeys to levels of 3, 10, 30 or 100 ppm Aroclor 1242 in the diet for up to 245 days. Mortality of all monkeys exposed to $\geq$10 ppm in the diet occurred by day 245. All exposed monkeys exhibited palpebral swelling and erythema, weight loss, rough hair coat, reduced hemoglobin and leukocytosis.

McNulty et al. (1980) also investigated the relative toxicity of 3,4,3',4'-tetra-CB; 2,5,2',5'-tetra-CB and Aroclor 1242. Groups of male rhesus monkeys were exposed to 3 ppm of 3,4,3',4'-tetra-CB or 2,5,2',5'-tetra-CB in the diet or a diet without added PCBs (control). The dosages were reduced to 1 ppm and again to 0.3 ppm because of rapidly developing morbidity in the three monkeys exposed to 3,4,3',4'-tetra-CB. Mortality of two subjects in this group had occurred by day 62. Mortality of the third subject on day 215 terminated this experiment. Necropsy revealed severe emaciation with a total absence of adipose tissue. In a second experiment, groups of young male rhesus monkeys were given diets containing 1 ppm of 3,4,3',4'-tetra-CB, 2,5,2',5'-tetra-CB or Aroclor 1242 in the diet (McNulty et al., 1980). At the end of the 133-day trial, all control animals, those exposed to 2,5,2',5'-tetra-CB and those exposed to Aroclor 1242 appeared normal. One of the 3,3',4,4'-tetra-CB subjects died on day 33. Findings upon necropsy examination of 3,3',4,4'-tetra-CB-treated animals were similar to those reported above.

As mentioned previously, minks are sensitive to PCB intoxication. A study (Aulerich and Ringer, 1977) indicated that 2 ppm of Aroclor 1016, 1221, 1242 or 1254 in the diet had no effect on body weight gain, hemoglobin or hematocrit in mink. In another study (Bleavins et al., 1980) Aroclor 1242 and 1016 were fed to male and female pastel mink for ~8 months. Aroclor 1242 was fed at 0, 5, 10, 20 or 40 ppm in the diet and Aroclor 1016 was fed at 0 or 20 ppm in the diet. Aroclor 1242 at levels $\geq$20 ppm in the diet resulted in 100% mortality. Aroclor 1016 at 20 ppm in the diet resulted in mortality of 25% (3/12) of the females exposed. Necropsy revealed emaciation, an almost complete absence of body fat and gastric ulceration.

Koller and Zinkl (1973) administered 300 ppm Aroclor 1221, 1242 or 1254 by stomach tube, once weekly for 14 weeks, to New Zealand White rabbits. Blood samples were taken every 2 weeks from the five males and five females in each group for determination of blood chemistries. After 2 weeks SGPT and SGOT levels were elevated in Aroclor 1254-treated males. Females developed elevated SGPT and SGOT at 4 and 8 weeks, respectively, after exposure. Aroclor 1221 failed to elevate serum levels of either enzyme throughout the study. Total serum protein, protein fraction levels and BUN did not differ from controls during the study. No hematologic differences were noted between control and treatment individuals. Serum cholesterol was elevated significantly in males treated with Aroclor 1254 as early as 7 weeks.

Developmental and Reproductive Toxicology

Developmental toxicology is 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, and 4) functional deficiency. Several studies have investigated the developmental toxicity of various mixtures of PCBs. Little evidence of gross abnormalities was found. Most reports deal with the developmental toxicity potential of PCBs and their ability to interfere with expected levels of fertility in many mammalian species. The more pertinent studies are summarized in Table V-10.

Rats. One of the first reports (Villeneuve et al., 1971a) examined the developmental toxicity of Aroclor 1254 in the Wistar rat. Aroclor 1254 in corn oil at doses up to 100 mg/kg bw/day was administered on days 6-15 of pregnancy to Wistar rats. This exposure failed to produce maternal toxicity (evaluated as body weight gain, fertility and litter size) or developmental toxicity (evaluated as number of litters, average litter size, resorption sites/litter, average litter weight, skeletal or visceral abnormalities). Exposure did result in a significant decrease in average fetal weight, but since the total number of fetuses per litter was increased, there was no effect on total litter weight.

Spencer (1982) investigated the reproductive toxicity of Aroclor 1254 in female Sprague-Dawley rats. Rats were fed diets containing Aroclor 1254 at levels up to 900 ppm diet from days 6-15 of pregnancy. Dietary levels of 300, 600 or 900 ppm led to a significant reduction in daily feed intake. No effect on the number of implantations was observed on days 6 or 12 of pregnancy. Average fetal weight/litter at birth was significantly reduced at dietary levels of $\geq$100 ppm. Fetal toxicity in the 600 and 900 ppm dosage groups precluded this measurement. Percentage live births/litter was

TABLE V-10

Summary: Teratogenetic, Feletoxic and Reproductive Effects of Orally Administered PCBs

Species/ Strain	Source of PCBs	Dosage Level and Duration of Treatment	Maternal Response	Progeny Response	Reference
Rabbit	Aroclor 1254	0, 1.0, 10.0, 12.5, 25.0, 50 mg/kg bw/day on days 1-28 of pregnancy; 25 mg/kg bw/day on days 7-28 of pregnancy	Dose ≥25 mg/kg bw: maternal death, weight loss; ≥10.0 mg/kg bw: hepatomegaly; 25 mg/kg bw days 7-28: reduced rate of gain.	≥12.5 mg/kg bw/day: fetal death, resorptions, abortions.	Villeneuve et al., 1971a
Rat/Wistar	Aroclor 1254	0, 6.25, 12.5, 25.0, 50, 100 mg/kg bw/day on days 6-15 of gestation	None reported	None reported	
Rat/Sherman	Aroclor 1254	0, 1, 5, 20, 100, 500 ppm diet from 3-4 weeks of age to termination of 1- or 2-generation study	None reported	F_{1a} 500 ppm: reduced litter size; 100 ppm: reduced litter size; F_{1b} 100 ppm: reduced survival at weaning; 20, 100 ppm: reduced litter size; F_{2a} 100 ppm: reduced litter size and reduced survival at weaning; 20 ppm: reduced litter size; F_{2b} 20, 100 ppm: reduced litter size.	Linder et al., 1974
	Aroclor 1260	0, 5, 20, 100, 500 ppm diet from 3-4 weeks of age to termination of 1- or 2-generation study	None reported	F_{1a} 500 ppm: reduced litter size and reduced survival at weaning. F_{1b} 500 ppm: reduced litter size.	
	Aroclor 1254	0, 10, 50, 100 mg/kg bw/day dosed on days 7-15 of gestation	None reported	F_1 100 mg/kg bw/day: reduced litter size.	
Rat/Sprague-Dawley	Aroclor 1254	0, 25, 50, 100, 200, 300, 600, 900 ppm diet/day on days 6-15 of pregnancy	≥600 ppm: partial anorexia and weight loss.	≥300 ppm: fetal death at delivery. ≥100 ppm: reduced litter weight.	Spencer, 1982
Mice/CD_1	3,3',4,4',5,5'-hexa-CB	0, 0.1, 1.0, 2.0, 4.0, 8, 16 mg/kg bw/day, on days 6-15 of gestation	≥8 mg/kg bw/day: reduced rate of gain, lethargy, vaginal bleeding.	≥4 mg/kg bw/day: fetal mortality, resorptions; ≥2 mg/kg bw/day: increased incidence of cleft palate; ≥4 mg/kg bw/day: increased incidence of hydronephrosis; ≥1 mg/kg bw/day: increased incidence of cream colored liver; ≥1 mg/kg bw/day: increased incidence of undersized renal papillae.	Marks et al., 1981

TABLE V-10 (cont.)

Species/ Strain	Source of PCBs	Dosage Level and Duration of Treatment	Maternal Response	Progeny Response	Reference
Mice/ddY	Kanechlor 500	0, 1.0, 2.0, 3.0, 4.0, 5.0 mg/day/mouse; days 6-15 of gestation	Mortality in high dose	≥1.0 mg/mouse/day: cleft palate	Watanabe and Sugahara, 1981
Rat/Sprague-Dawley	Aroclor 1221 1242 or 1260	0 or 30 mg/kg bw, days 14-20 of pregnancy	Not examined	None	Gellert and Wilson, 1979
Rat/Wistar	Aroclor 1254	0 or 70 mg/l drinking water (6.4 mg/kg bw/day); 9 weeks	Mortality at 7 weeks	Fetal resorption	Baker et al., 1977
Mice/NMRI	Clophen A60	0 or 0.025 mg/mouse/day; 72-76 days	Lengthened estrus cycle	Fetal resorption	Orberg and Kihlstrom, 1973
Mice/CBA	2,2',4,4', 5,5'-hexa-CB	0 or 0.5 mg/mouse/day; days 5-11 or 5-18 of pregnancy	Hepatomegaly	None	Mattson et al., 1981
Rabbit	Aroclor 1221, Aroclor 1254	0, 1.0 or 10 mg/kg bw; first 28 days of pregnancy	None	None	Villeneuve et al., 1971b
Mink	Aroclor 1242	0-40 ppm diet; 8 months	≥10 ppm: significantly increasing mortality; ≥5 ppm: complete reproductive failure;	Increased mortality; decreased litter biomass	Bleavins et al., 1980
	Aroclor 1016	20 ppm diet; 8 months	25% mortality, reduced fertility.	Increased preweaning mortality, decreased body weight by 4 weeks.	
Monkey/ cynamolgus	Aroclor 1254	0, 100 or 400 µg/kg bw/day; continuous starting at 60 days of pregnancy	Fingernail loss; immunologic incompetence.	Fetal mortality; immunologic incompetence.	Truelove et al., 1982
Monkey/ rhesus	Aroclor 1248	0, 2.5 or 5.0 ppm diet; 18 months starting 6 months pregestational	Facial edema, cachexia, hair loss, hyperpigmentation, lengthened menstrual cycle	Fetal death, infant facial and eyelid edema, loss of facial hair, facial hyperpigmentation, gastric hyperplasia and vomiting, lymphoid degeneration, hypocellular bone marrow, fatty liver.	Barsotti, et al., 1976; Allen et al., 1979b, 1980
	Aroclor 1248	0, 2.5 or 5.0 ppm diet; off treatment for 1 year	Persistent chloracne	Reduced neonatal weight, hyperpigmentation, hyperactivity, retarded learning ability.	
	Aroclor 1016	0.025, 0.25 or 1.0 ppm diet	None	Infants born to the 1.0 ppm diet group were significantly smaller than controls.	Barsotti and van Miller, 1984

NA - Not applicable

significantly depressed at the 300 and 600 ppm level. There were no live deliveries at the 900 ppm level.

Baker et al. (1977) administered Aroclor 1254 to Wistar rats through drinking water to study the toxicokinetics of this commercial mixture of PCBs. Drinking water contained 70 ppm Aroclor 1254 emulsified with 0.15% Tween 80. Daily Aroclor 1254 consumption was 6.4 mg/kg bw for 9 weeks. Fetal resorption and increased maternal mortality were reported during this exposure.

An extensive study on reproductive effects of PCBs in rats was performed by Linder et al. (1974). In a 1-generation study, pathogen-free female Sherman rats were fed diets containing either Aroclor 1254 or Aroclor 1260 at levels of 100 or 500 ppm starting at 3-4 weeks of age and terminating exposure after the weaning of the F_{1b} litter. Aroclor 1254 at the 500 ppm level resulted in reduction of the number of litters born, and litter size was reduced. Aroclor 1260 appeared to cause a significant decrease in litter size in F_{1a} rats at the 500 ppm level. F_{1a} survival was also significantly reduced at the 500 ppm level. Aroclor 1260 failed to produce evidence of reproductive toxicity at a level of 100 ppm. Similarly, in the 2-generation study in which pathogen-free male and female Sherman rats were fed diet levels of up to 100 ppm Aroclor 1254 or Aroclor 1260, F_{2a} litters were reduced in size at the 100 ppm level of Aroclor 1254. F_{2b} litters in Aroclor 1254-treated animals were reduced in size at both the 20 and 100 ppm level. These reductions in litter size were significant at the 0.5% confidence level with the exception of the F_{2a} 20 ppm litter, which was significant at the 5.0% confidence level. Ability of animals to wean was reduced by Aroclor 1254 in both studies. Survival at weaning was significantly

reduced in F_{1b} litters at the 100 ppm treatment level in the 1-generation study. F_{2a} litters also experienced a significant decrease in percent survival at weaning at the 100 ppm treatment level. Dietary levels of 5 ppm Aroclor 1250 and 100 ppm Aroclor 1260 had no effect on reproduction in rats exposed through two generations.

In a postimplantation exposure study, 100-day-old stock rats were treated with Aroclor 1254 in peanut oil by gavage at levels of 0, 10, 50 and 100 mg/kg bw/day on days 7-15 of gestation. A reduction in pup survival was observed only at the 100 mg/kg bw/day level (Linder et al., 1974). Reproduction and pup survival were not affected following exposure to 10 or 50 mg Aroclor 1254/kg bw/day or 100 mg Aroclor 1260/kg bw/day on days 7-15 of gestation (Linder et al., 1974).

Using a low level (30 mg/kg bw) of Aroclors 1221, 1242 and 1260 and various chlorinated pesticides, Gellert and Wilson (1979) investigated the effects of prenatal exposure on reproductive functions of F_1 males and females. Speculating that PCBs may have estrogenic qualities that could be expected to interfere with subsequent reproduction, Sprague-Dawley rats were treated by gavage on days 14-20 of pregnancy. At 6 months of age, F_1 females were examined for persistent vaginal estrus and anovulation, indicators of prenatal exposure to estrogenic substances. Although no significant increase in these parameters was found, the incidence seemed to be inversely related to the degree of chlorine saturation of the Aroclor tested. Male F_1 rats at 6 months of age were mated with known stock breeder females and then necropsied. The offspring were normal, and examination of adrenals, testes, epididymus and ventral prostates of the F_1 males revealed no lesions.

Dikshith et al. (1975) examined the effects of Aroclor 1254 on rat testis. Mature male Sprague-Dawley rats were treated by gavage for 7 consecutive days with 50 mg/kg bw Aroclor 1254. At the end of the 7-day treatment period, the rats were allowed a period of recovery. No signs of morbidity were observed. Necropsy examinations were performed on three rats from each group on days 1, 7, 15 and 30 days of recovery. The body weight of rats examined by necropsy at 30 days was significantly reduced compared with controls. Testicular and epididymal size and histological features were normal in treated rats with the exception of a slight increase in testicular interestitial tissue with increased acid phosphatase activity.

One recent study on early postnatally-administered PCBs to male rats was undertaken to determine effects on their subsequent reproductive performance (Sager, 1983). Dams received 8, 32 or 64 mg/kg bw Aroclor 1254 by gavage on days 1-3, 5, 7 and 9 of lactation. At 130 days of age, 3 or 4 males from each treatment group were randomly selected for observation of mating behavior and fertility. PCB treatment at all levels tested interfered with mating behavior and fertility as evidenced by a reduction in numbers of females impregnated. Testicular weights were significantly increased in the 32 and 64 mg/kg groups. Testiculomegaly and subnormal development of accessory sex glands was taken as evidence that PCBs administered in the early postnatal period interfered with circulating levels of androgens.

Mice. A commercial mixture of PCBs, Kanechlor 500, induced formation of cleft palate in mice (Watanabe and Sugahara, 1981). Pregnant ddY strain mice were injected daily on days 6 through 15 of gestation with PCB at 1.0, 2.0, 3.0, 4.0 or 5.0 mg/mouse/day. Maternal mortality was increased in the highest dose group. The incidence of cleft palate in live fetuses was

significant and dose-related. Additional experiments were performed on two other groups of mice. One group received 5 mg/day Kanechlor 500 on days 6-10 of gestation (25 mg total), and one group received 10 doses of 5 mg Kanechlor 500/day before mating (50 mg total) and an additional 10 daily doses during days 6-15 of gestation (100 mg total). Severe mortality was observed in the 100 mg group. The occurrence of resorbed or dead fetuses and cleft palate increased with the amount of PCBs received. Five instances of brachydactyly, four of syndactyly and one of cleft lip in PCB-treated fetuses were reported (Watanabe and Sugahara, 1981).

Using a low chlorinated PCB, 2,2'-di-CB, Torok (1978) reported an increase in fetal resorption and retardation of fetal development. Pregnant NMRI mice were dosed orally with 375, 500 or 750 mg/kg of this PCB daily for 3 days following appearance of the vaginal plug. Similarly, another group was dosed orally with 250 mg PCB/kg/day for 6 days. The author reported that the 375 mg/kg dose increased fetal resorptions and that doses $\geq$500 mg/kg caused delayed implantations.

In a study designed to evaluate the effects of the specific PCB isomer, 2,2',4,4',5,5'-hexa-CB, Mattson et al. (1981) were unable to increase fetal resorption in CBA mice mated syngeneically to CBA or allogenically to NMRI male mice. Animals were treated with hexa-CB at the level of 0.5 mg daily for either days 5-11 or 5-18 of gestation. All mice were killed the day following the last treatment except for five control and five treated mice from the second trial, which were allowed to give birth to permit examination of offspring. Treatment with PCB at this level did not result in significant increase in fetal resorption.

Marks et al. (1981) clearly demonstrated gross malformations in CD-1 mice resulting from treatment with 3,3',4,4',5,5'-hexa-CB. This isomer was chosen for these studies because it was found to be more toxic and more readily bioaccumulated, and to have a more pronounced toxic effect on liver, thymus and spleen than other isomers tested (Biocca et al., 1981). Pregnant mice were administered 0.1-16 mg/kg bw/day hexa-CB by gavage from day 6 through day 15 of gestation. Although no deaths occurred in exposed dams, lethargy and vaginal bleeding were observed in dams exposed to $\geq$8 mg/kg bw/day. Dams in the 8 and 16 mg/kg bw/day groups suffered a significant reduction in weight gain. Average numbers of live fetuses/dam in the PCB groups demonstrated a significant reduction in a dose-related fashion at doses $\geq$4 mg/kg bw/day. The average number of implants was reduced in the 8 mg/kg bw/day group and fetal resorptions were increased in the 8 and 16 mg/kg bw/day groups. A significant dose-related increase in the incidence of cleft palate occurred in groups dosed at $\geq$2 mg/kg bw/day. An increased incidence of hydronephrosis was also found to be dose-related.

In an effort to demonstrate that PCBs may induce microsomal hydroxylating enzymes that catalyze the breakdown of steroid hormones, Orberg and Kihlstrom (1973) investigated the ability of Clophen A-60 to affect reproduction in mice. NMRI strain sexually mature female mice were fed 0.025 mg/day Clophen A-60 for 72-76 days. Clophen A-60 was found to lengthen the estrus cycle and to reduce the rate of nidation.

Orberg (1977) failed to demonstrate any effect of pre- and postnatally-administered PCBs on the reproductive performance of mice. 2,4',5-Tri-CB or 2,2',4,4',5,5'-hexa-CB was fed at levels of 0.05 mg/day from day 5 of pregnancy to weaning at postpartum day 22 to NMRI strain mice. The males and

females exposed to PCBs *in utero* and by lactation were mated. No significant differences were found in conception rates and litter size.

Orberg (1978) further investigated the effects of 2,4',5-tri-CB and 2,2',4,4',5,5'-hexa-CB fed at two different dosage levels on reproduction in mice. NMRI mice were treated with 0.05 or 0.5 mg tri-CB/day, or 0.05 or 0.50 mg hexa-CB/day beginning on the first day of vaginal plug and continuing for 6 consecutive days. Animals exposed to the high dose of either congener had significantly lower frequencies of implanted ova than the control females. Furthermore, the exposures at both levels had no significant effect on the frequency of pregnancies or the number of implanted ova/pregnant female.

Rabbits. Villeneuve et al. (1971a) found rabbits to be sensitive to Aroclor 1254. In three separate experiments, pregnant rabbits were treated with Aroclor 1254 at levels up to 50.0 mg/kg bw/day by gavage for the first 28 days of pregnancy. An additional group of four rabbits was treated with 25 mg/kg bw on days 7-28 of pregnancy. Dead fetuses, resorptions and abortions were increased for groups treated with Aroclor 1254 at doses $\geq$12.5 mg/kg bw/day for the first 28 days of pregnancy. Rabbits treated on days 7-28 of pregnancy with 25.0 mg/kg bw experienced fewer dead fetuses, resorptions and abortions than what were observed in 50.0 mg/kg bw/day exposed animals. Two fetuses from dams in the 12.5 mg/kg bw/day group had subcutaneous cephalic hemorrhages and cranial asymmetry. Maternal toxicity was manifested as death of two dams in the 50.0 mg/kg bw group and one dam in the 25.0 mg/kg bw group. Other evidence of maternal toxicity consisted of weight loss in dams receiving 25 or 50 mg/kg bw and hepatomegaly in dams

receiving 10, 25 or 50 mg/kg bw. Dams treated with 25 mg/kg bw on days 7-28 of pregnancy exhibited decreased weight gain and hepatomegaly.

Another study from the same laboratory (Villeneuve et al., 1971b) reported no evidence of developmental toxicity to orally administered Aroclor 1221 or 1254 at levels of 1.0 or 10 mg/kg bw in rabbits. Mature dams were exposed to the Aroclors for the first 28 days of pregnancy. Nidation, fetal growth and development, litter size and placentation were all similar to control rabbits.

Other Species. Mink are especially sensitive to the toxic effects of PCBs. Feeding mink levels of Aroclor 1242 as low as 10 ppm in the diet for 8 months resulted in high mortality, while exposure at 5 ppm caused 25% mortality and reduced fertility of females (Bleavins et al., 1980). By 4 weeks, litters experienced increased mortality and decreased litter biomass. No teratogenicity was observed. Reproductive toxicity was related to feto-toxicity rather than interference with ovulation or nidation because fetal resorptions were found at all stages of gestation. In another experiment, dietary exposure to Aroclor 1016 at 20 ppm produced 25% mortality and reduced reproductive function (Bleavins et al., 1980). Kits nursed by dams fed Aroclor 1016 at 20 ppm had significantly lower body weight at 4 weeks of age. In addition, higher kit mortality between birth and 4 weeks of age was also noted.

Aulerich and Ringer (1977) exposed mink to Aroclor 1254 in the diet at a level of 2 ppm (see Table V-9). They observed a reduction in reproductive function with no apparent maternal toxicity. In another experiment, dietary

exposure to Aroclor 1016 at 2.0 ppm for 10 months had no efect on reproductive parameters, kit growth, and adult and kit mortality.

A comparison of the developmental toxic effects of Clophen A-50 and 2,2',4,4',5,5'-hexa-CB in guinea pigs was performed by Brunstroem et al. (1982) in three separate trials. In the first trial, groups of pregnant Dunkin Harley guinea pigs were exposed to Clophen A-50 at 2.2 mg/day for days 16-60 of gestation. Exposed animals received a total dose of 100 mg. In the second trial, groups of guinea pigs were exposed to a total dose of 25 mg hexa-CB distributed over days 16-60 of gestation. In the third trial, guinea pigs were exposed to a total of 100 mg hexa-CB over days 22-60 of gestation. All dams were unaffected by treatment. Significant numbers of abortions and dead fetuses were found in the Clophen A-50 group. No abortions occurred in the other treatment or control groups. According to the authors, the hexa-CB used in these trials contained <0.5 mg/kg PCDFs. They suggested that PCBs other than hexa-CB or possibly PCDFs or other contaminants in Clophen A-50 accounted for the developmental toxicity in guinea pigs.

Hansen et al. (1975) investigated the effects of PCBs on swine reproduction. Sows of mixed breeding were fed rations containing 0 or 20 ppm Aroclor 1242 throughout gestation and nursing. This study indicates that exposure to Aroclor 1242 apparently reduces the number of live pigs delivered/litter.

Two laboratories reported studies on PCB toxicity in nonhuman primates. Truelove et al. (1982) dosed 60-day pregnant cynomolgus monkeys with Aroclor

1254 at 100 or 400 µg/kg bw/day continuously until a termination of pregnancy. Monkeys dosed at the 100 µg/kg bw/day level delivered term, stillborn infants. The monkey dosed at the 400 µg/kg bw/day level delivered a live infant that subsequently succumbed at 139 days of age to pneumonia. Maternal toxicity was evidenced as fingernail loss and impaired immunocompetence as evaluated by titer developed to tetanus toxoid and sheep erythrocytes.

A longer-term and more intensive study examined the effects of Aroclor 1248 on reproduction in rhesus monkeys (Barsotti et al., 1976; Allen et al., 1979b, 1980). Aroclor 1248 was fed to groups of eight mature female monkeys weighing ~5.6 kg at levels of 2.5 or 5.0 ppm in the diet for ~18 months starting 6 months before breeding to untreated males. On the basis of food intake, the total Aroclor 1248 intake was calculated to be 270±25 and 498±50 mg for the 2.5 and 5.0 ppm diet groups, respectively. Analysis of this batch of Aroclor 1248 revealed ~1.7 ppm PCDFs. This would have provided 4.4 and 8.7 µg PCDFs/kg in the 2.5 and 5.0 ppm Aroclor 1248 diets, respectively. Treated females experienced weight loss and lengthened menstrual cycles accompanied by altered levels of progesterone and estradiol. Conceptions were normal for both groups. Monkeys receiving 2.5 mg/kg delivered five live infants and experienced three early abortions or fetal resorptions, and only one monkey receiving 5.0 mg/kg delivered a live infant. Adult females exhibited signs of toxicity. Live infants had reduced birth weights and, after 2 months of nursing, exhibited facial edema, hyperpigmentation and hair loss and palpebral edema and acneform lesions more severely than their mothers. Within the first year, 3 of these 6 infants had died.

Removing treated monkeys from treatment for 1 year allowed them to recover body weight and permitted facial lesions to heal. Menstrual cycles had returned to normal. These monkeys were then rebred to control males. No problems in conceptions were encountered. Full-term live infants weighed less than infants born to control animals. After nursing for 4 months, infants from previously exposed mothers developed focal areas of hyperpigmentation.

Three surviving infant monkeys from the first study (Barsotti and Allen, 1975; Allen and Barsotti, 1976; Allen et al., 1980) were subjected to locomotor activity and learning ability tests from 6-24 months of age (Bowman and Heironomus, 1981). These animals were infants of dams exposed to diets containing 2.5 ppm Aroclor 1248 for at least 6 months before breeding, through gestation and 3 months of nursing. All PCB-exposed infant monkeys exhibited hyperactivity and retarded learning ability when compared with offspring (4) of control females. Hyperactivity continued to increase with increasing age. These same three PCB-exposed monkeys and 3/4 control monkeys were retested for hyperactivity at 44 months of age. At this time the three PCB-exposed monkeys showed significant hypoactivity when compared with the controls.

After the original females had been removed from Aroclor 1248-containing diets for periods of 6-18 months, they were rebred (Bowman and Heironomus, 1981). No further exposure to PCBs was allowed. Infants from these females also showed hyperactivity when subjected to testing at 12 months of age.

In another study (Allen et al., 1979b), exposure of eight female monkeys to 0.5 or 1.0 ppm of Aroclor 1248 in the diet 3 times weekly for 7 months resulted in total intakes of ~8 or 16 ppm of Aroclor 1248 (see Table V-8). These animals showed no irregularities of menstrual cycle or alterations in serum estradiol or progesterone, and had normal fertility when bred. This exposure produced some fetal loss, infant birth weights were reduced and nursing infants developed focal areas of hyperpigmentation.

Subsequently, 24 adult female monkeys were exposed to diets containing 0.025, 0.25 or 1.0 ppm Aroclor 1016 (Barsotti and van Miller, 1984). After consuming the PCB diets for 6 months, the animals were bred in the 7th month of the experiment. Animals continued consuming PCB diets throughout gestation and 4 months of nursing. The author reported observing no abnormalities of clinical, gross or reproductive parameters. Infants from females exposed to 1.0 ppm diet exhibited significantly ($\leq$0.01) reduced birth weight.

Mutagenicity

Mutagenicity studies of PCBs in Salmonella typhimurium are summarized in Table V-11. PCBs have not shown positive results by themselves, but evidence exists that metabolic activation may result in mutagenic metabolites which may have potential activity with DNA resulting in mutagenic responses (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Suto, 1978; Stalnicki et al., 1979; Wang et al., 1979; Morales and Mathews, 1979). Evidence also exists that the position of the chlorines on the biphenyl ring influences potential mutagenicity. In addition, it appears that S-9 fractions from different strains may cause different results.

TABLE V-11

Summary of Mutagenicity Assays of PCBs in Salmonella typhimurium

Type of Assay	Type of S-9 Activation	PCB Source	PCB Dose	Results for S. typhimurium strains					Reference
				TA1537	TA1539	TA98	TA100	TA1538	
Plate	none	Aroclor 1254	0.5-500 µl/plate	-	-	-	-	NA	Schoeny et al., 1979
Plate	noninduced	Aroclor 1254	0.5-500 µl/plate	-	-	-	-	NA	
Plate	Aroclor 1254 induced	Aroclor 1254	0.5-500 µl/plate	-	-	-	-	NA	
Plate	none	4-mono-CB	1-200 µg/plate	NR[b]	NR	NR	NR		Schoeny, 1982
	PCB[a]			-	NA	NA	NA		
	PB[a]			NA	-	NA	NA		
	3MC[a]			NA	NA	NA	-		
	corn oil[a]			NA	NA	-	NA		
	PCB[c]	3,4,3',4'-tetra-CB	5-200 µg/plate	NA	NA	NA	-		
	3MC[c]			NA	NA	-	NA		
	PCB[c]	2,4,2',4'-tetra-CB	5-200 µg/plate	NA	NA	NA	-		
	3MC[c]			NA	NA	-	NA		
	PCB[c]	2,4,6,2',4',6'-hexa-CB	5-200 µg/plate	NA	NA	NA	-		
	3MC[c]			NA	NA	-	NA		
Plate	rabbit liver microsomal preparations	4-mono-CB	10-200 µg/plate	NR	NR	NR	NR	++	Wyndham et al., 1976
		Aroclor 1221		NR	NR	NR	NR	+	
		2,2',5,5'-tetra-CB		NR	NR	NR	NR	-	
		Aroclor 1254		NR	NR	NR	NR	-	

[a]At 0, 10, 50 and 100 µl/plate

[b]The text did not indicate what strains were tested for mutagenicity without S-9; results were reported as negative.

[c]50 µl/plate

NA = Not applicable; NR = Not reported

+ = Positive; - = Negative

Schoeny et al. (1979) tested Aroclor 1254 for mutagenicity at eight concentrations ranging from 0.5-500 µl/plate in strains TA1535, TA1537, TA98 and TA100 of S. typhimurium. Aroclor 1254 alone, activated by S-9 hepatic fractions from untreated or Aroclor 1254-induced Sprague-Dawley rats, failed to manifest mutagenicity. Subsequently, this same laboratory, recognizing the heterogeneous nature of commercial Aroclor, conducted a study of the mutagenicity of four separate PCB congeners (Schoeny, 1982). Using materials of 99% purity, eight doses of 4-chlorobiphenyl and five doses each of 3,4,3',4'-tetra-CB; 2,4,2',4'-tetra-CB and 2,4,6,2',4',6'-hexa-CB were tested for mutagenicity in S. typhimurium (see Table V-11). Mutagenicity was not demonstrated with any of these PCBs with or without the addition of hepatic S-9 fractions. In this same study, the author likewise failed to demonstrate mutagenicity of dibenzofuran or various polychlorinated dibenzofurans, often considered common contaminants of PCBs.

Wyndham et al. (1976) have attempted to relate degree of mutagenicity to degree of chlorine substitutions on the biphenyl moiety. Using levels of 10, 50, 100 or 200 µg/plate of the 4-mono-CB, Aroclor 1221 [average chlorine content 1.15 (2 Cl/molecule)], 2,2',5,5'-tetra-CB (4 Cl/molecule) or Aroclor 1254 (average 4.96 Cl/molecule), these authors demonstrated a pronounced mutagenicity (>2000 mutant colonies/plate) of 4-mono-CB compared with the more highly chlorinated PCBs.

Heddle and Bruce (1977) examined the mutagenicity of Aroclor 1254 in a group of 61 potential mutagens and compared mutagenicity with the production of cytogenetic effects in mice. Aroclor 1254 was found to be nonmutagenic in the S. typhimurium bioassay and negative in both cytogenetic evaluations.

S. typhimurium strains TA1535, TA1537, TA98 and TA100 both with and without S-9 activation were tested.

One study examined dominant lethality in rats attributable to PCBs (Green et al., 1975b). Mature, random-bred Osborne-Mendel male rats were given Aroclor 1242 by gavage in single doses of 625, 1250 or 2500 mg/kg bw. In a second study, Aroclor 1254 was given by gavage at levels of 75, 150 or 300 mg/kg/day. Treatment groups consisted of 100 animals each; negative controls were treated by gavage with corn oil alone and positive controls were treated with a known mutagen, TEM. Significant fetal loss occurred only in TEM-treated positive controls. Similarly, a feeding trial with Aroclor 1254 at levels of 25 or 100 ppm diet for 70 days produced no significant fetal loss. Positive controls were not used.

Nilsson and Ramel (1974) reported briefly on a study to determine clastogenic effects of PCBs in Drosophila melanogaster carrying sex-linked color markers. Clophen A-30 (30% chlorine) or Clophen A-50 (50% chlorine) was incorporated into the media at 250 or 200 mg/ℓ, respectively. Treatment was given during the entire larval period or during 1 week to adult flies. These levels were chosen on the basis of the results of preliminary trials using levels of 62.5, 125, 250 or 500 mg/ℓ substrate of Clophen A-30 or levels of 25, 50, 200 mg/ℓ substrate of Clophen A-50 to determine the toxic effects of these PCB products on larval development. Differences between the Clophen A-30 group and its controls were not significant. The incidence of XO males in the Clophen A-50 treated group was significantly ($p<0.01$) greater than its controls. A larger Clophen A-50 trial was therefore performed using 20 mg/ℓ substrate larval treatment of parental males.

These authors concluded that the products tested did not indicate clastogenic effects, but pointed out that these products differed from commercially available PCB products in that the impurities ordinarily present in commercial products were not present here.

A cytogenetic study of Aroclor in rats was performed by Green et al. (1975a). Aroclor 1242 was given orally in single doses of 1250, 2500 or 5000 mg/kg bw or at multiple doses of 500 mg/kg/day for 4 days to groups of eight male, random-bred Osborne-Mendel rats. Aroclor 1254 was orally administered at 75, 150 or 300 mg/kg/days for 5 consecutive days to groups of eight rats. The animals were sacrificed 24 hours after the last dose was given. Aroclor 1242, the more toxic product, did not produce cytogenetic damage in spermatogonia or in cells from the bone marrow. Aroclor 1254 did not show any evidence of cytogenetic damage in the bone marrow cells. The effects of this product on spermatogonia were not evaluated. The number of bone marrow cells observed in mitosis appeared to be depressed ($p<0.05$) in the Aroclor 1254 groups at the mid (150 mg/kg/day) and high (300 mg/kg/day) treatment levels. Mitosis in bone marrow cells of Aroclor 1242-treated groups did not appear to be depressed, but spermatogonial mitosis did appear to be reduced in the 500 mg/kg/day for 4 days ($p<0.01$) and the 5000 mg/kg ($p<0.05$) groups. A later cytogenetic study of bone marrow and spermatogonia in male Holtzman rats (Garthoff et al., 1977) confirmed the negative findings of the previously cited study.

Likewise, Dikshith et al. (1975), in a more comprehensive study of the effects of orally administered Aroclor 1254 on rat testis, found no significant evidence of chromosomal aberration caused by PCBs. Aroclor 1254 was

administered by gavage to 18 mature, male Sprague-Dawley rats at the level of 50 mg/kg bw. The configurations of chromosomes appeared similar in both the control and treatment groups. A few chromosomal abnormalities were observed but appeared to be sporadic.

Watanabe et al. (1981) investigated the mutagenicity of PCBs alone and in combination with DMN or MNNG. Kanechlor 500 was dissolved in corn oil or 95% ethanol and administered at the rate of 100 mg/kg bw/day for 6 days to 5-week-old male ddY mice weighing 25-30 g. DMN (25 mg/kg bw) or MNNG (100 mg/kg bw) in aqueous solutions were administered 24 hours after the last dose of PCB. The number of cells containing micronuclei observed in PCE/1000 cells counted from bone marrow taken 30 hours after DMN or MNNG was given was considered the endpoint of mutagenicity. These results of PCB treatment did not differ significantly from controls (DMN or MNNG) and the authors concluded that Kanechlor 500 had "almost no effect" and no synergistic or addition effect with DMN or MNNG. PCBs alone or in combination with MNNG failed to increase numbers of micronucleated polychromatic erythrocytes.

Cytogenetic examinations were performed on 3- to 6-day-old ring dove (Streptopchia risoria) embryos from ring doves fed Aroclor 1254 for an extended length of time at the level of 10 ppm in the diet (Peakall et al., 1972). Negative and positive controls (X-ray treated) were used. Chromosomal aberrations were recorded for the largest eight chromosome pairs occurring in metaphases of allantois and limb bud cells. The authors considered the results indicative of a possible clastogenic action of PCBs in dove embryos.

Carcinogenesis

PCBs have been tested for carcinogenicity in rats and in mice by incorporation of particular commercial PCB preparations into the diet. Eight separate PCB feeding studies and one study of topical application to the skin are considered. Studies in which the PCB preparations were administered in conjunction with other agents are also discussed in this section.

Carcinogenicity. The feeding studies demonstrate the carcinogenicity of some commercial PCB preparations although it is not known which of the PCB congeners in such preparations, or which of their metabolites, are responsible for the carcinogenicity demonstrated by the tests. The liver appears to be the primary target organ that exhibits a tumorigenic and carcinogenic response to PCB exposure. The studies reviewed had, in varying degrees, shortcomings that modify the meaning of the results and the contribution the study made to the overall assessment of PCB carcinogenicity.

Rat Studies -- PCBs have produced a variety of oncogenic effects in the rat liver. Historically, adenofibrosis was the first hepatic lesion to be described in animals chronically exposed to PCB mixtures (Kimbrough et al., 1972; Kimura and Baba, 1973). Kimura and Baba (1973) studied Kanechlor 400 incorporated into the test diet of male and female Donryu rats fed diets initially at 38.5 ppm and increased periodically to an upper limit of 616 ppm to keep pace with body weight gain. The upper level resulted in severe body weight loss and was accordingly reduced to 462 ppm for the remainder of the trial. The duration of the study ranged from 159-538 days for the different animals, but there were two intervals of 4 weeks each during which

the Kanechlor feeding was stopped so that the total feeding of Kanechlor was ~400 days. Female rats consumed 700-1500 mg and male rats consumed 450-1800 mg Kanchelor 400 by the end of the trial.

Adenomatous nodules in the liver were found in 6/10 female rats that had consumed >1200 mg of the Kanechlor 400. The females that had received <1200 mg Kanechlor 400 and the males had no such lesions. All treated animals, of both sexes, showed fatty degeneration of the liver.

It is important in evaluating this study to consider the weight data reported by the investigators. These data were sufficient to determine that the treated animals showed weight losses of >20%. Such decreases in weight gain may indicate that the MTD was exceeded. Table V-12 shows the percentage of weight gain for various doses and for controls.

It is clear from these weight data that in all cases the treated animals received doses of Kanechlor 400 that exceeded the MTD as judged by current criteria. Toxic symptoms not only included failure of rats to gain weight at a normal rate but 80% of the females and 10% of the males showed depilation; 70% of the females and 60% of the males had lung abscesses; 30% of the females and 10% of the males had intracranial abscesses; fatty degeneration of the adrenal was also found in treated animals. These lesions were not reported in the control animals.

In summary, the study was too short and the exposure level too high to provide a good experimental basis for the determination of the carcinogenic potential of the PCB preparation used.

TABLE V-12

Change in Rat Body Weight Following Chronic Exposure to Kanechlor 400*

PCB in Diet (ppm)	No. Animals	Initial Weight (g)	Final Weight (g)	Percent Difference
		MALES		
450	1	199	309	+55
900	1	192	273	+42
>1200	8	210	259	+23
Control	5	205	462	+125
		FEMALES		
700	1	158	137	-13
1100	3	160	162	0
>1200	6	196	196	0
Control	5	196	323	+65

*Source: Kimura and Baba, 1973

Ito et al. (1974) have investigated Kanechlors 300, 400 and 500 in male Wistar rats by administration of 100, 500 or 1000 ppm of each of the test preparations in the diet for 28 weeks to 1 year. The initial weights for each group and their respective weight gains are given in Table V-13.

The figures indicate that the weight gain was inversely related to the dose of Kanechlor used for the 40- and 52-week exposure groups. In all cases (for 52-week exposure) the average percentage weight gain was below that observed with controls, but only marginally below controls for the lowest dose groups of 100 ppm. The weight figures indicate that at 100 ppm for 52 weeks, Kanechlors 300 and 500 did not produce a toxic manifestation represented in weight loss. At the 100 ppm level the liver weights were (expressed as percentage of body weight) 2.4% for controls, 2.9% for the Kanechlor 300 and 3.7% for the Kanechlor 500. There was no amyloidosis, cholangiofibrosis or fibrosis at 100 ppm for these two Kanechlors. At higher doses oval cell proliferation, bile duct proliferation, fatty changes and cellular hypertrophy were seen. Since the 100 ppm level did not seem to produce other toxic manifestations the finding of hepatic nodular hyperplasia, which the investigators considered to be preneoplastic, in 3/25 animals treated with Kanechlor 500 and 1/22 animals treated with Kanechlor 300 is noteworthy. The study does not provide data on the progression of preneoplastic to neoplastic effects since it was terminated after 52 weeks.

In the case of Kanechlor 400, all three of the dietary levels produced apparent abnormal weight changes, as an increase of 23% in weight over the 40-week period is lower than would be expected. At the highest dose, 3/10 of the animals showed nodular hyperplasia and at 100 ppm 2/16 cases of

TABLE V-13

Change in Rat Body Weight Following Chronic Exposure to Several Kanechlor Formulations*

Product	ppm	Initial Weight Gain Average	Percent Increased Average	No. Animals
		52-Week Exposure Cases		
K-500	1000	126	129	13
	500	123	207	16
	100	124	300	25
K-300	1000	128	228	15
	500	135	239	19
	100	125	304	22
Control	0	130	325	18
		40-Week Exposure Cases		
K-400	1000	163	23	10
	100	175	129	16
Control	0	NA	NA	NA
		28-Week Exposure Cases		
K-400	500	188	53	8
Control	0	NA	NA	NA

*Source: Ito et al., 1974

NA = Not applicable

nodular hyperplasia appeared. These findings were made at 40 weeks. This study was flawed with respect to short duration and small number of animals used in the experiment.

While the investigators considered hepatic nodular hyperplasia to represent preneoplastic lesions and, therefore, the tumorigenicity of the Kanechlors, the experiment falls short of demonstrating tumorigenicity. The study is inconclusive because of the short duration, small starting numbers of animals in each group and still smaller numbers of animals at risk. However, the nodular hyperplasia that appeared as early as 40 weeks precludes adding this study to a negative finding. In addition, effectiveness of the Kanechlor in producing tumors was not a function of the level of chlorination of the PCBs in the mixture.

Kimbrough et al. (1975) was the first to report that Aroclor 1260 unequivocally produced hepatocellular carcinomas in female Sherman rats when 100 ppm dietary level was administered for 21 months (630 days). In this study, complete histopathology on all major organs was performed on 200 treated rats. There was a slight but statistically significant decrease in weight gain after 3 months in the treated group. The difference in weight gain was not large enough to consider the dose level to have exceeded the MTD. There were no other definite dose-related signs of toxicity.

Hepatocellular carcinoma was found in only 0.58% of the controls (1/173) and in 14% (26/184) of the treated animals. In addition, while 78% (144/184) of the treated animals developed neoplastic liver nodules, no control animals did. All in all, there was <1% incidence of neoplastic liver lesions in controls as compared with 92% (170/184) in treated animals.

Although only a single dose was selected and only female animals employed, the study demonstrates hepatocarcinogenicity of Aroclor 1260 in female Sherman rats. Kimbrough et al. (1972), using 10 animals of each sex given each of three doses (100, 500 and 1000 ppm) of Aroclors 1260 and 1254, did not produce either neoplastic nodules or hepatocellular carcinoma in this same strain of rat when the study ran less than a year. In this preliminary study Aroclor 1254 produced adenofibrosis in 10/10 male rats. This finding suggests that hepatocellular carcinoma results when the dose is low enough to permit the study to be run for a sufficient length of time without interfering toxicity. The 14% incidence of hepatocellular carcinomas in the large experiment also explains why it would be unlikely to have detected this cancer in experiments run on a small number of animals: 14% of 24 animals would be 3-4 animals and hepatocellular carcinoma would only have appeared after about a year. Experiments that reduced the number below 24 before the earliest time to tumor would not be expected to yield a detectable carcinoma incidence.

Even though this experiment is probably an adequate animal study to use for risk assessment, it also has a problem in that a mixture of compounds was tumorigenic. The active ingredient(s) in the mixture is most likely limited to a few of the molecular species. A tumor yield of 14%, which is due to the presence of a molecular species that constitutes only a fraction of the composition of the administered material, would be considered potent.

The carcinogenicity of PCBs was investigated in a study sponsored by NCI (1978). Groups of 24 F344 rats of each sex were fed diets containing

Aroclor 1254 at 25, 50 or 100 ppm for 104-105 weeks. Proliferative lesions in the liver were not found in controls but were found in the treated animals as shown in Table V-14.

The data indicate a dose-related nodular hyperplasia in both sexes and three cases of hepatocellular carcinomas among treated males at the 100 ppm dose. Although the incidence of hepatocellular carcinomas was not statistically significant, it is important to consider the following points.

In a preliminary study using 10 Sherman rats of each sex, Kimbrough et al. (1972) did not produce hepatocellular carcinomas with doses of 100, 500 or 1000 ppm administered for a duration of less than a year. But in the other study (Kimbrough et al., 1975), which lasted 2 years, female Sherman rats had a 14% incidence of hepatocellular carcinoma as a result of treatment with 100 ppm Aroclor 1260. In the NCI (1978) study the incidence of hepatocellular carcinomas in males at 100 ppm group was 3/24; only 20 animals survived. Since incidence is more precisely expressed as the ratio of the number of animals with tumor/number of animals at risk, the figure is probably closer to 2/20 or 10%. In either case, the incidence of 8-10%, or even 14%, as was found in the Kimbrough et al. (1975) study, would not be statistically significant with group sizes of 24 animals. The test was simply not sensitive enough to detect statistically significant differences at this level of potency. The lack of statistical significance in the NCI study has to be understood in terms of the highly insensitive nature of the assay used. A system that employed 24 animals per group would require a true difference in incidence between controls and treated groups of 35% in order to have a 90% chance of being significant at the $p=0.05$ level. A 90% chance of finding a significant difference at the $p=0.05$ level when the

TABLE V-14

Proliferative Lesions of the Liver in Fischer Rats Fed Aroclor 1254*

	Males		Females	
	Hepatocellular Carcinomas	Hyperplastic Nodules	Hepatocellular Carcinomas	Hyperplastic Nodules
Controls	0	0	0	0
25 ppm	0	5/24	0	6/24
50 ppm	1/24	8/24	1/24	9/22
100 ppm	3/24	12/24	2/24	17/24

*Source: NCI, 1978

difference between controls and treated incidence is of the order of 9%, as it is in this study, would require 117 animals each for control and treated groups. It is therefore a question of biological significance, rather than statistical significance, in determining whether an 8-10% cancer yield represents a positive finding. Although this yield could not be used to demonstrate the carcinogenicity of the test agent, it is indeed consistent with the 14% yield obtained by Kimbrough et al. (1975) and lends support to that finding.

The NCI (1978) data were re-examined by Morgan et al. (1981) with respect to gastric adenocarcinomas that occurred in the rats. All 191 stomachs of rats from that study were available for further sectioning and examination. Sectioning at the pyloric junction revealed "lesions" upon gross examination in 3/47, 5/48, 8/48 and 17/48 of rats fed diets containing 0, 25, 50 or 100 ppm Aroclor 1254, respectively. There did not seem to be sex-related differences in the incidence of these lesions. Histologically, adenocarcinomas were found in 1, 3 and 2 of the stomachs identified as having lesions in the 25, 50 or 100 mg/kg Aroclor 1254 diet groups, respectively. None were detected in the controls. Remaining lesions were identified as "metaplasia," the significance of which was not stated. Determining the occurrence of gastric adenocarcinoma in control rats to be <2% (0/47), the authors calculated the likelihood of six carcinomas occurring in the stomachs of 144 treated animals to be <5% if occurrence was random. Morgan et al. (1981) concluded that Aroclor 1254 may produce adenocarcinomas in the stomachs of rats.

A recent paper reevaluating this same study (Ward, 1985), cites a dose-related depression of body weight gain for both sexes and a decrease in survival for male rats. Increased incidence of gastric intestinal metaplasia and adenocarcinoma was confirmed. Hepatocellular adenomas, carcinomas and eosinophilic and vacuolated hepatocellular foci were usually found in dosed rats only and in these animals their numbers were significantly increased. The conclusion of the author was that the appearance of the potentially preneoplastic lesions and tumors in the liver and stomach of the PCB-treated rats did not occur spontaneously.

The hepatocarcinogenic effect of dietary administration of 100 ppm Clophen A-30 or A-60 (Authors stated that Clophen A-30 and A-60 did not contain chlorinated dibenzofurans) for 832 days was tested in male weanling rats (Schaeffer et al., 1984). Twenty-one percent of the Clophen A-60 treated animals that died in the first 800 days experienced hepatocellular carcinoma, while only 2% of the animals died with similar lesions in the Clophen A-60. Preneoplastic lesions were first observed after day 500 followed by tumors after 700 days on the PCB diets. An increase in neoplastic nodules and hepatocellular carcinomas was observed to increase with time. Statistically significant increases of hepatocellular carcinomas were observed in male rats fed Clophen A-60. However, rat fed with Clophen A-30, had a statistically significant increases of neoplastic nodules or/and hepatocellular carcinomas together. Interestingly, the total mortality rate and the incidence of thymoma and inflammation of the genital/urinary tract in the experimental animals was reduced when compared with the controls. This protective effect has been seen in other halogenated aromatic hydrocarbons (Kociba et al., 1979).

Two points should be made in regard to this study. First, the study was done only in males, and females appear to be more sensitive to the tumorigenic effects of PCBs (Kimura and Baba, 1973; Norback and Weltman, 1985). Second, the study was conducted in PCB mixtures that are apparently free of dibenzofurans.

In the Norback and Weltman (1985) study, Sprague-Dawley rats were selected because of low incidence of spontaneous liver tumors. Male and female weaning Sprague-Dawley rats initially weighing 100 g were divided into two groups of 70 males and 70 females. They were fed basal diet (Purina rat chow, St. Louis, MO) mixed with corn oil (a PCB mixture), Aroclor 1260 (Monsanto Chemical Co., St. Louis, MO) at a concentration of 100 ppm for 16 months and 50 ppm for an additional 8 months, followed by a control diet for 5 months. A control group received a basal diet with added corn oil for 18 months and basal diet alone for an additional 5 months. Both groups received water ad libitum. Sequential morphological changes were evaluated to determine the progress of liver lesions. The medial and left lobes of the liver of 10 etherized rats (2 male controls, 2 female controls, 3 male PCB-treated, and 3 female PCB-treated rats for each time period) were removed at 1, 3, 6, 9, 12, 15 and 18 months. Partial hepatectomy was performed once per animals in these groups. At 24 months similar groups and at 29 months all remaining animals were sacrificed. Throughout the study moribund rats were sacrificed. At death all rats were necropsied. Selected organs were prepared for microscopy. The sequential morphologic changes were evaluated throughout the study and results are presented in Table V-15. In the PCB-exposed group the following hepatocellular lesions were developed in sequence: centrolobular cell hypertrophy at 1 month, foci of cell alteration at 3 months, areas at 6 months, neoplastic

TABLE V-15

Progression of Preneoplastic and Neoplastic Hepatocellular Lesions in Male and Female Sprague-Dawley Rats Exposed to Aroclor 1260[a,b]

Lesion	Number of Livers with Lesions of Each Three Sampled															
	1 Month		3 Months		6 Months		9 Months		12 Months		15 Months		18 Months		24 Months	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Focus	0	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Area	0	0	0	0	1	0	2	1	0	3	1	3	0	3	3	2
Neoplastic nodule	0	0	0	0	0	0	0	0	0	1	0	3	0	3	1	1
Trabecular carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	2
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

[a]Source: Norback and Weltman, 1985

[b]These lesions were not present in sequentially sampled control liver.

nodules at 12 months, trabecular carcinoma at 15 months, and adenocarcinoma at 24 months. These lesions were not present in sequentially sampled control liver. In addition, simple and cystic chloangioma at 18 and 23 months, respectively, and adenofibrosis at 22 months were present. With the exception of hepatocyte hypertrophy and adenofibrosis, all lesions contained cells that were positive for gamma glutamyl transpeptidase activity. The percentage of animals with hepatocellular neoplasms occurring in animals that survived for 18 months or longer are presented in Table V-16. Females had the highest incidence of hepatocellular neoplasm; >95% developed tumors (45/47, 1/49, $p<10^{-*}$). Few males developed tumors (7/46, 0/32, p=0.02), neoplastic nodules were present in 11% and hepatocellular carcinoma in 4%. Only one hepatocellular neoplasm occurred in female control rat and there was none in male control animals. The incidence of hepatocellular neoplasms in females was strikingly greater than in males. In conclusion, Norback and Weltman (1985) found positive hepatocellular carcinomas in male and female Sprague-Dawley rats fed Aroclor 1260 in the diet for a period of 2 years.

Mouse Studies -- Kanechlors 500, 400 and 300 were administered to male dd mice for 32 weeks at dietary levels of 500, 250 and 100 ppm (Nagasaki et al., 1972). The nine different experimental groups had 12 animals/group and the controls had 6 animals/group. All of the animals survived the entire 32 weeks of the test and there was no apparent weight difference between control and treated animals although liver weight as a percentage of body weight was elevated in all treated groups.

In the first report of this experiment by Nagasaki et al. (1972) results were given as grossly observable nodular hyperplasia in 7/12 (58.3%) of the animals fed 500 ppm of the Kanechlor 500. Microscopic examination revealed

TABLE V-16

Incidence of Hepatocellular Neoplasms in Male and Female Sprague-Dawley Rats Exposed to Aroclor 1260[a]

Number of Animals	% Incidence in Treated Animals[b]		% Incidence in Control Animals[b]	
	M	F	M	F
	46[c]	47[d]	32[c]	49[e]
Trabecular carcinoma[f]	4 (2)	40 (19)	0	0
Adenocarcinoma[f,g]	0	51 (24)	0	0
Neoplastic nodule only	11 (5)	4 (2)	0	2 (1)
Negative	85 (39)	4 (2)	100	98 (48)

[a]Source: Norback and Weltman, 1985

[b]Figures in parentheses denote number of animals that survived ≥18 months.

[c]Includes 8 animals that had received a partial hepatectomy during the first 18 months.

[d]Includes 7 animals that had received a partial hepatectomy during the first 18 months.

[e]Includes 10 animals that had received a partial hepatectomy during the first 18 months.

[f]Animals containing neoplastic nodules plus carcinoma were only included in the carcinoma category.

[g]Animals with trabecular carcinoma and adenocarcinoma were only placed in adenocarcinoma category.

5/12 (41.7%) of these animals had hepatomas. There were no tumors in the control animals or other test groups. In a more detailed report of this experiment Ito et al. (1973) gave the yield of liver tumors as 7/12 (58.3%) liver nodules and 5/12 (41.7%) hepatocellular carcinomas.

This study demonstrates that Kanechlor 500 is capable of producing hepatocellular carcinoma in male dd mice when given at 500 ppm in the diet. The carcinogenic potential of the Kanechlor 500 is qualitatively demonstrated but quantitative application of the information obtained requires some considerations not immediately obvious from a statement of exposure level and tumor yield. The composition of the Kanechlor 500 was given as 55% penta-CB, 26.5% tetra-CB, 12.6% hexa-CB and 5.0% di-CB. Kanechlor products contain other halogenated aromatic hydrocarbons including PCDFs. The consequences of these contaminants on the process of carcinogenicity of the PCB mixture is unknown; however, the findings of hepatocellular carcinoma in the study of Clophens A-30 and 50 (devoid of PCDFs) in rodents (Shaeffer et al. 1984) indicates that PCB mixtures alone are capable of producing hepatocellular carcinoma in rodents.

Kimbrough and Linder (1974) fed Aroclor 1254 to two groups of male BALB/CJ mice. There were 50 mice per treatment group and two groups of control mice (50 animals each). The treated groups each received 300 ppm of Aroclor 1254 in their diet; one group received the PCB-containing diet for 11 months and the second group received the PCB-containing diet for 6 months followed by a 5-month recovery period in which they received a normal diet. There were a large number of deaths in the experiment that were a result of

animal housing conditions and were not due to toxicity. At the end of [illegible] months the surviving animals were sacrificed. Only those animals that showed gross abnormalities were examined microscopically.

The livers of animals treated with the Aroclor congeners were enlarged. Control animals had liver weights that were, on the average, 6% of their body weight. Treated animals had livers that were 7.5% of their body weight for the group exposed for 6 months and 25.5% of their body weight for those exposed for 11 months. Livers of treated animals showed multiple abnormalities including abnormal porphyrin metabolism as indicated by UV fluorescence. Adenofibrosis, a possible premalignant lesion, was also found among treated mice.

At the end of 11 months the surviving animals were sacrificed and the incidence of tumors of the liver was noted: 0/34 and 0/24 for the two control groups and 9/22 (40.1%) (10 hepatomas in 9 animals) in the 11-month exposure group; 1/24 (4%) of the animals in the 6-month exposure group had hepatomas. It should be noted that the BALB/CJ mouse has a low spontaneous incidence of hepatoma strain.

The experiment provides positive evidence that Aroclor 1254 is capable of producing a 40% incidence of hepatoma in male BALB/CJ mice at a dosage level of 50 mg/kg/day given for 11 months. The study provides confirmatory evidence of the carcinogenicity of commercial PCB mixtures in mice. In this case 300 ppm Aroclor 1254 produced a 40% incidence of hepatoma in male BALB/CJ mice in 44 weeks, and in the Ito et al. (1973) study Kanechlor 500 at 500 ppm in the diet for 32 weeks produced a 40% incidence of hepatocellular carcinoma in male dd mice.

The mouse studies, therefore, give strong evidence of PCB carcinogenicity. Table V-17 summarizes the findings on the PCB feeding studies with respect to liver tumorigenicity and carcinogenicity.

Summary and Conclusions

Several animal bioassay studies were of adequate quality to assess the carcinogenic potentials of specific commercial PCB mixtures. The early bioassay studies of PCBs conducted by Kimura and Baba (1973), Ito et al. (1973) and Kimbrough and Linder (1974) were all inadequate to assess the carcinogenic potential of PCBs because of small group size or period of exposure extending for <1 year. In particular, the Ito et. al. (1973) study in which dd male mice fed Kanechlor 500 at 550 ppm for 32 weeks produced hepatocellular carcinomas. The study by Kimbrough and Linder (1974) in which 50 BALB/CJ male mice were fed diets containing 300 ppm Aroclor 1254 for 11 months was suggestive that Aroclor 1254 was producing a carcinogen effect in liver. Of the 22 animals surviving PCB treatment for 11 months, all had areas of adenofibrosis in the liver, and 7 had histologically identified heptomas. In a long-term study by Kimbrough et. al. (1975), Sherman strain female rats fed 100 ppm Aroclor 1260 in their diets for 21 months induced statistically significant increases of hepatocellular carcinomas (26/184) and neoplastic liver nodules (144/184). Only 1 of 173 control animals developed a carcinoma; no neo- plastic nodules were observed.

In the cancer bioassay (NCI, 1978) study, where 24 male and 24 female Fischer rats/group were fed diets containing 0, 25, 50 or 100 ppm Aroclor 1254, although dose-related increases in the nodular hyperplasia were observed, there was no statistically significant increases of neoplastic

TABLE V-17

Effects on Liver Tumorigenesis and Carcinogenesis: Feeding Studies Using Various Commercial PCB Preparations

Species/ Strain/Sex	Agent	Duration	Exposure (ppm)	No. Animals	Results and Comment	Reference
Rats/Sherman (F)	Aroclor 1260	90 weeks	100	200/group	Hepatocellular carcinoma 14% (26/184) compared with 0.58% (1/173) controls, 78% neoplastic nodules compared with 0 in controls, no other treatment-related toxicity, study well done but limited to single dose and to females: shows carcinogenicity in female rats of Aroclor 1260.	Kimbrough et al., 1975
Rats/Sprague-Dawley (M&F)	Aroclor 1260	29 months	100 for 16 months, 50 for 8 months, none for 5 months	70/group	95% hepatocellular tumors in female rats 45/47, 15% in male rats 7/46	Norback and Weltman, 1985
Rats/Fischer 344 (M&F)	Aroclor 1254	104-105 weeks	100 50	24/group	In males at 100 ppm, 8-10% hepatocellular carcinoma. Not statistically significant but study design would have required 35% or greater incidence for statistically significance. Results consistent with Kimbrough et al. (1975) and supports effect in males.	NCI, 1978
Rats/Donryu (M&F)	Kanechlor 400	22-77 weeks	38-462	10/group	Excessive toxicity, MTD exceeded, adenomatous nodules in females with total dose of 1200 mg or more; test too short, too few animals at risk, excessive toxicity. Test inadequate.	Kimura and Baba, 1973
Rats/Wistar (M)	Kanechlors 500 400 300	28-52 weeks	 1000 500 100	22-257/group	Nodular hyperplasia with Kanechlor 500 and Kanechlor 300, not statistically significant, duration of study too short, excessive toxicity. Test inadequate.	Ito et al., 1974
Mice/dd (M)	Kanechlors 500 400 300	32 weeks	 500 250 100	12/group	Hepatocellular carcinoma with Kanechlor 500 at 500 ppm 41.7% (5/12) and liver nodules in 58.3% (7/12), demonstrates carcinogenicity in male mice.	Ito et al., 1973

TABLE V-17 (cont.)

Species/ Strain/Sex	Agent	Duration	Exposure (ppm)	No. Animals	Results and Comment	Reference
Mice/BALB/CJ (M)	Aroclor 1254	1) 44 weeks 2) 24 weeks + 5 months recovery	300	50/group	Hepatoma 40.1% (9/22)*, none in controls in 44-week group	Kimbrough and Linder, 1974
Rat/Wistar (M)	Clophen A30	118-119 weeks	100	152/group	Statistically significant ($p<0.05$) increases of neoplastic nodules and hepatocellular carcinomas.	Schaeffer et al., 1984
	A60	118-119 weeks	100	141/group	Induced statistically significant ($p<0.05$) increases of hepatocellular carcinomas.	

*Animal deaths were not due to toxicity but to housing. Demonstrates tumorigenicity of Aroclor 1254 in mice.

lesions. In addition, adenocarcinomas were observed in stomach, jejunum or cecum in treated animals. Morgan et al. (1981), in a later review of tissue specimen (NCI, 1978) detected, three additional adenocarcinomas of the stomach at sites of alkaline phosphatase (AP) positive. The NCI (1978) and Morgan et al. (1981) results are especially important in light of the fact that the sample sizes used by NCI were unusually small.

Saeffer et al. (1984) tested Clohen A-30 and Clophen A-60 in Wistar male rats by long-term feeding over a period of 118-119 weeks. Clophen A-60 induced a statiscally significantly increased incidences of hepatocellular carcinomas in rats. However, Clophen A-30 induced statistically significant increased incidence of neoplastic nodules, carcinomas alone were not significant.

In a more recent study of Norback and Weltman (1985) where 70 male and 70 female Sprague-Dawley rats were fed a diet containing polychlorinate biphenyl mixture (Aroclor 1260, 100 ppm for 16 months and 50 ppm for an additional 8 months) for 2 years followed by a control diet for 5 months, Aroclor 1260 induced highly statistically significant increases of liver tumors in female rats (45/47 treated vs. control 1/48). In males, liver tumor incidences were statistically significant but less striking (7/46 treated vs. control 0/32). These results strongly support earlier hepatocellular tumor evidence in Sherman rats fed Aroclor 1260 in the Kimbrough et al. (1975) study. Polychlorinated biphenyl Aroclor 1260 induced significant hepatocellular carcinogenic effects in two rat studies (Kimbrough et al., 1975; Norback and Weltman, 1985). Kanechlor 500 induced statistically significant incidences of liver tumors in dd mice fed 550 ppm for 32 weeks.

Aroclor 1254 also produced carcinogenic effects in mice (BALB/CJ) and rats (Fischer 344), and results are dose-related but not statistically significant.

This level of carcinogenic evidence in rat and mice for some commercial PCBs (Aroclor 1260, Kanechlor 500 and Aroclor 1254) constitutes a "sufficient" level of carcinogenic evidence for PCBs in animals, using the EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986c). The multiple studies with Aroclor 1260 and one study with Clophen A-60 provides a sufficient animal cancer evidence. The bioassay results for Kanechlor 500, Arochlor 1254 and Clophen A-30, when viewed individually have only limited animal evidence; their not being multiple assays or species with clear statistical significance. Taken collectively however, along with an argument for a hypothesis that sturcture-activity-relationship provides a basis for recommending that PCB mixtures of any composition should be regarded as having the potential to be probable human carcinogens and thus in the weight-of-evidence category of Group B2. Obviously, the mixture components of the five commercial PCB preparations have common characteristic(s) which influence animal carcinogenicity. The decision to regard all PCB's as Group B2 compounds has uncertainty since with present knowledge it cannot be verified, albielt the decision is judged to a prudent public health choice at the present time.

The conclusion that PCBs are carcinogenic to rodents is reached by the International Agency for Research on Cancer (IARC). In its evaluation of the Carcinogen Risk of Chemicals to Humans, it is stated that "Kanechlor 500 and Aroclor 1254 are carcinogenic in mice, and Aroclor 1260 is carcinogenic in rats."

The question arises as to how to use these studies for risk assessment. It is difficult if not in fact impossible at present to scientifically to assess the toxic nature of the mixtures of the majority of the commercial preparations. The biological significance of this heterogeneity is that each of the isomers has its own particular toxicokinetic, metabolic and enzyme induction profile that is as much a function of the position of its chlorine substituents and the total number of chlorine substituents it contains. The extent to which any particular isomer contributes to or antagonizes the carcinogenic process is not known. The resultant carcinogenicity observed when the mixture is administered may be the work of one individual isomer, present in a small quantity, or of another isomer present to a larger extent, e.g., 25% of the composition of the mixture.

Other Related Studies

Promotional and Antipromotional Studies. Long-term exposure to mixed commercial PCBs has been associated with the development of hepatocarcinogenic effects in mice and rats. There is little evidence to suggest that pure PCBs are mutagenic or otherwise genotoxic. The role of PCB-induced liver microsomes as potent activators of many chemicals to mutagenic derivatives has been established. Recent evidence indicates that PCBs may also be protective against other carcinogenic events.

Promotion -- Ito et al. (1973) evaluated Kanechlor 500 in combination with BHC (Table V-18). These data show that when male dd mice were given Kanechlor 500 (250 ppm) in their diet for 32 weeks with or without one of the BHC compounds, they responded by yielding a higher incidence of hepatocellular carcinoma than when either the BHC or the Kanechlor was given alone.

TABLE V-18

Action of Kanechlor 500 and α-, β- or γ-Benzene Hexachloride*

Test Compound(s) (ppm)	Nodular Hyperplasia (%)	Hepatocellular Carcinoma (%)
α-BHC (250)	23/30 (76.7)	8/30 (26.7)
α-BHC (250) + PCB (250)	21/30 (80.8)	15/30 (57.6)
α-BHC (100)	0/26	0/26
α-BHC (100) + PCB (250)	8/25 (32.0)	1/25 (4.0)
α-BHC (50)	0/28	0/26
α-BHC (50) + PCB (250)	9/30 (30.0)	2/30 (6.7)
β-BHC (250)	0/26	0/26
β-BHC (250) + PCB (250)	16/29 (55.2)	6/29 (20.7)
β-BHC (100)	0/26	0/26
β-BHC (100) + PCB (250)	5/30 (16.7)	1/30 (3.3)
β-BHC (50)	0	0
β-BHC (50) + PCB (250)	0	0
γ-BHC (250)	0	0
γ-BHC (250) + PCB (250)	0	0
γ-BHC (100)	0	0
γ-BHC (100) + PCB (250)	0	0
γ-BHC (50)	0	0
γ-BHC (50) + PCB (250)	0	0
PCB (250)	0/20	0/20
Controls	0/20	0/20

*Source: Ito et al., 1973

In a brief communication of a short-term study, Ito et al. (1978) demonstrated the ability of PCB (mixture not stated or characterized) and other organic compounds to enhance nodular liver hyperplasia induced by feeding 2-FAA, a known liver cancer inducer, to rats. Male Fischer rats weighing 155 g were used. Two groups of control rats were fed diets containing 200 ppm 2-FAA for the 10-week trial; one group was partially hepatectomized in the third week of the study. There were two PCB treatment groups, both fed a diet containing 1000 ppm PCB for the entire 10-week experimental period, and one group partially hepatectomized in the third week of the study. PCB-fed rats had livers containing significantly ($p<0.05$) more hyperplastic nodules/10 cm^2 than control rats. Partial hepatectomy significantly ($p<0.001$) increased the incidence of nodular hyperplasia in the treatment groups.

The data show that while each agent alone produced some reduction in growth compared with controls, the combined effects were substantial. It is not possible to tell from this experiment whether the effects observed on tumor growth were due to a general systemic debilitation or whether the effects represent specific drug-related responses. The overall toxicity of the combined agents was not adjusted so that it would be no greater than the level of toxicity of each alone.

A report published by DiGiovanni et al. (1978) in which 100 µg of Aroclor 1254 was applied to the skin of CD-1 mice followed by repeated applications of the phorbol ester promoter, DMBA, stated that the data showed weak initiator activity with only 0.2 papillomas per mouse. The tumor-promoting activity of Aroclor 1254 was investigated in a study by Berry et al. (1978). Groups of 30 female CD-1 mice were used. The animals

were initiated with 0.2 g DMBA; 1 week later a positive control received 2 µg TPA and an experimental group received 100 µg Aroclor 1254. The promoter and the Aroclor applications were made twice weekly for 30 weeks. TPA promotion resulted in 92% of the animals with papillomas while none of the Aroclor 1254 treated animals developed tumors. It was concluded that at the dose of Aroclor 1254 used in the study of the preparation was not a skin tumor promoter in this system. General toxicity precluded use of larger doses in the experiment.

Antitumorigenic -- In the study of Makiura et al. (1974) Kanechlor 500, at 0.05% in the diet for 24 weeks, did not produce detectable tumors for the 24 weeks of the experiment. When this regimen was modified to add 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB), 2-FAA or diethylnitrosamine (DEN) at carcinogenic levels the combined effect was to reduce the incidence of tumors to zero. The tumor incidence in Sprague-Dawley rats with these three agents was 65% (3'-MeDAB), 54% (2-FAA) and 92% (DEN) liver tumors. In paired combination 3'-MeDAB and DEN produced 92% liver tumor incidence, which was reduced to 7.7% when PCB was also given. When 2-FAA and DEN were given together the tumor yield was 82% and in the experiment with these two agents plus PCB the yield was zero. The combined agents produced extreme toxicity as shown by the weight records, shown in Table V-19.

Nishizumi (1980) demonstrated the ability of placentally transferred PCBs to inhibit DEN-induced hepatomas. Groups of ten 10-week-old female Wistar rats were treated with 200 or 40 mg/kg bw/day Kanechlor 500 (Ito et al., 1973) by gavage on days 5, 10 and 15 of gestation. A group of 10 olive oil-treated rats served as vehicle controls. At 28 days of age, one F_1 offspring from each litter was killed for quantitation of liver PCBs.

TABLE V-19

Percent Weight Change in Kanechlor 500 Exposed Rats*

Weight Change %		Weight Change %		Weight Change %	
Control	+180	Control	+180	Control	+180
3-MeDAB	+150	PCB + 3-MeDAB	+107	PCB + 3-MeDAB + DEN	+65
DEN	+137	PCB + DEN	+73	PCB + 2-FAA + DEN	+52
2-FAA	+116	PCB + 2-FAA	+100		
PCB	+112				

*Source: Adapted from Makiura et al., 1974

MeDAB = 3'-methyl-4-dimethyl-aminoazobenzene; DEN = Diethylnitrosamine; 2-FAA = N-2-fluorenylacetamide

Remaining F_1 offspring were exposed to 50 mg/DEN in drinking water continuously for 5 weeks. At 16, 20 and 24 weeks after the start of exposure to DEN, for 6-8 F_1 rats from each treatment group, liver weight was recorded as percent of body weight and livers were sectioned and grossly examined for "tumors" >5 mm diameter.

Dams showed no signs of maternal toxicity during gestation or the following 6 months (Nishizumi, 1980). There was no evidence of fetal toxicity; average litter size was 6.2, 6.5 and 7.1 in the 400, 40 and 0 mg/kg groups, respectively. The 500 mg/kg groups experienced several losses of F_1 progeny (numbers not reported) and slight depression in rate of weight gain (body weight not given) before weaning.

The authors reported that almost all liver nodules >5 mm in diameter were histologically hepatocellular carcinomas and that some nodules >5 mm were neoplastic nodules (number not report) (Nishizumi, 1980). The number of nodules >5 mm diameter was therefore chosen as the endpoint indicator of hepatocarcinogenic potency. The result of this study are summarized in Table V-20. Liver weight as percent of F_1 body weight did not differ statistically between treatment and control groups. Although liver weight and average number of liver tumors/rat were reported as separate figures for male and female F_1 progeny, it was unclear if statistical analysis compared treatment animals with control animals by sex or collectively. Significant ($p<0.05$) reduction in number of liver tumors after 20 weeks occurred in both sexes of rats in the high-dose group, and in the low-dose males.

TABLE V-20

The Liver and Body Weight Ratio and the Number of Liver Tumors Produced in Offspring Rats Exposed to PCB through Their Dams and Treated with DEN after Weaning[a,b]

Group No.	Treatment		Sex of Offspring	Liver Weight as Percent Body Weight		Average Number of Liver Tumors (>5 mm)/Rat	
	Dam	Offspring		20 week	24 week	20 week	24 week
1	PCB 200/mg/kg 3 times	DEN 50 ppm 5 weeks	male	5.3 ± 0.1	6.4 ± 0.3	1.0 ± p04[c] (6,4,6)	2.0 ± 0.7[c] (14,5,7)
			female	5.1 ± 0.3	6.2 ± 0.2	0[c] (0,0,8)	0.4 ± 0.3 (3,2,8)
2	PCB 40/mg/kg 3 times	DEN 50 ppm 5 weeks	male	5.3 ± 0.2	6.3 ± 0.5	1.3 ± 0.4[c] (10,6,8)	2.8 ± 0.7 (17,6,6)
			female	5.5 ± 0.1	5.8 ± 0.2	0.6 ± 0.3 (5,4,8)	0.7 ± 0.4 (5,3,7)
3	None	DEN 50 ppm 5 weeks	male	6.0 ± 0.4	7.5 ± 0.6	3.0 ± 0.7 (21,6,7)	4.6 ± 0.7 (37,8,8)
			female	5.6 ± 0.3	6.1 ± 0.4	1.1 ± 0.4 (9,5,8)	1.4 ± 0.5 (10,4,7)

[a]Source: Nishizumi, 1980

[b]The data are expressed as means ± SE. Numbers in parentheses are the total number of liver tumors/group, the number of rats bearing liver tumors, and the number of rats sacrificed, in that order.

[c]Significant at the 5% level as compared with group 3.

At the 24-week examination, significant ($p<0.05$) reduction in tumor incidence occurred only in high-dose males (see Table V-18). The authors reported liver PCB values in 28-day-old F_1 individuals of 360+30, 18+7 and <1 ppm for high-dose, low-dose and control groups, respectively. They therefore suggested that placental transfer of PCBs protected rats from DEN-induced tumors.

A recent study was conducted to evaluate the mechanisms of PCB modulation of 2-FAA-induced carcinogenesis by 2-FAA. The results of the PCBs tested (2,2',4,4'-tetra-CB, 3,3,',4,4'-tetra-CB, 2,2',5,5'-tetra-CB 2,2',4,4',5,5'-hexa-CB and the Aroclor 1254) indicated that in spite of predictable inducer specific opposite influences of the different types of PCBs on cytocidal toxicity of 2-FAA, all PCBs similarly reduce nodule selection by 2-FAA initiated livers. This ability for reduced growth of nodules correlated with the ability of all PCBs to consistently enhance regenerations of liver mass, indicating antipromoting activities against mitoinhibitory carcinogens.

Cocarcinogenicity -- A study of the cocarcinogenic effect of PCB on 3-methylcholanthrene (3-MC) induced cervical cancer was performed in mice (Uchiyama et al., 1974). Adult virgin female dd mice were fed control diets or diets containing 10 ppm for 15 weeks or 100 ppm for 8 weeks of Kanechlor 400. Cotton thread impregnated with 3-MC was inserted into the cervix and through the anterior horn, and left in place for 4 weeks. PCB did not increase the incidence of cervical epithelial change induced by 3-MC, although effective numbers surviving the experiment were small (20 mice in each PCB-fed group). A simultaneous study using 10 ppm and 100 ppm DDT showed considerable tendency to induce cervical carcinoma, which may be

considered a positive control. In this trial using small numbers and a short experimental period, the authors found that PCB fed at these levels did not effectively enhance 3-MC-induced cervical carcinoma.

Considerations in Evaluating the Carcinogenic or Anticarcinogenic Potency of the PCB Preparations Tested. The manufacturing process for commercial PCB products, such as the Aroclors, yields products composed of a mixture of 20-60 different polychlorinated biphenyl molecules. Individual lots of Aroclors of the same average chlorine content differ greatly in both their components and amounts of each component. The extent to this variable composition can be seen from the analyses of three different Aroclor 1260 preparations carried out in different laboratories. One preparation contained 26 PCBs, another 48 different PCBs and the third was only partially analyzed. The number of isomers found in the preparations for each level of chlorination is shown in Table V-21.

In addition to the variability in polychlorinated biphenyls in the commercial PCB preparations, there are also a number of impurities in the products. Among the impurities are PCDFs, which are highly toxic and are under test for carcinogenicity.

Several points concerning the interpretation of carcinogenicity data, and risk assessments based on the data, hinge upon the recognition of the qualitative and quantitative variability among commercial preparations.

1. Data on purified isomers show that the toxic, metabolic and pharmacokinetic behavior of the different component molecules varies not only with the degree of chlorination, but also with the position of the chlorine atoms.

TABLE V-21

Number of Isomers at Each Chlorinated Level for Three Different Aroclor 1260 Preparations*

Chlorination Level	Albro, 1976	Sissons and Welti, 1971	Tas and Vos, 1971
Dichloro-	0	7	NR
Trichloro-	0	7	NR
Tetrachloro-	2	3	NR
Pentachloro-	8	7	NR
Hexachloro-	5	8	4
Heptachloro-	6	5	3
Octachloro-	3	7	NR
Nonochloro-	2	3	NR
Decachloro-	0	1	NR
Total	26	48	7

*Source: Adapted from NIOSH, 1977

NR = Not reported

2. Metabolism of purified isomers has been extensively studied. The hydroxylated metabolites of some 18 different individual PCBs were analyzed. It appears that predictable patterns of hydroxylation occur that indicate that the major pathway for most of the molecules involves direct hydroxylation. At least three different molecules among those studied produced products that indicated utilization of an alternate pathway. These three compounds were 4,4'-di-CB, 2,2',5,5'-tetra-CB and 2,2',4,4',5,5'-hexa-CB. The alternate pathway for these three compounds involves the formation of arene oxide intermediates. Such intermediates would be expected to be carcinogens and mutagens based on studies on well known carcinogens. If the carcinogenicity of the commercial preparations was due solely to these components the potency of the preparations could be calculated on the amount of these isomers present, the percentage of parent compound that utilized this alternate pathway and the pharmacokinetics of the intermediates formed. Table V-22 shows the results of analyses of three different Aroclor 1260, and three different Aroclor 1254 preparations for the presence of these arene oxide-forming compounds.

   Since only a small fraction of the parent compound utilizes the arene oxide pathway, it is highly unlikely that the carcinogenic potential of PCB mixtures is due entirely to this genotoxic reaction. Indeed, the genotoxicity of the products and even these specific isomers is in doubt as judged by short-term mutagenicity tests. If the carcinogenicity observed with the Aroclors is due to the initiating activity of epoxides that may be formed as metabolic intermediates, then the activity in the preparations is too low to be detected *in vitro*, or requires other *in vivo* conditions to be expressed.

   The metabolic data, along with the information on chemical analyses, and the *in vitro* tests all suggest that if these components do act as initiators their role in the carcinogenicity may be contributory but is unlikely to be the sole mechanism involved. Recent findings indicate that short-term exposures to 2,2',4,4',5,5'-hexa-CB, 2,2',4,4'-tetra-CB and Aroclor 1254 during liver cell proliferation do not show initiating action in an *in vivo* assay that detects both hepatic and nonhepatic initiating carcinogens (Hayes et al., 1985). It is, therefore, unsatisfactory to calculate the potency on the basis of exposure to "possible" active components, or to calculate the potency on the basis of exposure to any of the other components, some of which are scarcely metabolized at all.

3. One of the most striking findings concerning the variability of the components of the commercial products is the differing enzyme inducing capacities of particular isomers even at the same level of chlorination. The enzymes induced range from those that are involved in metabolism of PCBs themselves to others that have been implicated as activators and inactivators of other procarcinogens or carcinogens, respectively (Cytochrome P-450 and P-448 associated monooxygenase systems).

TABLE V-22

Analyses of Three Different Aroclor 1260 and Three Different Aroclor 1254 Preparations for the Presence of PCB Isomers Known to Utilize, to Some Degree, A Metabolic Pathway that Forms Arene Oxide Intermediates[a]

Aroclor	4,4'-Dichloro-	2,2',5,5'-Tetrachloro-	2,2',4,4',5,5'-Hexachloro-
1260 (Albro)	absent	absent	<4%
1260 (Sissons)	minor peak	minor peak	major peak
1260 (Tas)	b/	b/	minor peak
1254 (Albro)	absent	8%	4%
1254 (Sissons)	minor peak	major peak	major peak
1254 (Willis)	absent	minor peak	minor peak

[a]Source: Adapted from NIOSH, 1977

[b]Probably not analyzed

The mixed nature of the PCBs would be reflected in mixed enzyme induction, some of which will be capable of reducing the carcinogenic effect and some of which will increase the carcinogenic effects.

4. These examples show why the test data on the carcinogenicity of PCBs generated by use of commercial preparations such as the Aroclors and Kanechlors can provide only a net effect picture of the many and varied effects of the individual components in the preparations. The carcinogenicity that is manifested reflects the sum of vectors that represent partial additive, synergistic and antagonistic effects of numerous individual components. Potency and exposure are basic parameters used in risk estimation.

5. It can be said, however, that it is very likely that the potency of any commercial PCB preparation may be considerably higher or lower than any figure obtained by utilizing the dietary level of exposure as a basis for calculation.

VI. HEALTH EFFECTS IN HUMANS

General Background

Human exposure to PCBs may come from direct contact with industrial products, accidental contamination of foodstuffs or from association with contaminated environmental components. Whatever the source, PCB exposure can occur by ingestion, respiration or dermal absorption.

Exposure to PCBs results in the retention of certain PCB isomers and congeners in human tissues and fluids because of its chemical nature. The levels of PCBs vary with the route of exposure, geographical location, and sex and weight of the individual. In humans with no occupational exposure, PCB residue analyses have shown mixtures of higher chlorinated biphenyls that exhibit a compositional pattern differentiated from that of the commercial PCB preparations. Occupational exposure leads to PCB GC patterns in most cases characteristic of exposure to a PCB mixture with 54% chlorine (Wolff et al., 1982a,b). All types of exposure lead to the retention and bioaccumulation of specific PCB isomers and congeners based on their chemical structure and stability (Parkinson et al., 1980a).

PCB residues in humans have been demonstrated worldwide. In North America, the majority of the general population has PCBs in adipose tissue at levels up to 2 ppm (Yobs, 1972; Grant et al., 1976); however, other populations from other countries, for example Germany, have been reported to have higher PCB adipose concentrations (Acker and Schulte, 1970). Few studies have reported the composition of these total PCB residues.

The identification of specific PCB structures in human tissues may be important not only for assessment of long-term persistence but also for evaluation of potential health effects. The importance of the latter is due to the specificity of toxicity and inducibility of mixed function oxidase enzymes by these persistent PCB isomers and congeners. At the present time, the consequence of the persistence and bioaccumulation of these specific PCB congeners and isomers is unknown.

Acute and Short-Term Exposure

Unlike animal studies (Chapter V), there is little information regarding acute or short-term PCB exposure conditions nor any reports of possible consequences of the exposure in humans. The majority of the data on PCBs and humans comes from long-term exposure incidents, that is, occupational exposure or undetermined exposure duration such as occurred with direct introduction of PCB-containing material into the food chain from contaminated rice oil.

Chronic Exposure

Because of the chemical complexities of PCBs and the nature of PCB exposure in humans, it is not surprising that data on the behavior of specific PCB isomers and congeners as well as on effects of contaminants alone or in combination on the human system do not exist.

The problems associated with considering PCBs as one entity is presented in the literature on human health effects of PCBs. As previously pointed out, individual PCB isomers and congeners as well as the contaminants of PCB

mixtures vary extensively in their biologic, ecologic and toxicologic behaviors. However, for the most part, reports on human PCB exposure do not consider this fact and analytical data are presented as total PCBs.

At the onset it is important to make the distinction as to the type of PCB compound and the exposure conditions that have generated the literature on human health effects. The importance of clinical and toxicological data obtained from the relatively large numbers of humans exposed to PCBs cannot be ignored but must be placed in proper perspective.

Occupational Exposure. In the past 60 years, large numbers of workers have been exposed to PCBs in the manufacture or use of PCB-containing products; however, evaluation of any health effects is complicated by exposure to other chemicals. With this consideration the following sections summarize the information on PCB exposure and resultant health effects.

Historically, the original toxicological data on PCBs were produced in occupational settings. Exposure to PCBs may occur through absorption by skin or respiratory or alimentary tracts. These studies were reviewed in detail by NIOSH (1977).

Generally speaking, symptoms associated with PCB exposure do not correlate with duration and intensity of exposure in the workplace. However, PCB residues in serum is proportional to that of the adipose tissue and had a positive correlation with exposure conditions and alterations in some clinical parameters, such as elevation of SGPT (Wolff et al., 1982a,b; Ouw et al., 1976; Maroni et al., 1981a,b; Fischbein et al., 1979).

Skin -- The most commonly encountered dermatologic symptom associated with PCB exposure is chloracne. Chloracne is produced upon exposure to chlorinated hydrocarbons, for example, napthalenes and biphenyls. The skin lesion manifests itself as follicular keratosis with comedo formation and acneform eruptions. At first the lesion was thought to be a contact phenomenon as it developed on skin not covered by clothing, but subsequently it has been determined that systemic exposure to PCBs will also produce the dermatitis.

Differences in the lesions occur with the amount of chemical exposure, patient age and lesion site. Although there is one report that correlated time of exposure with severity of lesions (Schwartz, 1943), other reports indicate that there is no good correlation of occurrence of chloracne and its severity with duration of employment (Fischbein et al., 1979; Ouw et al., 1976). Thus, it appears that individual susceptibility to chloracne is more important than duration and extent of PCB exposure.

Many case studies in the literature describe varying degrees of chloracne as a result of occupational exposure to PCBs. Early case studies of occupational PCB exposure were reported by Jones and Alden (1936), Drinker et al. (1937), Schwartz (1943) and Meigs et al. (1954). Jones and Alden (1936) reported 16 cases of chloracne among workers employed in the manufacture of PCBs; these are summarized in Table VI-1. These workers were also exposed to impure benzene.

PCB air concentrations have been reported and related to the occurrence of chloracne. The air concentration of 0.1 mg Aroclor/m^3 was associated

TABLE VI-1

Summary of the Symptoms in Sixteen Cases of Acneform Eruption*

Case Number	Age (years)	Race	Duration of Exposure (months)	Type of Skin	Type of Eruption
1	22	white	6	seborrheic; previous acne	diffuse comedones; few cysts
2	28	white	5	average	diffuse comedones; few cysts
3	32	white	NR	seborrheic	diffuse comedones; large cysts and pustules
4	36	white	10	average dry	diffuse comedones; large cysts and abscesses
5	28	white	NR	average	diffuse comedones; few cysts on face and neck
6	30	white	8	seborrheic; previous acne	diffuse comedones; deep abscesses on neck; severe cysts
7	20	Negro	8	seborrheic	erythematous diffuse comedones; few small cysts
8	19	Negro	5	average	few scattered comedones; occasional cysts
9	26	Negro	NR	seborrheic	diffuse comedones; cysts; small abscesses
10	37	white	9	average	scattered comedones; occasional abscesses
11	56	white	NR	dry	scattered comedones; occasional abscesses

TABLE VI-1 (cont.)

Case Number	Age (years)	Race	Duration of Exposure (months)	Type of Skin	Type of Eruption
12	20	white	2	seborrheic	few comedones; occasional abscesses
13	37	white	NR	average	occasional comedones
14	23	Negro	12	average	very few comedones
15	22	white	NR	seborrheic	scattered comedones
16	20	Negro	NR	seborrheic	diffuse comedones; few cysts on back and face

*Source: Jones and Alden, 1936

NR = Not reported

with seven cases of chloracne among 14 workers 19 months after initiation of exposure (Meigs et al., 1954). The mean length of exposure was 14.3 months for affected workers and 11.4 months for unaffected workers.

Ouw et al. (1976) compared dermatologic parameters of 34 electrical industry workers exposed to electrical grade (no impurities) Aroclor 1242 with those of 30 control volunteers. Major worker complaints consisted of burning of the eyes, face and skin. One worker had chloracne without systemic effects, and five workers had eczematous hand and leg rashes. These dermatologic effects occurred at an air concentration of <1 mg/m^3 PCB.

A subsequent study of capacitor manufacturing workers recorded the air levels (8-hour TWA) of PCBs as 0-11.0 mg/m^3 (Fischbein et al., 1979). The clinical study surveyed a cross-section of 326 capacitor manufacturing workers (168 males, 158 females; mean years of employment, >15) exposed to various PCB mixtures (Aroclors 1254, 1242, 1016 and 1221). Both plants surveyed in this study also used chlorinated benzenes. The duration of PCB exposure and age distribution by sex of the capacitor manufacturing workers are given in Tables VI-2 and VI-3, respectively. Dermatologic symptoms, including rash, burning sensation, acne, pigmentation (darkening), and thickening and discoloration of the fingernails, were reported. The prevalence of these dermatologic symptoms is given in Table VI-4.

Maroni et al. (1981b) reported blood PCB concentrations of 41-1319 ppb in 80 electrical workers (40 male, 40 female) employed in Italian electric capacitor manufacturing and testing plants. Of the 80 workers, 67 were

TABLE VI-2

Duration of PCB Exposure of 326 Capacitor Manufacturing Workers*

Duration (years)	Number of Workers	Percent
<5	33	10.1
5.0-9.9	68	20.9
10.0-14.9	57	17.5
15.0-19.9	37	11.4
20.0-24.9	95	29.1
≥25.0	36	11.0

*Source: Fischbein et al., 1979

TABLE VI-3

Age Distribution of 326 Capacitor Manufacturing Workers by Sex*

Age (years)	Total Number Examined	Males	Females
<30	49	33	16
30-39	61	41	20
40-49	88	48	40
50-59	93	27	66
60-69	25	13	12
≥70	10	6	4
Total	326	168	158

*Based on data from Fischbein et al., 1979

TABLE VI-4

Prevalence of Reported Dermatologic Symptoms Among 326 Capacitor Manufacturing Workers*

Symptom	Number	Percent
Rash	128	39.3
Burning sensation	81	24.8
Acne	35	10.7
Pigmentation (darkening)	8	2.5
Thickening	12	3.7
Discoloration of fingernails	8	2.5

*Source: Fischbein et al., 1979

exposed to Pyralene 3010 (a PCB mixture containing 42% chlorine) and 13 were exposed to Apirolio (a PCB mixture containing 42% chlorine). The mean age of the workers was 37±8 years, and the mean duration of employment was 12±6 years. There were six cases of chloracne among the 80 workers, as shown in Table VI-5.

Reproductive System -- Quantitative and qualitative examination of PCB residues in blood of women occupationally exposed to PCBs and their nursed children were conducted (Kuwabara et al., 1978). The data obtained indicated that PCBs are retained in the children's body for many years after breast feeding and a longer feeding of mothers' milk increased PCB levels in the blood of the children. In addition, the GC pattern of PCBs present in the mothers differed from that of the children. The health implications of such an occurrence is unknown.

Clinical Observations. Exposure to PCBs has been associated with a wide variety of alterations in clinical parameters, both subjective and objective. The following paragraphs give summaries of various studies in a historical manner.

Of seven workers intermittently exposed to PCB vapors who developed chloracne all had normal blood cell counts, urinalysis and blood pressures (Meigs et al., 1954). Six of these individuals had normal liver function tests, which included direct and total bilirubin determinations and 24- and 48-hour cephalin flocculation, thymol turbidity and alkaline phosphatase determinations. The other affected worker had borderline cephalin flocculation and thymol turbidity, which was improved 13 months later.

TABLE VI-5

Clinical Features of Six Electrical Workers with Chloracne*

Case No.	Age (years)	Age at First PCB Exposure	Skin Lesions		
			Age at Onset	Current Findings	Affected Regions
1	49	27	39	vermicular scars, comedones, superficial cysts and suppurative folliculitis	abdomen, thighs
2	26	16	22	vermicular scars, comedones, superficial cysts, and suppurative folliculitis	face, neck
3	50	20	23	vermicular scars, comedones, superficial cysts, and supperative folliculitis	neck, shoulders arms, back
4	43	28	40	vermicular scars	arms, back, legs
5	38	24	37	folliculitis (possibly chloracne)	scrotum
6	49	42	45	comedones with erythema (possibly chloracne)	neck, sternum

*Source: Maroni et al., 1981a,b

Although in the previous study PCBs were not found to alter hepatic function as judged by the clinical tests, Aroclor 1016 has been reported to alter drug metabolism through the mechanism of hepatic enzyme induction in exposed workers (Alvares et al., 1977). A significantly decreased mean antipyrine half-life (10.8 hours) in five exposed workers as compared with nonexposed control subjects (half-life of 15.6 hours) was reported. There was also increased metabolic clearance rates in workers exposed to Aroclor 1016. Therefore, the author suggests that PCBs accelerate the rate of drug metabolism in man. No systemic toxic effects were reported among the PCB-exposed workers.

In another study, apparent systemic dysfunctions occurred. Warshaw et al. (1979) reported the incidence of various symptoms in capacitor manufacturing workers to be: pulmonary and ocular symptoms as indicated by cough (13.8%), wheezing (3.4%), tightness in chest (10.1%) and upper respiratory or eye irritation (48.2%). There were some abnormal results found in biochemical and hematologic tests. In pulmonary function studies, a decreased forced vital capacity was seen in 34/243 workers examined (14%), but no abnormalities were seen in chest X-rays.

Health conditions of 80 electrical workers exposed for many years to PCB mixtures who had blood PCB concentrations of 41-1319 µg/kg were reported (Maroni et al., 1981a,b). Sixteen of the males had liver abnormalities, including hepatomegaly and hepatic dysfunction (indicated by an increase in serum enzymatic activities); for 20% of these, the blood PCB concentration was <200 ppb. No liver abnormalities were reported among exposed female workers. There were two cases of bleeding hemangioma, one of whom also had chronic myelocytic leukemia.

Direct Introduction of PCBs into Foodstuffs

Yusho Incident. The first documentation of human effects as a result of ingestion of PCBs was derived from the Japanese poisoning incident that occurred in 1968. In 1968, the victims suffered an acute toxicosis from consuming rice oil contaminated with an industrial oil (a commercial brand of PCBs), Kanechlor-400 consisting of a mixture of polychlorinated biphenyls (PCB), polychlorinated dibenzofurans (PCDF) and polychlorinated quinones (PCQ). The average total amount of PCBs consumed was estimated to be ~2 g, with ~0.5 g being the least total amount consumed by an affected group of some 325 people at the time (Kuratsune et al., 1972). The PCB oil that got into the rice oil was estimated to contain 5000 ppm PCDFs, some 250 times more concentrated than the 18 ppm found in Kanechlor 500 by GC/MS methods (Nagayama et al., 1976). The presence of the potent toxicant PCDFs in the Yusho oil probably contributed to the overall toxicologic effects seen in Yusho patients.

Yu-Cheng Incident. A similar mass outbreak of a peculiar skin disease was recorded in Taichung and Changhwa in Central Taiwan. The cause of the disease was later identified to be the ingestion of rice bran oil contaminated with PCBs, and there were >1900 victims. Blood PCB levels of 66 affected persons ranged from 11-720 ppb (mean 49 ppb) at ~9-12 months after consumption of the PCB-contaminated oil (Chen et al., 1980).

The presence of polychlorinated quaterphenyls and dibenzofurans was documented (Chen et al., 1981). The PCDF levels in the Taiwan episode were less than that in Japan. The rice oil consumed in Taiwan consisted of larger percentages of penta-, hexa- and heptachlorobiphenyls than did that

consumed by the Japanese. The concentration of PCBs and PCDFs in six different samples of the contaminated oil are given in Table VI-6.

Prevalence of PCDFs in rice oil and in tissues of Yusho and Yu-Cheng victims strongly suggests that PCDFs are the resonsible compounds for adverse health-effects in these incidents. This is substantiated by the observations that PCBs and polychlorinated quaterphenyls, (PCQ) which were also detected in the rice oil samples from these incidents, fail to cause toxic response similar to those of PCDFs in experimental animals. (Masuda and Yoshimura, 1984; Masuda et al., 1985; Kunita et al., 1984, 1985; Kikuchi, 1984; Chen et al., 1984, 1985; Miyata et al., 1985; Kashimoto et al., 1985).

Although the PCDF concentrations in Yu-Cheng incident rice oil were lower than in the Yusho oil, it has been estimated that the average intake during the exposure period was more or less identical: 973, 3.8 and 586 mg in Yu-Cheng (Chen et al., 1985) and 633, 3.3 and 596 mg in Yusho victims (Hayabuchi et al., 1979) for PCBs, PCDFs and PCQs, respectively. The tissue distribution of PCDFs with the relative concentrations of the various isomers indicates that in liver and other tissues the major congeners detected were 1,2,4,7,8- and 2,3,4,7,8-PeCDFs and 1,2,4,7,8-HxCDF. Minor quantify of 2,3,7,8-TCDF and 1,2,3,4,6,7,8-HxCDF were also found (Masuda et al., 1985; Chen et al., 1985).

All the PCDFs retained had at least 3 chlorine atoms at the 2,3,7,8 positions and no vicinal hydrogens in the dibenzofuran ring. Though unhalogenated vicinal-C-atom congeners were present in the rice oil no such unhalogenated congenes were detected in the Yu-Cheng patients (Chen and

Hites, 1983). Rappe et al. (1979) also reported similar observation in a Yusho patient.

A correlation between the severity of clinical symptomatology in Yusho patients and the estimated contaminated oil ingestion (PCBs+PCFDs+PCQs) was reported (Kuratsune et al., 1972; Nagayama et al., 1976; Hayabuchi et al., 1979). However there is much evidence to support the hypothesis that PCDFs and not PCBs are responsible for the disease. Analysis of the concentrations of PCDF and PCB in the liver and adipose tissue of Yusho patients and of control subjects killed in traffic accidents revealed comparable PCB concentrations in tissues of the two groups, but PCDF (in the range of ppb) only in the organs of Yusho patients (Masuda and Kuroki, 1982). Other evidence of the importatnce of PCDF and PCB in determining the Yusho and Yu-Cheng syndrome has been obtained more recently. Kashimoto et al. (1985) compared the blood levels of Yusho (11 years after the outbreak) and Yu-Cheng patients with that of occupationally PCB exposed workers (19 years after termination) and unexposed people. In spite of high levels of PCBs in all the samples, detectavle amounts of PCDFs were only found in the blood of Yu-Cheng patients. In 113 Yu-Cheng patients there was a clear correlation between the blood PCDF concentration and the severity of dermatological symptoms. PCQs were present in the blood of all the Yu-Cheng patients 6 months after exposure and in 54 of the 56 living Yusho patients 11 years after the outbreak. The presence of PCQs in blood can be considered a good marker of past ingestion of contaminated oil.

In the blood of Yu-Cheng patients there was a sidtinctive PCB pattern, very different from the original pattern (Masuda et al., 1985) and richer in the more chlorinated isomers (for example, 2,3,4,5,3',4'-hexa-CB is a PCB

that is highly bioaccumulative). This distinctive chromatogram has now been adopted as one of the criteria for identification of Yu-Cheng disease.

Preliminary data in the three Taiwan Yusho patients indicated that in the first year after exposure blood concentrations of penta- and hexa-CDF dropped 20 and 15%, respectively. Thus, the half-time of highly-chlorinated PCDF in man appears to exceed 1 year (Rappe et al., 1983). Rappe et al. (1979) actually detected reliable levels of PCDF in blood of Yusho patients 10 years after the intoxication. Of particular interest is the detection of high concentrations (100-500 ppt) of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF in the placenta if Yusho women 5 years after exposure (Wong et al., 1982).

Noncarcinogenic Toxic Effects Observed

Skin. Kuratsune et al. (1969) reported that the most notable symptoms of Yusho among 189 patients included dark brown pigmentation of nails and skin, follicular accentuation, acneform eruptions, increased eye discharge, increased sweating at the palms and feeling of weakness. The percent distribution of symptoms among 189 Yusho patients is summarized in Table VI-7. Acneform eruptions and pigmentations were most prevalent. With passage of time these dermal symptoms improved considerably but the patients still experienced some dermal conditions after several years (Urake and Asahi, 1985).

Similarly, the major clinical signs of contaminated rice oil ingestion in the Yu-Cheng incident were skin disorders such as pigmentation and acneform eruptions (Chang et al., 1980a,b).

Immune System. PCB exposure in the human has been shown to affect the immune system. Shigematsu et al. (1978) reported that human subjects who consumed PCB contaminated rice oil were more susceptible to respiratory tract infections. Yu-Cheng patients had lower serum IgA and IgM, decreased percentages of T cell subpopulations (Lii, Y-C and Wu, Y-C, 1985, Chang et al., 1980a,b) and decreased delayed type skin hypersensitivity response to streptokinase and streptodornase (Chang et al., 1980a,b, 1981).

Reproductive System. The maternal-perinatal system also appeared to be affected with the consumption of PCB-contaminated rice oil. From these incidents it is apparent that PCBs cross the placenta and can be transmitted in mothers milk (Abe et al., 1975; Yoshimura, 1974; Kodama and Ota, 1980; Kuratsune, 1976).

Embryos, fetuses and neonates (2-3 months old) are a subpopulation at special risk because of inherent physiological differences from the adult human. This subpopulation usually lacks the hepatic microsomal enzyme systems, including the glucuronidation pathway, that are capable of oxidizing PCBs to facilitate the detoxification and excretion of these compounds (Calabrese and Sorenson, 1977; Gillette, 1967; Nyhan, 1961). Breast-fed infants are at greater risk also because of a steroid excreted in human breast milk, but not in cow's milk, that inhibits glucuronyl transferase activity, and thus glucuronidation and excretion of toxicants such as PCBs, by >20% (Calabrese and Sorenson, 1977; Gartner and Arias, 1966).

Yamashita (1977) reported four cases of infants born to mothers who had Yusho during pregnancy. The amount of PCB-contaminated oil consumed during pregnancy was ~1.1-10.5 ℓ. Maternal symptoms included acneform eruptions,

TABLE VI-6

Concentration of PCBs and PCDFs in the Toxic Rice-Bran Oils That Caused "PCB Poisoning" in Taichung, Taiwan*

Sample No.	PCB (ppm)	PCDF (ppm)	PCB/PCDF Ratio
1	405	1.68	241
2	53	0.180	294
3	99	0.399	248
4	78	0.250	312
5	77	0.209	368
6	65	0.297	219

*Source: Chen et al., 1981

TABLE VI-7

Percent Distribution of Signs and Symptoms of Yusho Among 189 Persons*

Symptoms	Males (n=89)	Females (n=100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	24.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

*Source: Kuratsune et al., 1969

follicular accentuation; dark brown pigmentation on the skin, mucous membranes and nails; and hypersecretion of the meibomian gland. Three of the four infants, including one full-term (40 weeks gestation), one premature (36 weeks gestation), and one 2 weeks later than term (42 weeks gestation), were small-for-gestational age (both weight and height). Other clinical features among the four infants included dark brown pigmentation on the skin and mucous membranes, gingival hyperplasia, eruption of teeth at birth, spotted calcification on the parieto-occipital skull and the large or wide fontanels and sagittal suture, facial edema and exophthalmic eyes.

Hsu et al. (1985) reported 39 infants showing hyperpigmentation were born from poisoned mothers in Yu-Cheng incident.

Kuratsune et al. (1969) summarized four studies (Yamaguchi et al., 1971; Taki et al., 1969; Funatsu et al., 1971; Kikuchi et al., 1969) of 10 live and 3 stillborn births from February 15 to January 31, 1968, to 11 females with Yusho during pregnancy and 2 wives of males with Yusho during the female's pregnancy. The amount of Kanechlor-contaminated oil consumed during pregnancy was 0.3-2.6 ℓ (Yamaguchi et al., 1971). Of 10 live and 2 stillborn births, 9 had unusually grayish, dark-brown stained skin, 5 had similar pigmentation of the gingiva and nails and most had increased eye discharge (Yamaguchi et al., 1971; Taki et al., 1969; Funatsu et al., 1971). Of the 13 infants, 12 were described as smaller than the national Japanese standards and 4 as small-for-dates babies (Yamaguchi et al., 1971; Taki et al., 1969).

Yoshimura (1971) compared the growth of 42 school-aged children with Yusho (23 males, 19 females) with that of 719 sex-matched classmates described as being "healthy." For the years 1967-1969, the height and weight gains of girls with Yusho were unaffected, while boys with Yusho had significant height and weight gains.

Clinical Observations. The initial Yusho symptoms, reported among 136 patients, are summarized in Table VI-8. Based on the estimated amounts of Kanechlor-contaminated rice oil consumed in Table VI-9 and the clinical severity of resulting effects in different age groups in Table VI-10, a qualitative dose-response relationship was prepared (Kuratsune et al., 1972).

The clinical abnormalities displayed by Yu-Cheng patients were decreased red blood cell counts, increased total white cell counts and decreased hemoglobin. The patients presented with swelling of the eyelids and increased discharge from the eyes, headache, nausea and numbness of the limbs (Chang et al., 1980b).

Clinical parameters evaluating liver function were suggestive of hepatic dysfunction in both the Yusho and Yu-Cheng patients. Inverse correlation between serum bilirubin concentration in Yusho patients and blood PCB levels, with mean serum bilirubin concentrations of 0.48 ± 0.26 mg/100 mℓ in 121 Yusho patients and 0.87 ± 0.33 mg/100 mℓ in 257 healthy adult controls have been noted. Increased serum triglyceride concentration was observed in Yusho patients. Similarly, increased triglycerides and elevated activities of serum transaminases and alkaline phosphatase were recorded in the Yu-Cheng patients (Chang et al., 1980a).

TABLE VI-8

Initial Symptoms of Yusho Among 136 Persons*

Initial Symptoms	Patients	
	No.	%
Swelling of upper eyelids, increased eye discharge	52	38.3
Acne-form eruption, follicular accentuation	45	33.1
Edematous swelling of limbs	9	6.6
Languishment	4	2.9
Disturbances in digestive canal	4	2.9
Numbness and other neurological signs	9	6.6
Pigmentation of skin	13	9.6
Total	136	100.0

*Source: Goto and Higuchi, 1969

TABLE VI-9

Relationship Between the Amount of Kanechlor-Contaminated Rice Oil Consumed and Clinical Severity of Yusho*

Estimated Amount of Oil Consumed	Nonaffected		Light Cases		Severe Cases		Total	
	No.	%	No.	%	No.	%	No.	%
<720 mℓ	10	12	39	49	31	39	80	100
720-1440 mℓ	0	0	14	31	31	69	45	100
>1440 mℓ	0	0	3	14	18	86	21	100

*Source: Kuratsune et al., 1972

TABLE VI-10

Relationship Between Clinical Severity of Yusho and Age of Affected Persons[a]

Estimated Amount of Oil Consumed	Age (years)	Number of Patients By Clinical Severity							
		Nonaffected		"Light"[b]		"Severe"[b]		Total	
		No.	%	No.	%	No.	%	No.	%
<720 mℓ	<12	3	16.7	13	72.2	2	11.1	18	100
	13-29	2	8.3	7	29.2	15	62.5	24	100
	≥30	5	13.1	19	50.0	14	36.9	38	100
	Total	10	12.5	39	48.8	31	38.7	80	100
720-1440 mℓ	<12	0	0	5	50.0	5	50.0	10	100
	13-29	0	0	1	6.7	14	93.3	15	100
	≥30	0	0	8	40.0	12	60.0	20	100
	Total	0	0	14	31.2	31	68.8	45	100

[a]Source: Kuratsune et al., 1972

[b]Clinical severity was classified as "light" or "severe," as defined by Goto and Higuchi (1969); further details enumerating clinical features of this classification scheme were not reported.

PCB exposure in experimental animals is known to cause abnormal urinary excretion of heme precursors, thus the urinary excretion of these precursors were examined in both the Yusho and Yu-Cheng patients. PCB poisoning caused an increased excretion of delta-aminolevulinic acid (0.72-1.00 mg/24 hours) and uroporphyrin (13.6-41.2 µg/24 hours), but not in the excretion of porphobilinogen or coproporphyrin (Chang et al., 1980b). Similar studies on Yusho patients failed to reveal any differences in porphyrin metabolism; however, the studies were conducted long time after the incident (Strik et al., 1979; Nonaka et al., 1979).

Human Cancer Studies (Inhalation and Dermal Contact)

Two brief reports in the literature have noted an increased incidence of malignant melanomas in workers heavily exposed to PCBs. Bahn et al. (1976, 1977) reported two malignant melanomas in 31 research and development employees (6.5%) of a New Jersey U.S. petrochemical plant that had used Aroclor 1254 for 9 years (ending in the late 1950s). Quantified exposure levels or concentrations are not given. This incidence was significantly greater than expected ($p<0.001$), based on a person-year analysis and comparison with the Third National Cancer Survey incidence rates (NCI, 1975). Only 0.04 malignant melanomas would be expected among 31 persons for a rate of 0.13%. In a second group of 41 refinery workers exposed to "low" levels of Aroclor (quantified exposure levels not reported), one had a malignant melanoma. Exposure to other potential and known carcinogenic substances was not evaluated although they were believed to be present (Lawrence, 1977).

NIOSH (1977) expanded upon the report on New Jersey petrochemical workers by noting that eight cancers were observed in the study population of 51 research and development employees and 41 refinery plant employees

known to have been exposed to Aroclor 1254 followed to January 1, 1976 while 5.7 were expected when compared with that of a similar sample of the U.S. population. Of the eight, three were melanomas while two were pancreatic cancer. Both were significantly increased over expected cases according to the authors, although no figures were provided of expected cases. PCB exposure histories were based upon recollections of two company employees. A more extensive investigation was reported by NIOSH to be in progress by a B.N. Kightlinger in a written communication to NIOSH. However, to date we have been unsuccessful in acquiring information about this more extensive investigation. Details about this study are sketchy at best in all three reports.

Davidorf and Knupp (1979) calculated the incidence of ocular melanoma on a county-wide basis in the State of Ohio over an 11-year period from 1967-1977. This survey was prompted by reports of an association of cutaneous melanomas with ultraviolet radiation or exposure to PCBs. The authors identified counties with industries that might use PCBs and counties with known high concentrations of PCBs determined by level of PCBs found in fish as well as location of industries known to produce PCBs. The purpose was to evaluate the incidence of ocular melanomas with respect to proximity to areas of high concentrations. Information on primary choroidal melanomas was obtained from "institutions," such as hospitals and tumor registers in Ohio and adjacent states who may have had adult residents as patients. Some 698 white Ohio patients were identified from this endeavor.

Over the 11-year period, an average incidence of 1.09 cases/100,000/year were found. This incidence did not differ significantly with any single year's incidence. The authors did note, however, that other studies

reported an incidence of 0.6 cases/100,000/year (Scotto et al., 1976). The authors attribute the difference to the use of medical records at hospitals and not just tumor registry data. The county incidences over the 11-year period also did not reveal any pattern of distribution that was correlated with areas of high PCB occurrence. The authors suggest this may in part be due to small population sizes in certain areas they thought were clinically over-represented. This was compounded by the fact that fewer persons in poorer rural areas tend to seek early medical care.

Brown and Jones (1981) conducted a retrospective cohort mortality study on 2567 workers who had completed at least 3 months of employment at any time in any area of two capacitor manufacturing plants where potential for exposure to PCBs existed. PCBs had been used at the facilities for >30 years before the cut-off date of the study on January 1, 1976. Aroclor 1254 was used first but changed over the years to Aroclor 1242 and finally to Aroclor 1016. Workers exposed to trichloroethylene (TCE) were excluded from the cohort. Time-weighted average (TWA) personal air samples in the two plants ranged from 24-1260 μg PCB/m^3. Vital status ascertainment was 98% complete. Observed deaths were contrasted with expected deaths based upon U.S. white male and female deaths. All cause mortality was lower than expected in plant 1 (73 observed deaths vs. 76.7 expected) as well as in plant 2 (90 observed vs. 105.6 expected). Combining two cohorts produced a nonsignificant excess risk of liver cancer (3 observed deaths vs. 1.07 expected) and a nonsignificant excess risk of rectal cancer (4 observed deaths vs. 1.19 expected). This excess risk of rectal cancer was limited to females of plant 2 (3 observed vs. 0.5 expected).

No apparent pattern of response in liver cancer was found according to the years since first employment (presumably first exposure). All deaths from liver cancer occurred before the 20th year of latency. A slight, non-significant excess risk of cirrhosis of the liver was found after the 20th year of latency (3 observed vs. 1.49 expected) as well as a nonsignificant excess risk of cancer of the rectum (2 observed vs. 0.36 expected) after the 20th year of latency.

The authors point out that because of the relative number of deaths in this cohort, conclusions drawn from the study are only tentative. Although it appears to be a rather large cohort, relatively few deaths were reported to have occurred. Indeed, in the group of workers who have reached the 20 year latency period, eight cancer deaths occurred while 13.24 were expected. This may be an indication that the cohort consisted of either mostly youthful employees or else older employees who only recently had their first exposure (first employment).

Recently, the author provided an unpublished update of his 1981 study (Brown, 1986) in which he added an additional 7 years of follow-up, thus increasing the number of deaths to 295. This was still lower than expected at 318. Cancer mortality totaled 62 deaths vs. 80 expected. In the later draft the authors noted a statistically significant excess risk of cancer of the liver and biliary passages (5 observed vs. 1.9 expected; $p<0.05$). The excess chiefly occurred in women employed in one plant. The author again pointed out that these findings are"difficult to interpret" with respect to exposure to PCBs.

But Brown (1986) did offer some evidence to support a causal relationship. In an environmental survey conducted in 1977 by NIOSH, and reported on in the earlier paper by Brown and Jones (1981), personal TWA exposures to PCBs (Aroclor 1016) ranged from 24 mg/m³-393 mg/m³ at plant 1 while at plant 2 they were higher at 381 mg/m³-1260 mg/m³. Four of the five liver cancers occurred in female employees at plants 2. All occurred after the 15th year of follow-up from beginning date of employment. All began working at a time when levels of exposure were likely to be highest. Furthermore, this group (Female employees at plant 2) contributed 41% of the total person-years to the analysis, the largest contribution. However, since the two plants may differ in alcohol consumption, dietary habits and ethnic composition as was pointed out by the author, it would be prudent to continue following this cohort in order to confirm that the excess risk of liver and biliary passageway cancer is real. Further analytical work on this cohort is continuing. It would be prudent to regard these findings cautiously suggestive.

Bertazzi et al. (1987) completed a retrospective prospective mortality study of 544 male and 1556 female employees of a capacitor-making facility in a small industrial town of Northern Italy. Small capacitors were made for electrical and electronic use while large capacitors were impregnated with PCBs since 1946. Aroclor 1254 and Pyralene 1476 were used until 1964. After 1964, they were progressively replaced by Pyralene 3010 and 3011 until 1970 when the lower chlorinated Pyralenes were excusively used. In 1980, the use of PCBs was completely abandoned. Maximum consumption of PCBs occurred in 1967-1968. Trichloroethylene was used in the final step of manufacturing. The workers employed in this last step are described by the

authors as being protected with efficient ventilation. Certain unique capacitors were made in which alkylbenzene and expoxy resins were used but few individuals were involved with this.

Because of reports of chloracne among autoclave operators in 1954, environmental air samples were measured. For Aroclor 1254 the values ranged from 5200-6800 $\mu g/m^3$. Again, in 1977 because of the appearance of 4 cases of chloracne, environmental air samples of Pyralene 3010 ranged from 48 $\mu g/m^3$ to 275 mg/m^3. In additon, the quantity of PCBs of workers hands and workplace surfaces were measured first in 1977 and then again in 1982 (2 years <u>after</u> used of PCBs was abandoned). These results will be found in Table VI-11. It is noted by the authors that a degree of contamination continued to persist until 1982.

The authors contrasted observed mortality with that expected from 1946 to 1982 based upon national and local Italian mortality rates. Compared to the size of the cohort relatively few deaths [30 (5.5%) male and 34 (2.2%) female] were recorded by 1982 with almost a complete vital status ascertainment on the remaining members of the cohort. Less than one half of 1% remained untraced.

Overall mortality was not different from expected in males but significantly higher than expected in females when contrasted with local rates (Table VI-12). However, deaths from cancer were significantly higher than expected in males whether national or local rates were used (14 observed versus 1.7 national and 2.2 local, $p<0.05$). Of these one was due to liver cancer and one was biliary tract cancer. Cancer deaths (12) in

TABLE IV-11

Minimum and Maximum Values of PCBs Recovered from Workplace Surfaces and Workers Hands Before and After PCBs Banning (1980) and Cleaning Operations*

	Year	No. of Samples	Values (ug/cm^2) Min.	Max.
Workplace Surfaces	1977	18	0.2	159.0
	1982	14	0.003	6.3
Workers Hands	1977	9	0.3	9.2
	1982	12	0.09	1.5

*Source: Adopted from Bertazzi et al. (1987)

TABLE IV-12

Mortality From Selected Causes of
Male and Female Workers Exposed to PCBs
(Bertazzi et al., 1987)

Cause of Death (ICD 8th Revision)	Observed Deaths	Reference Mortality	
		National Expected	Local Expected
MALES			
All Causes	30	27.8	29.8
Malignant Tumors (140-209)	14	5.5*	7.6*
Gastrointestinal Tract (150-159)	6	1.7*	2.2*
Hematologic Neoplasms (200-209)	3	0.8	1.1
FEMALES			
All Causes	34	25.8	16.5*
Malignant Tumors (140-209)	12	7.7	5.3*
Hematologic Neoplasms (200-209)	4	1.5	1.1*

*$p<0.05$

females workers were also elevated by comparison with local rates (5.3 expected, $p<0.05$). However, this excess risk did not translate into an increased significant risk of cause specific cancer. No liver or biliary cancer deaths were noted in females. Both males and females did experience an increased nonsignificant risk of hematologic neoplasms (see Table IV-12) which remains unexplained at this time.

There are several problems with this study that precludes its use at this time in upgrading the classification of the weight-of-evidence of carcinogenicity. There is an absence of significant site-specific cancer in both males and females. However, this is due to the inadequate power of the study to detect as significant an elevated risk of site-specific cancer. In actuality, this cohort needs further follow-up to determine if any trends are apparent since so few deaths have occurred by the cut-off period in this study. Latent factors were not examined probably because of the small number of deaths observed during the follow-up period. Additionally, other possible confounders may be present. Possibly trace amounts of dibenzofurans (PCDFs) may be found in the PCBs. Other substances such as trichloroethylene, alkylbenzene and epoxy resins have also been reported in the plant by the authors. Furthermore, the study does not consider the healthy worker effect in its comparison with national and local death rates nor does it analyse latent effects except on an individual case by case basis.

Human Cancer Studies (PCBs Poisoning Episodes - Ingestion Only)

Amano et al. (1984) recently completed a 16-year cohort mortality study of 1086 victims of the Yusho incident in Japan. The 581 males and 505 females sustained a total of 70 deaths (42 males vs. 45.81 expected and 28

females vs. 31.03 expected through October 21, 1983, over age 40 based upon Japanese national death rates). Expected deaths were derived from basic death rate data (sex-, age- period-adjusted) for each cause generated by the Welfare Ministry of Japan. In persons over 40 years of age overall cancer mortality was greater than expected in men but no different in women. In men 19 cancer deaths occurred vs. 11.50 expected, and in women 7 cancer deaths occurred vs. 7.20 expected. However, by organ site, only the risk of liver cancer was consistently high in both men and women during the entire 16-year period of observation. Even after a 9-year latent period, the risk of liver cancer in males was significant (5 observed, 0.75 expected, $p<0.01$). The risk of liver cancer was also significantly elevated after 9 years observation time utilizing just the rates of Fukuoka prefecture only, the province where the Yusho incidence occurred (Table VI-13).

However, in follow-up studies done on the victims of the rice oil poisoning incident, particular isomers of the ingested PCBs were found in liver tissue in the proportion 4-1 compared with PCDFs several years later. They appear to persist in liver tissue to a greater extent than do PCBs, which also persist in both liver and adipose tissue (Kuratsune et al., 1975).

The Amano et al. (1984) paper that has been translated from Japanese is not without problems. First, the information concerning the diagnosis of liver cancer in the victims is described as having been obtained from the family of the victims. These diagnoses are not described in this paper as having been verified. Second, the sum of the expected deaths in the tables do not add up to total expected deaths thus leading to speculation that this paper is perhaps preliminary or lacks scientific review, although it was

TABLE VI-13

Risk of Death From Cancer of the Liver in Oil Poisoned Patients by Sex and Period of Observation, Japan and in Fukuoka Prefecture*

Region	Sex and Period of Observation	Observed	Expected
Japan	Males	6	1.22 ($p < .01$)
	1969-1976	1	0.44
	1977-1983	5	0.75 ($p<0.01$)
	Females	2	0.54
	1969-1976	1	0.19
	1977-1983	1	0.24
Fukuoka Prefecture	Males		
	1977-1983	3	0.66 ($p<0.05$)
	Females		
	1977-1983	1	0.17

*Source: Amano et al., 1984

published in a Japanese journal. Third, no information is given regarding job histories or the influence of alcoholism or smoking. The influence of type B hepatitis with respect to the risk of liver cancer in these patients "can be dismissed" according to the authors because there appeared to be no difference between the Australian antigen positive rate of the oil poisoned patients and that of healthy blood donors.

In view of the problems that need to be addressed in this study a definite conclusion that PCBs caused the significant risk of liver cancer in these patients cannot be made. However, the finding of a definite elevated liver cancer risk in the Yusho victims cannot be dismissed. Further confirmatory research needs to be accomplished. Until the questions above are answered it is not possible to classify the human carcinogenicity evidence as more than suggestive with respect to exposure to PCBs.

In an effort to determine whether the increased risk of liver cancer reported by Amano et al. (1984) in the 1086 victims of the Yusho incident was real or only artificial, the Cancer Assessment Group (CAG) communicated with Dr. Masanori Kuratsune of Nakamura Gakuen College for further information. Dr. Kuratsune and his colleagues in a preliminary analysis provided mortality data on a much expanded cohort of some 1821 officially recognized Yusho patients by the Ministry of Health and Welfare by the end of 1983. From the cohort the authors excluded nine deceased individuals who were posthumously recognized as Yusho and another 51 who could "not be confirmed for survival (vital status)," leaving 1761 (97.5%) whose vital status was determined through the end of 1983. One hundred-twenty deaths (79 males and 41 females) occurred and were contrasted with expected deaths based upon

National Japanese death rates, age-, sex- and calendar time-specific. Male expected deaths equaled 66.13, while female expected deaths equaled 48.9. Malignant neoplasms in males totaled 34 as compared with 15.51 expected ($p<0.01$). This significantly increased risk was entirely due to a significant excess risk of liver cancer (9 observed vs. 1.61 expected., $p<0.01$) and a statistically significant excess risk of cancer of the lung trachea and bronchus (8 observed vs. 2.45 expected., $p<0.01$). In females, only liver cancer appeared excessive albeit nonsignificant (2 observed vs. 0.66 expected). Even if death rates of Fukuoka and Nagasaki prefectures were used as the comparison population, the locale where the rice oil poisoning took place, the risk of liver cancer remained statistically significant.

Although the elevated risk of liver cancer is real, the authors are reluctant to attribute it to the poisoning because of the unusual distribution of deaths. In Nagasaki prefecture where some 550 patients live, only one male liver cancer patient was seen, but in Fukuoka prefecture eight liver cancers were identified out of >700 patients residing there. Deaths from liver cancer are not different from expected in Nagasaki prefecture. The authors reported that they were examining the medical records of the decedents to confirm the diagnosis of liver cancer.

Unfortunately, mortality for each prefecture is not separated; hence, it is difficult to determine if age, sex or socio-economic factors or lack of access to medical care facilities or other factors could be the reason for the differential liver cancer mortality in patients of these two prefectures. Latency was also not examined. However, the incident occurred in 1968 and affected a large number of persons with certifiable disease; hence, all live patients had to have been observed at least a minimum of 15 years.

But, as was noted in the Amano et al (1984) review, these patients were exposed to polychlorinated dibenzofurans and polychlorinated quinones as well. Further efforts are under way to clarify questions about this study. It would be premature to conclude that these results are anything more than suggestive at this time with respect to classifying PCBs as carcinogenic to humans.

Yu-Cheng Incident. An outbreak of a similar nature was reported among some 2000 persons in the Taichung and Changhwa provinces of Taiwan in March of 1979. In October of 1979 the illness was found to be the result of the ingestion of rice oil contaminated with polychlorinated biphenyls (PCB). Chen et al. (1980) reported on blood PCB levels of 66 victims for which they had prepared gas chromatograms. Basically, blood concentration residues ranged from 11-720 ppb in these patients. The mean value was 49 ppb; most values were under 100 ppb. In only two instances were the concentrations greater at 120-720 ppb. The authors reported that the higher value of 720 ppb occurred in a patient who had difficulty in metabolizing and excreting PCB components. They also maintain that blood PCB levels of these patients are "much higher" than those of 72 Japanese Yusho patients (Koda and Masuda, 1975) although Koda and Masuda reported the mean PCB value in Yusho patients was 5.9 ppb with a standard deviation of 4.5 ppb. Chen et al. (1980) maintained that this difference is due to a lengthy time lapse from the exposure to PCB in Yusho patients before measurements were taken compared with a much shorter time lapse in Yu-Cheng patients before measurements were taken. Furthermore, the patients of Yu-Cheng consumed a larger proportion of highly chlorinated PCBs compared with those of Yusho and, as a result, they will be retained longer in the body according to the authors.

The most important observation about this study is that another mass poisoning episode took place similar to that of the Yusho incident but it was more recent and the 2000 or so victims must be monitored and followed to determine if an excess risk of liver cancer asserts itself after a suitable latent period has lapsed. No data on cancer morbidity and mortality has been reported yet. As of this writing, 6 years is not an ample time period in which an excessive risk of liver cancer would assert itself in this cohort. In a later report Chen et al. (1981) noted as well the presence of polychlorinated dibenzofurans in samples of the toxic rice-bran oils analysed. The ratios of PCB to that of PCDF ranged from 219 to 368 to 1 in six samples.

Human Cancer Studies - Summary

Two brief reports of one study of melanoma in workers exposed to PCBs and an update of the same study by NIOSH reported a statistically significant elevated risk of melanoma based on three cases. However, it was reported that exposure to PCB could not be evaluated and that these same workers were subject to other potential carcinogens in their work.

An ecological study of incidence rates of ocular melanoma in Ohio counties revealed no pattern of association with geographic distribution of areas of high PCB concentrations. However, the measurement of exposure involved estimating the levels of PCBs in fish and the location of PCB production sites. It is highly unlikely that any positive correlation of one with the other could be determined given the methodological limitations of the design.

A retrospective cohort mortality study in 1981 and a published update of the same study by the same author in 1986 revealed a statistically significant excess of liver and biliary passageway cancer in workers at two capacitor manufacturing plants. However, four of the five liver and biliary passageways cancers occurred to female workers of one plant and only one to males exposed at the other. It cannot be concluded yet that this supports a casual association because of the small number of deaths involved. The author maintains the findings are only tentative. Several additional years of follow-up should be added as well as an evaluation of the possible confounding effects of diet, alcohol and perhaps other potential carcinogens found in the workplace in this study.

In another retrospective study by Bertazzi et al. (1987) 554 male and 1556 female employees of a capacitor-making facility in Italy were found to have significantly higher risks of total cancer in male as well as female employees. With respect to site, gastrointestinal tract cancer was significantly elevated in males. Included in this group of six GI tract cancers was one liver cancer while a second was biliary tract cancer. Additionally cancer of the hematopoetic tissue was elevated in both sexes but not significantly so except in females contrasted with expected local mortality. Aside from an elevated non-significant risk of hematologic neoplasms, no clearcut and site-specific risk could be identified. Latency was not considered. No definite concludion regarding a causal association between cancer of the GI tract and exposure to PCBs could be drawn from the results of this study since the risk for females was elevated; and the remaining tumor sites identified in this category have not been previously shown to be associated with exposure to PCBs.

Amano et al. (1984) and Kuratsune (1986) reported a statistically significant excess risk of liver cancer in Yusho patients followed over 16 years in both male and female victims. The authors regard these findings as only tentative because the excess was found only in one prefecture and not the other. Furthermore, the victims consumed polychlorinated dibenzofurans and polychlorinated quinones in much smaller quantities at the same time as the PCBs. Hence exposure to these other chemicals cannot be ruled out as possible contributors to the excess risk of liver cancer in Yusho patient. These authors are refining their data at this time and reexamining their results.

Although these data seem to suggest a possible carcinogenic effect through the ingestion route and possibly inhalation route in humans, because of the tentative nature of the findings, and the fact that refinement and reevaluation of the results are underway as well as possible concurrent exposure to other potential carcinogens, CAG regards the human data at this time as inadequate but suggestive.

However, it has recently been learned (Moolenaar, 1987) that the International Agency for Research on Cancer (IARC) has classified the human health data as "limited" (2A) based upon the findings of the Bertazzi et al. (1987) and Brown (1986) studies. However, lack of site concordance and small power in these studies precludes EPA from classifying the weight of evidence higher than inadequate at this time.

Health Effects (Other than Cancer) - Summary

Since the start of their production, PCBs have become constituents of environmental media and they have bioaccumulated in animals and humans. The consequences of the presence of PCBs is not fully understood. The following section summarizes the studies available for evaluation of the environmental health effects of PCBs.

Unlike the occupational exposure and contaminated rice oil situations, environmental exposure to PCBs has not been reported to cause overt toxic symptoms such as chloracne. The literature indicates that environmental PCB exposure may induce more subtle biochemical alterations.

It is not clear whether PCB mixtures are solely responsible for adverse health effects or whether contamination of PCB mixtures with PCDFs caused the toxic response. In Yusho and Yu-Cheng poisoning incidents, the presence of PCDFs in the contaminated risce oil and in the liver and other tissues of the victims indicates that PCDFs were the responsible toxic compounds.

Reproductive System. Evidence for fetotoxicity comes primarily from laboratory studies (Chapter V); however, a recent report indicates that the human perinatal system may also be a target for PCB toxicity. A study of individuals who consumed moderate quantities of PCB-contaminated lake fish indicated that PCBs crossed the placenta. PCB exposure, as measured by both contaminated fish consumption and cord serum PCB levels, predicted lower birth weight and smaller head circumference of infants born to these mothers (Fein et al., 1984).

High PCB serum levels were found in some women who had recent or former missed abortions with mean PCB serum levels of 103.04, 82.00 and 20.69 ppb for recent missed abortions, former missed abortions and control groups, respectively (Bercovici et al., 1983). Some women with premature delivery had mean PCB serum levels of 128 ppb in the premature delivery group vs. 26.5 ppb in the control group (Wasserman et al., 1982). The higher PCB serum levels were associated with increased incomplete abortions (Bercovici et al., 1983) and premature deliveries (Wassermann et al., 1982), but a definitive causal relationship cannot be established, as only small numbers of women were examined (up to 17 symptomatic; up to 10 asymptomatic), and some of these women had high serum levels of some organochlorine insecticides (DDT isomers and their metabolites, lindane, dieldrin, heptachlor epoxide).

Clinical Observations. PCBs were discovered in sewage sludge used for fertilizer in Bloomington, Indiana. The metabolic consequences of PCB exposure were studied (Baker et al., 1980). Serum PCB levels in sludge users were not different from those of other members of the community not using the sludge. In sludge users PCB levels were associated positively with degree of garden care and negatively with wearing gloves but not correlated with amount of sludge used or duration of exposure. Plasma triglyceride levels increased significantly with PCB concentrations.

Kreiss et al. (1981) examined 458 volunteers from Triana, Alabama, $\geq$12 years of age, and correlated serum PCB levels (Aroclor 1260) with elevated blood pressure. The mean serum PCB level among this group was 17.2 ppb.

Three classifications of blood pressure measurements were used: normal (systolic of <140 mm Hg and diastolic of <90 mm Hg), borderline hypertension (systolic of 140-159 mm Hg and diastolic of 90-94 mm Hg) and hypertension (systolic of $\geq$95 mm Hg). The incidence of borderline and definite hypertension was increased 30% more than would be expected for a general population with the same age, race and sex composition.

VII. MECHANISMS OF TOXICITY

Introduction

Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and naphthalenes (PCNs) are a class of structurally-related chlorinated aromatics that are industrial products or by-products and are formed during the combustion of industrial and municipal waste. The toxic and biologic effects of commercial PCB mixtures and individual isomers and congeners are dependent on a number of factors including the dose of the toxin and the sex, age, species and strain of animal used. The toxic responses observed in several animal species include a wasting syndrome, thymic atrophy and immunotoxicity, reproductive toxicity, endocrine effects, hepatotoxicity and porphyria, chloracne and related dermal lesions, carcinogenicity and the induction of diverse enzymes including several hepatic drug-metabolizing enzymes (Safe, 1984; Safe et al., 1982, 1985b; McConnell, 1980b; Kimbrough et al., 1978; Matthews et al., 1978; Poland and Knutson, 1982; Parkinson and Safe, 1981). Moreover, it has also been noted that PCBs, PCDFs, PCDDs and PCNs elicit many similar biologic and toxic responses in laboratory animals and humans, and the major differences within this class of chemical pollutants are quantitative in nature.

The proposed mechanism of action of the toxic halogenated aromatics has initially been derived from studies using the most toxic member of this class of chemicals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The synthesis of radiolabeled [^{3}H]-2,3,7,8-TCDD with high specific activity (52.5 Ci/mmol) resulted in the identification of a specific binding protein in hepatic cytosol of "responsive" C57Bl/6J mice; in contrast minimal binding activity was observed in "non-responsive" DBA/2J hepatic cytosol (Poland

et al., 1976). The role of this Ah receptor protein in the mechanism of action of toxic halogenated aromatics has been thoroughly investigated and satisfies most of the specific criteria that support a receptor mediated cellular process (Poland et al., 1979, 1983; Nebert, 1979, 1980; Nebert et al., 1981, 1983; Nebert and Jensen, 1979; Okey, 1983; Poland and Glover, 1980; Safe, 1986). These criteria include the following: 1) the existence of a finite number of binding or receptor sites and therefore saturable binding, 2) high affinity ligand binding that is commensurate with the usually low levels of circulating hormones, 3) stereoselective binding capacity for the receptor and 4) tissue or organ response specificity for the receptor ligand. The role of the 2,3,7,8-TCDD (or aryl hydrocarbon, Ah) receptor in mediating the biologic and toxic effects of PCBs is supported by several studies that are summarized in the following sections.

Role of the 2,3,7,8-TCDD Receptor Protein

Structure-Activity Relationships.

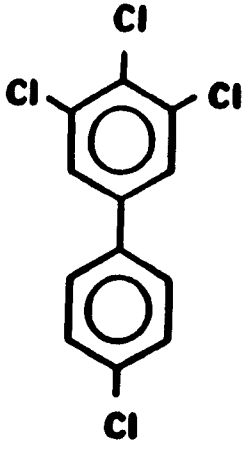
Induction of Cytochrome P-450-Dependent Monooxygenases -- It was initially reported (Alvares et al., 1973; Alvares and Kappas, 1975; Litterst et al., 1972) that Aroclor 1254 and some related commercial PCBs were unique "mixed"-type inducers of the hepatic cytochrome P-450 dependent monooxygenases. Aroclor 1254 induced microsomal benzo[a]pyrene hydroxylase (or aryl hydrocarbon hydroxylase, AHH) and N-dealkylase enzymes. The induced microsomal enzyme activities, and the spectral and electrophoretic characteristics of the proteins were similar to those observed after coadministration of the classical monooxygenase enzyme inducers, phenobarbital and 3-MC. Subsequent studies have shown that the activities induced by Aroclor 1254 are due to the preferential induction of cytochromes P-450a, P-450b, P-450c,

P-450d and P-450e. Phenobarbital preferentially induces cytochromes P-450b+e, 3-MC preferentially induces cytochromes P-450c and d and both compounds induce cytochrome P-450a to P-450e (Ryan et al., 1977, 1979; Botelho et al., 1979; Thomas et al., 1983).

Several studies with selected PCDD, PCDF and PCB congeners have shown that there was a rank order correlation between the toxicity of a compound and its activity as an inducer of AHH (Poland et al., 1979). Thus, induction of this enzyme activity (which is associated with cytochrome P-450c) has served as a bioassay for identifying the most toxic PCB isomers and congeners.

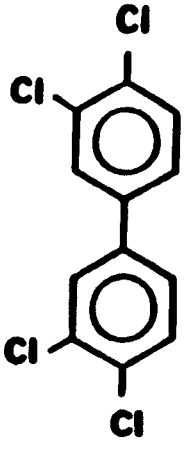
In vitro and in vivo structure-activity relationships for PCBs as inducers of AHH and cytochrome P-450c showed that the most active compounds, 3,4,4',5-tetra-CB, 3,3',4,4'-tetra-CB, 3,3',4,4',5-penta-CB and 3,3',4,4',5,5'-hexa-CB, required chlorine substitution at both para and at least two or more meta positions (Poland and Glover, 1977; Parkinson et al., 1981a). These four PCB congeners contain no ortho substituents and are all approximate isostereomers of 2,3,7,8-TCDD. Not surprisingly these compounds all bind with relatively high affinity to the cytosolic receptor protein and are also acutely toxic (Bandiera et al., 1982; Leece et al., 1985). However, analytical studies indicate that the four coplanar PCBs are minor constituents of the more active commercial PCBs, Aroclor 1254 and Aroclor 1260 (Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985a; Albro et al., 1981; Mullin et al., 1981) and this fact prompted others (Safe, 1984; Sawyer and Safe, 1982; Parkinson et al., 1980a,b, 1981a,b, 1982, 1983b; Greenlee and Irons, 1981; Robertson et al., 1984) to identify the active compounds present in these mixtures.

The introduction of a single ortho-chloro substituent into the biphenyl ring results in decreased coplanarity between the two phenyl rings. It was initially assumed that reduction in coplanarity of these compounds would reduce their binding to the cytosolic receptor and eliminate AHH induction activities. The effects of ortho substituents on PCB activity were evaluated by synthesizing all the mono-ortho analogs of the most active coplanar PCBs (that is, 3,4,4,5-tetra-CB, 3,3,4,4-tetra-CB, 3,3',4,4',5- penta-CB and 3,3',4,4',5,5'-hexa-CB) (Figure VII-1) and determining the mixed-function oxidase enzyme-inducting activities in rat hepatoma H-4-II E cells, and immature male Wistar and Long-Evans rats (Sawyer and Safe, 1982; Parkinson et al., 1981a, 1983b). All of these compounds induce hepatic microsomal AHH and DMAP N-demethylase in the Wistar rats and cytochromes P-450a to P-450e in the Long-Evans rats. It was apparent that the mono-ortho analogs of the coplanar PCBs resembled phenobarbital plus 3-MC (coadministered) and Aroclor 1254 in their mode of drug-metabolizing enzyme induction. A comparison of the in vivo and in vitro induction activities of the coplanar and mono-ortho coplanar PCBs clearly shows that the orthochloro substituent diminishes but does not eliminate the induction activity. These studies clearly identify the structures of the active chlorinated biphenyl components in the commercial PCB. Several mono-ortho coplanar PCBs, including 2,3,3',4,4'-penta-CB, 2,3',4,4',5-penta-CB, 2,3,3',4,4',5- hexa-CB and 2,3,3',4,4',5,5'-hepta-CB have been identified in a number of commercial formulations including the Aroclors, Phenoclors and Kanechlors (Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985a; Albro et al., 1981; Mullin et al., 1981).



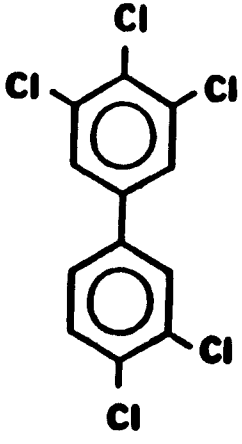
2',3,4,4',5

2,3,4,4',5



2,3,3',4,4'

2,3',4,4',5



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2,3',4,4',5,5'

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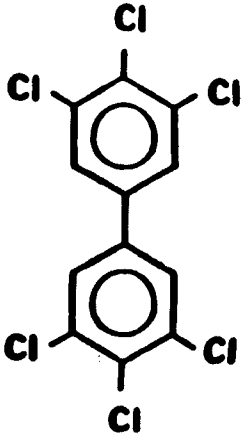

2,3,3',4,4',5,5'

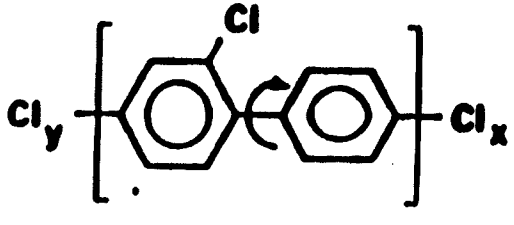

FIGURE VII-1

Coplanar and Mono-ortho Coplanar PCB Analogs

The effects of two ortho-chloro substituents on the AHH and cytochrome P-450c induction activities of the di-ortho coplanar analogs were determined. The results (Parkinson et al., 1981a,b; Greenlee and Irons, 1981) indicated that in male Wistar rats (dose level 300 μmole/kg) at least five members of this group, namely 2,2',3,3',4,4'-hexa-CB, 2,3,3',4,4',6-hexa-CB, 2,2',3,4,4',5'-hexa-CB, 2,3,4,4',5,6-hexa-CB and 2,2',3,3',4,4',5-hepta-CB, exhibited a mixed-type induction pattern. Using the more sensitive cytochrome P-450 isozyme immunoquantitation assay, it was shown that these five PCBs and at least two additional compounds, 2,3',4,4',5-penta-CB and 2,3',4,4',5',6-hexa-CB, induced cytochromes P-450a to P-450e in male Long-Evans rats (dose level 500 μmole/kg) (Parkinson et al., 1981a). Since not all the di-ortho coplanar PCBs were evaluated as inducers of cytochrome P-450c, the isozyme associated with AHH induction, it is possible that other members of this group may also induce this hemoprotein. 2,2',4,4',5,5'-Hexa-CB was the only di-ortho coplanar PCB that did not induce cytochromes P-450c and P-450d but, like phenobarbital, induced cytochromes P-450a and P-450b + P-450e (Parkinson et al., 1981a). Subsequent studies have not identified any other PCBs that induce AHH activity.

Receptor Binding Affinities -- The direct binding of radiolabeled PCBs to the 2,3,7,8-TCDD receptor protein has not been investigated. However, competitive binding studies using [^{3}H]-2,3,7,8-TCDD as the radioligand have been reported (Bandiera et al., 1982). The structure-activity relationships reported for PCBs as AHH inducers and as competitive ligands for the cytosolic receptor protein were comparable; the coplanar PCB isomers and congeners bound with higher affinity than the monoortho coplanar analogs (see Figure VII-1). Several compounds that do not induce hepatic microsomal

AHH or cytochrome P-450c exhibit low affinity for the receptor (EC_{50} $>10^{-5}$ M) and these values were considered nonspecific lipophilic interactions between the ligands and the hydrophobic protein binding site (Table VII-I).

PCB Toxicity -- Several studies report the toxicities of diverse PCB isomers and congeners and the results clearly demonstrate that the coplanar congeners are the most toxic group of PCB compounds. Pretreatment of rodents with the 3,3',4,4'-tetra-CB, 3,3',4,4',5-penta-CB and 3,3',4,4',5,5'-hexa-CB results in hepatic damage, porphyria, reproductive toxicity, thymic atrophy, marked increases in liver lipids, edema (in mice and chicks) and hepatomegaly (Parkinson et al., 1983b; Leece et al., 1985; Goldstein et al., 1976; Kohli et al., 1979; Biocca et al., 1981; McKinney et al., 1976; Yoshihara et al., 1979; Puhvel et al., 1982; Kawanishi et al., 1978; Swain et al., 1983; Silkworth and Grabstein, 1982; Silkworth et al., 1984). In the rhesus macaques (Macaca mulatta), 3,3',4,4',5,5'-hexa-CB was toxic at dietary dose levels <1 ppm whereas the 2,2',4,4',5,5'-, 2,2',4,4',6,6'- and 2,2',3,3',6,6'-hexa-CBs caused no discernible adverse effects at dose levels up to 65 ppm (McNulty, 1985); comparable structure-activity relationships were also noted in mink (Auerlich et al., 1985).

Several studies report that many of the mono-ortho coplanar PCB analogs are also toxic (Safe, 1984; Parkinson et al., 1980a,b, 1981a,b, 1982, 1983b; Bandiera et al., 1982; Leece et al., 1985; Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985b; Albro et al., 1981; Mullin et al., 1981; Greenlee and Irons, 1981; Robertson et al., 1984; Goldstein et al., 1976; Kohli et al., 1979; Biocca et al., 1981; McKinney et al., 1976;

TABLE VII-1

PCBs: Summary of Structure-Function Relationships

PCB Structures (Number)	Cytochromes P-450 Induction[a] (% of control)		Relative % Activity		
			AHH Induction		
	P-450c + P-450d	P-450b + P-450e	In vivo[b]	In vitro[c]	Receptor Binding[d]
Coplanar PCBs - I[e] (3)	4100-1800	no induction	+++	100-1%	100-35%
Coplanar PCBs - II[f] (2)	1500-1100	1400-600	++	3×10^{-2}[g]	0.5[g]
Mono-ortho Coplanars (8)	2400-750	4700-2600	++	$0.3\text{-}2.4 \times 10^{-5}$	6-1.5
Di-ortho Coplanars (12)	900-250	6300-1000	+	Inactive	≤ 0.3[h]
2,2',4,4',5,5'-Hexa-CB	no induction	7300	Inactive	Inactive	≤ 0.3
2,3,7,8-TCDD	3500	no induction	+++++	400	2500

[a] Male Long-Evans rats (dose: 500 mol/kg)

[b] Male Wistar rats (dose: 300 mol/kg)

[c] Rat hepatoma H-4-II-E cells

[d] Determined by the competitive displacement of [^{3}H] TCDD bound to male Wistar rat hepatic cytosol

[e] 3,3',4,4'-tetra-CB, 3,3',4,4',5-penta-CB and 3,3',4,4',5,5'-hexa-CB

[f] 3,4,4'-tri-CB and 3,4,4',5-tetra-CB

[g] Determined only for 3,4,4',5-tetra-CB

[h] Represents nonspecific binding

Yoshihara et al., 1979; Yamamoto et al., 1976; Ax and Hansen, 1975). For example, 2,3,3',4,4'-penta-CB administered to mice results in a wasting syndrome (weight loss), edema, liver lipid accumulation, extensive hepatic damage, and splenic atrophy. 2,3',4,4',5-penta-CB causes 100% embryo mortality in eggs from pullets receiving the PCB in their diet at a level of 20 ppm (Ax and Hansen, 1975); administration of 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB to rats causes increased liver weights, increased liver lipids and thymic atrophy; 2,3,3',4,4',5-hexa-CB, 2,3,4,4',5-penta-CB, 2,3,3',4,4',5'-hexa-CB, 2,3,3',4,4',5'-hexa-CB and 2,3,3',4,4'-penta-CB cause thymic atrophy in male rats. Quantitative structure-activity relationships for several coplanar and mono-ortho coplanar PCBs has recently been reported (Leece et al., 1985). A comparison of the ED_{50} values for AHH/ethoxyresorufin O-deethylase (EROD) induction, body weight loss and thymic atrophy in the rat clearly demonstrates the higher toxicity of the formed group of compounds. Moreover, there was an excellent linear correlation between the in vitro AHH/EROD induction potencies of these compounds and their in vivo toxicities and AHH/EROD induction potencies.

The data indicate that the mono-ortho analogs of the coplanar PCBs elicit toxic effects that resemble (qualitatively) 2,3,7,8-TCDD; several of these compounds (2,3,3',4,4'-penta-CB, 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB) have been identified in commercial PCBs and as residues in human tissues (Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985a; Albro et al., 1981; Mullin et al., 1981).

The toxicity of the di-ortho coplanar PCBs has not been systematically investigated; however, two members of this group, 2,2',3,3',4,4'- and

2,2',3,4,4',5'-hexa-CB are porphyrinogenic in rats after long-term feeding studies (Stonard and Grieg, 1976). Both of these compounds are among the most active di-ortho coplanar PCB inducers of rat hepatic microsomal AHH and cytochrome P-450c (Parkinson et al., 1983b) and warrant further studies.

Pharmacogenetic Studies and Response Specificity. Pharmacogenetic studies with genetically inbred mice have been utilized to probe the mechanism of action of 2,3,7,8-TCDD, PCBs and related compounds (Poland et al., 1983; Nebert et al., 1981, 1983; Okey, 1983; Nebert, 1979, 1980; Nebert and Jensen, 1979; Poland and Glover, 1980). Responsive mice, typified by the C57Bl/6 strain contain relatively high cytosolic receptor protein levels in hepatic and some extrahepatic tissues whereas nonresponsive mice, typified by the DBA/2 strain contain relatively low (to nondetectable) levels of the cytosolic receptor. Studies with 2,3,7,8-TCDD in inbred mice have clearly shown that many of the biologic and toxic effects elicited by this compound segregate with the Ah (or 2,3,7,8-TCDD) receptor locus (Poland et al., 1983; Nebert et al., 1981, 1983; Okey, 1983; Nebert, 1979, 1980; Nebert and Jensen, 1979; Poland and Glover, 1980). Moreover, it has been demonstrated in genetic cross and backcross experiments between C57Bl/6 and DBA/2 mice that the trait of Ah or 2,3,7,8-TCDD responsiveness is inherited in a simple autosomal dominant mode. The differential activities of several coplanar and mono-ortho coplanar PCBs in responsive and nonresponsive mice also confirms the role of the receptor in mediating several biologic and toxic effects including AHH/EROD induction (Parkinson et al., 1982; Robertson et al., 1984) thymic atrophy (Parkinson et al., 1982; Robertson et al., 1984), body weight loss (Parkinson et al., 1982; Robertson et al., 1984) and immunotoxicity (Silkworth and Grabstein, 1982; Silkworth et al., 1984; Clark

et al., 1983). These experiments with inbred mice also demonstrate that the presence of the receptor in the species also influences response specificity to the biologic and toxic effects of PCBs.

Summary. The genetic studies with inbred mice and the extensive structure-function relationships summarized previously support the proposed receptor-mediated mechanism of action for PCBs and related toxic halogenated aryl hydrocarbons. The precise role of the receptor ligand complex has been determined for the induction of cytochrome P-450c (Tukey et al., 1981; Israel and Whitlock, 1984; Jones et al., 1985) and involves nuclear translocation of the ligand receptor complex, interaction with nuclear binding site(s) followed by induction of the mRNA for cytochrome P-450c. Although the initial toxin-receptor interactions are probably involved in the ultimate expression of some of the toxic effects of PCBs, 2,3,7,8-TCDD and related compounds, the subsequent steps that lead to the diverse toxic responses have not been delineated.

Role of Metabolism in PCB Toxicity

Although PCBs produce a number of diverse toxic responses in a number of organs, the chemical species responsible for the toxicity are not known. It has been suggested that the parent compound, reactive intermediates formed during metabolism and metabolites of PCBs all produce toxic effects. For example, it was suggested that PCB-induced porphyria was produced by the parent compound (Strik et al., 1979). Other investigators have suggested that the cytotoxic and mutagenic effects of PCBs result from reactive arene oxides that are formed during metabolism (Allen and Norback, 1977; Wyndham et al., 1976). PCBs that contain vicinal unsubstituted carbon atoms are

substrates for oxidative metabolism by highly reactive arene oxide intermediates that interact with cellular macromolecules such as DNA, RNA and protein (Safe, 1980; Wyndham and Safe, 1978; Wyndham et al., 1976; Morales and Matthews, 1979; Hesse et al., 1978; Hargraves and Allen, 1979; Hesse and Wolff, 1977; Wong et al., 1979; Stadnicki et al., 1979). For example, the mutagenicity of 4-chlorobiphenyl was expressed only following its metabolism (Wyndham et al., 1976). In vitro studies in a Chinese hamster ovary cell line demonstrated that 4-chlorobiphenyl was metabolized to hydroxylated products and that 4-chlorobiphenyl-equivalents bound covalently to DNA, RNA, and protein and produced DNA damage as demonstrated by induction of unscheduled DNA synthesis (Wong et al., 1979). Other investigators reported that the arene oxide intermediate, 3,4-dihydro-3,4-epoxy-2,5-tetra-CB, was more potent than either 4-hydroxy-2,2',5,5'-tetra-CB or 2,2',5,5'-tetra-CB as a cytotoxicant and as an initiator of single strand breaks in DNA when incubated with L-929 cells (Stadnicki et al., 1979; Stadnicki and Allen, 1979). In vivo studies in mice demonstrated that 2,2',3,3',6,6'-hexa-CB bound covalently to hepatic RNA and protein at a level at least one order of magnitude greater than the essentially nonmetabolized isomer, 2,2',4,4',5,5'-hexa-CB (Morales and Matthews, 1979). These investigators also observed that 2,2',3,3',6,6'-hexa-CB bound covalently to DNA while 2,2',4,4',5,5'-hexa-CB did not.

Although most toxicity studies have focused on the parent PCB or reactive intermediates formed during the metabolism of PCBs, there is evidence that certain metabolites may cause toxicity. A monohydroxylated metabolite of 3,4,3',4'-tetra-CB has a lower LD_{50} in mice than the parent compound (Yamamoto and Yoshimura, 1973). PCB methyl sulphones are stable

lipophilic metabolites formed during biotransformation of PCB by the mercapturic acid pathway. These metabolites have been found to selectively accumulate in the apical cytoplasm of nonciliated bronchiolar (Clara) cells of the rat lung (Lund et al., 1985). This selective in vivo uptake appears to be due to the presence of a protein with high affinity and capacity for binding PCB methyl sulfones. This binding protein is present in Clara cells and the tracheobronchoalveolar lavage fluid from rats, mice and humans (Brandt, 1986; Lund et al., 1986a). Methylthio and methylsulfonyl PCBs have been identified in lung tissue from Yusho patients and healthy controls (Haraguchi et al., 1984, 1986). Lund et al. (1986a) proposed that the binding protein was responsible for the observed tendency of these PCB metabolites to accumulate in the lung tissue of humans. While the toxicological significance of these findings is not known, it has been suggested that these metabolites may be in part responsible for the persistent respiratory distress seen in the victims of PCB poisonings in Japan (Yusho) and the decreased lung vital capacity in workers exposed to PCBs (Shigematsu et al., 1978; Warshaw et al., 1979). In apparently the only study on the effect of PCB metabolites on lung function, Lund et al. (1986b) reported that 4-methylsulphonyl-2,2',5,5'-tetra-CB inhibited a cytochrome P-450-dependent enzyme activity in mouse lung, while inducing this activity in mouse liver. Thus, while these results suggest that PCB metabolites may mediate specific toxic responses of PCBs, further studies are needed to confirm the role of metabolism in the expression of toxicity.

Other Mechanisms

It is apparent that many PCB isomers and congeners that do not bind to the 2,3,7,8-TCDD receptor protein elicit a broad spectrum of biologic and

some toxic effects. Several compounds induce a number of microsomal cytochrome P-450 isozymes and related monooxygenase, glutathione transferases, epoxide hydrolase and glucuronyl transferases and resemble phenobarbital in their mode of induction of the drug-metabolizing enzymes (Parkinson et al., 1983b; Orberg, 1976; Denomme et al., 1983). Their mechanism of action is unknown. In addition, other studies have demonstrated that diverse commercial PCB mixtures and individual compounds inhibit mitochrondrial function (Nishihara, 1984), exhibit mild estrogenic properties in female rats (Bitman and Cecil, 1970), act as cancer promoters in hairless mice and rats (Poland et al., 1982; Preston et al., 1981) exhibit anticarcinogenic properties in other laboratory animal models for carcinogenesis (Kerkvliet and Kimeldoof, 1977), are inactive in the Solt-Farber model for liver tumors (Hayes et al., 1985) and cause delayed pregnancy in NMRI mice (Torok, 1978). Some of these activities may contribute to the toxicity of PCBs.

It is also possible that interactive effects may also play a significant role in PCB toxicology. A recent study has reported that 2,2',4,4',5,5'-hexa-CB (and other related congeners), a compound that does not induce 2,3,7,8-TCDD receptor-mediated effects, elevates hepatic cytosolic receptor protein levels (>2-fold) in the rat and mouse (Denomme et al., 1986). Moreover, rats pretreated with 2,2',4,4',5,5'-hexa-CB are more responsive to the induction of hepatic microsomal AHH and EROD by planar and mono-ortho coplanar PCB congeners (Leece et al., 1986). These results confirm the importance of the cytosolic receptor protein in the mechanism of action of PCBs and suggest that nonadditive interactive effects that are due to receptor modulation (Birnbaum et al., 1985) may influence the activity of PCB mixtures and related toxic aryl hydrocarbons.

Summary

Data on purified PCB isomers have established that the toxic, metabolic and toxicokinetic behavior of the different component molecules varies not only with the degree of chlorination (greater toxic potency with greater degree of chlorination) but also with the position of the chlorine atoms. The relative toxicity and persistence of four pure hexa-CB isomers was examined in mice; 3,4,5-sym-hexa-CB was found to be the most toxic (LD_{50} = 19 mg/kg bw/day) and persistent (levels in liver and adipose tissue) isomer, followed by 2,4,6-sym-hexa-CB > 2,4,5-sym-hexa-CB, > 2,3,6-sym-hexa-CB. Although structure-activity relationships are most interesting for this class of compounds, it is also important to note that highly toxic, coplanar PCB isomers, such as 3,4,5-sym-hexa-CB, have only been detected as very minor constituents of commercial PCB formulations.

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = \_\_\_\_ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1986a) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell\text{/day}} = \_\_\_\_ \text{ mg/}\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (\_\_\_ \ell\text{/day})} = \_\_\_\_ \text{ mg/}\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

The evidence of human exposure to PCBs from finished drinking water is limited. A single finished groundwater sample in each of the National Organic Monitoring Survey (NOMS) II and III contained PCBs in minimum quantifiable detectable limits that ranged from 0.1-0.2 µg/ℓ, respectively. PCBs were detected in all three phases of the NOMS of finished surface water. In this survey of finished surface drinking water, PCBs were detected in two samples of NOMS I at levels of 0.13 and 1.4 µg/ℓ; in NOMS II, two samples contained 0.1 µg/ℓ and one sample had 0.2 µg/ℓ of PCBs; and only one sample of NOMS III contained PCBs at a concentration of 0.2 µg/ℓ. Schroeder and Barnes (1983) showed that PCB removal from Hudson River water ranged between 80 and 90% with levels in finished drinking water seldom exceeding 100 ng/ℓ. Congeners of Aroclor 1016 were also detected in finished drinking water with the Hudson River as its source at a median concentration of 85 ng/ℓ (Brinkman et al., 1981).

Groundwater from 32 of 163 wells in New Jersey had PCBs with concentrations ranging from 0.6-127 µg/ℓ. Many of these wells sampled were from highly industrialized and populated areas of the state. Congeners of Aroclor 1016 have been detected in the water distribution system of an upstate New York public water supply system near a heavily polluted section of the Hudson River at a concentration level of 69-100 ng/ℓ (Brinkman et al., 1980, 1981). The impounded water contained a uniform level of Aroclor 1016 congeners (Dority Reservoir, 70-130 ng/ℓ; New Reservoir, 110-120 ng/ℓ; Distribution system, 69-100 ng/ℓ) while rain water was much higher (1300 ng/ℓ). Low levels of Aroclor 1254 congeners (up to 36 ng/ℓ) were detected in the New Reservoir only. The high levels of PCBs in the Hudson River (360 ng/ℓ) near Fort Edward was thought to be responsible for high impounded water levels. Finished tap water did not show evidence of Aroclor 1254 congeners (<12 ng/ℓ). The median concentration of Aroclor 1016 congeners was 85 ng/ℓ in finished tap water. One sample at the chlorination site was 30% higher in Aroclor 1016 congeners than at a household tap.

The Aroclor 1016 origin was confirmed by identifying at least five specific surrogate congeners by retention time from a possible 19 congeners. The 19 congeners were: 4-Cl-CB/2,2'-Cl_2-CB (also Aroclor 1221); 2,4'-Cl_2CB (also Aroclor 1221); 2,2',5'-Cl_3-CB, 2,2',4'-Cl_3-CB; 2,2',3'- and 3,2',6'-Cl_3-CB; 4,2',6'-Cl_3-CB; two unidentified Cl_3-CBs; 3,3',5'-Cl_3-CB; 3,2',4'-Cl_3-CB; 2,4,4'-Cl_3-CB (also Aroclor 1221); 2,3',4'-Cl_3-CB; 2,5,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',5'-Cl_4-CB (also Aroclor 1254); 2,3,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',4'-Cl_4-CB (also Aroclor 1254); 2,3,2',3'-Cl_4-CB (also Aroclor 1254); and two unspecified Cl_4-CBs (one of which also arose from Aroclor

1254). Thus, 10 of the 19 congeners selected were unambiguously from Aroclor 1016, with 6 being resolved specific congeners. In this study, 60 congeners were utilized to identify the possible presence of Aroclors 1221, 1016, 1254 and 1260. Each peak chosen provided an independent estimate of the quantity of the Aroclor using the appropriate response factor for each congener. The concentration of the Aroclor was calculated as the average of the concentrations by each of the five chosen peaks. Representative samples were confirmed by GC/MS. The detection limit was 50 pg, equivalent to a 12 ng/ℓ (12 ppt) concentration in 2 ℓ of water subjected to the analysis technique.

It is clear the least chlorinated congeners are the PCBs that might be expected to occur in drinking waters produced from nonchlorinated processes. Chlorination may lead to the presence of higher chlorinated PCBs for Aroclor 1221 and below but not for Aroclor 1242 and above (Aly and Badawy, 1986). Most of the residues in human tissues are highly chlorinated (Holt et al., 1986; Ansari et al., 1986; Safe, 1984; Bush et al., 1985b). This is characteristic of exposure through food sources such as fish, birds or human milk. The less chlorinated congeners dominate in inhalation and drinking water exposures.

PCBs in the Hudson River (from Aroclors 1221, 1242, 1248, 1254 and 1260) are still at levels causing concern (Brown et al., 1985; Bush et al., 1985a). The more soluble less chlorinated congeners dominated in waters without sediments, and the highly chlorinated congeners were associated with particulate matter (Bush et al., 1985a; Brown et al., 1985; Baker et al., 1985). This also applied to wet deposition (Mazurek and Simoneit, 1985).

The PCB residues in sediment, ambient water and fish in the United States have been highest in the Hudson River, the Great Lakes apart from Lake Superior, the Ohio River, the upper Mississippi and the Cape Fear River in North Carolina. In the Great Lakes there is evidence for seasonal cycling of PCB levels (Baker et al., 1985). PCBs in air, plants, milk and wild fowl also confirm the continuing extensive PCB contamination in the Hudson River basin.

In the Hudson River in 1983 a specific congener analysis revealed that half of the PCB transport (see Table IV-1) is represented by 2-, 2,2'- and 2,6-PCB (Bush et al., 1985a), although these congeners are also volatile and biodegradable. A specific congener analysis revealed that fish in the Hudson River obtained much of their bioaccumulated PCB load from food chain vectors (Bush et al., 1985a).

PCBs were found in the water of a small upstate New York public water supply system near the heavily polluted section of the Hudson River (Brinkman et al., 1981).

Noncarcinogenic Effects

Tests of the acute lethality of PCB products in laboratory animals, with the possible exception of the guinea pig, suggest that, in general, PCB commercial products have similar acute toxicity regardless of route of administration, species or age of animal. The single dose oral LD_{50} values for commercial PCB formulations in rats, rabbits, mice and mink range from 0.5-11.3 g/kg bw (Grant and Phillips, 1974; Bruckner et al., 1973; Kimbrough et al., 1978; Fishbein, 1974; Garthoff et al., 1981; Aulerich and

Ringer, 1977). Route of administration also had little effect (<1 order of magnitude) on lethality with the lethal dose for dermal administration in rabbits ranging from 0.8-3.2 g/kg bw (Nelson et al., 1972); while the lethal dose in mice administered PCBs by i.p. injection, ranged from 0.9-1.2 g/kg bw (Lewin et al., 1972). The role of the toxic PCDF impurities in these effects is unknown.

There are two indications of major differences in the acute toxicity of PCBs. First, there is limited evidence that the guinea pig may be more sensitive to the lethality of PCBs than other species. This species is also more sensitive to toxic PCDFs. Miller (1944) observed 100% mortality in a small group of guinea pigs receiving two oral doses of PCB (43% chlorine) at levels of 67 mg/animal at 7-day intervals. In a study with perhaps the most potent PCB isomer, McConnell and McKinney (1978) reported a LD_{50-30} of 0.5 mg/kg bw for 3,4,5-sym-hexa-CB in guinea pigs. This indication of possible large interspecies differences in sensitivity is of concern in species-to-species extrapolation when there is insufficient data to indicate which experimental animal most accurately reflects the sensitivity of humans. The second problem concerns the possible large difference in toxicity of specific congeners and isomers of PCBs. Limited mortality data were available from a study by Biocca et al. (1981), in which four different hexa-CBs were administered in the diet to mice for 28 days. They reported LD_{50-28} values ranging from 86.8 ppm (19 mg/kg bw/day) to >300 ppm (>64 mg/kg bw/day), with 3,3',4,4',5,5'-hexa-CB being the most potent and persistent isomer investigated. Probably even larger differences will be encountered as more congeners and isomers are tested. It is expected that the lower chlorinated congeners will be eliminated more quickly in humans than the highly chlorinated ones.

Some data are available on the nonlethal acute toxicity of PCBs administered by the oral route for periods of 30 days or less. The effects described in these studies were alterations of the liver, thyroid and reproductive system. Rosin and Martin (1983) reported that a dose of 30 mg/kg bw/day of Aroclor 1254 for 14 days to CD-1 mice decreased phenobarbital sleeping time, indicating a substantial induction of microsomal enzymes. Exposure of ICR mice to diets containing 250 or 62.5 ppm of Aroclor 1254 for 14 days (Sanders et al., 1974) resulted, respectively, in hepatomegaly and elevated serum corticosterone (the latter presumably as a result of altered liver steroid metabolism). These exposures are equivalent to doses of 32.8 and 8.1 ppm/day, assuming a mouse consumes 13% of its body weight per day.

Few studies have been designed to define the minimum effective oral doses required to induce hepatic enzyme activities. Chu et al. (1977) reported induction of hepatic mixed function oxidase (MFO) activity in male weanling rats exposed to Aroclor 1254 or 1260 in the diet at 20 ppm for 28 days. Similarly, Garthoff et al. (1977) reported that 5 ppm of Aroclor 1254 in the diet for 3 weeks resulted in induction of hepatic aminopyrine demethylase activity, while exposure at the same dose for 5 weeks produced a significant increase in liver weight in male Holtzman rats. Increases in liver-to-body weight ratio appear to be one of the sensitive indicators of PCB exposure. Grant and Phillips (1974) observed increased liver weight at doses as low as 5 mg/kg bw/day in male and female Wistar rats receiving Aroclor 1254 for 7 days. Carter (1983) observed significant hepatomegaly in rats ingesting diets containing as little as 20 ppm Aroclor 1254 (1 mg/kg bw/day) for 4, 8 and 14 days.

Besides changes in the liver, other effects reported for exposure to low levels of PCBs were increased thyroid activity in Sherman rats maintained on diets containing 250 ppm of Aroclor 1254 (12.5 mg/kg bw) for 14 days. Administration of Aroclor 1254 by gavage for 21 days at a dose of 0.05 g/kg bw/day resulted in weight loss and decreased body temperature in Sprague-Dawley rats (Komives, 1979; Komives and Alayoku, 1980). Ultrastructural evidence suggesting increased thyroid gland activity has also been found in Osborne-Mendel rats maintained on diets containing 5 ppm of Aroclor 1254 (0.25 mg/kg bw/day) for 4 weeks (Collins and Capen, 1980b). This exposure level also resulted in increased liver enzymes in Holtzman rats (Garthoff et al., 1977).

The toxicity resulting from PCB exposures of between 30 and 90 days has been more extensively studied. Alterations in liver ultrastructure occurred at doses of Aroclor 1254 as low as 5 ppm diet for 5 weeks in Holtzman rats (Kasza et al., 1978b). In the mouse (MNRI) a dose of Clophen A-60 as low as 0.025 mg/mouse (0.8 mg/kg bw/day, assuming a mouse weight 0.03 kg) for 62 days increased the estrous cycle, probably as a result of PCB-induced changes in liver steroid metabolism (Orberg and Kihlstrom, 1973). At higher dietary concentrations of 167 ppm (22 mg/kg bw) for 6 weeks, Aroclor 1016 and 1242 decreased the immunologic capability of BALB/CJ mice (Loose et al., 1978a).

Although other species have been tested to a lesser extent for this duration, the LOEL in these species were similar to those described for rats and mice. Rabbits exposed to diets containing 3.7 ppm of Aroclor 1254 (0.18 mg/kg bw/day, assuming a rabbit consumes 4.9% of its body weight/day) for 8 weeks developed no significant hepatomegaly, although atrophy of the

cortical tissues in the thymus was noted (Street and Sharma, 1975). In the guinea pig, Vos and van Genderen (1973) reported that diets containing 250 ppm of Clophen A-60 (7 mg/kg bw/day, assuming a guinea pig consumes 2.8% of its body weight/day) for 4-7 weeks was lethal; while diets containing 50 ppm Clophen A-60 or Aroclor 1260 (1.4 mg/kg bw) for 4-7 weeks produced immunosuppression. Allen et al. (1974a) and Allen (1975) observed comedones and facial edema in rhesus monkeys ingesting diets containing 25 ppm Aroclor (1.1 mg/kg bw, assuming a monkey consumes 4.2% of its body weight/day) for 2 months. The LOELs observed in these species were slightly higher than the LOELs reported in rats and mice.

Studies of chronic exposure ($\geq$90 days) to PCBs have failed to use sufficiently low doses to define a NOAEL in rats. In Sprague-Dawley rats, Allen et al. (1976) and Allen and Abrahamson (1979) reported that a 52-week exposure to diets containing 100 ppm of Aroclor 1248, 1254 or 1262 (5 mg/kg bw/day) followed by a 13-week observation period resulted in hepatomegaly and liver necrosis. At a lower exposure of 75 ppm in the diet (3.75 mg/kg bw/day) for 36 weeks, Sprague-Dawley rats developed focal necrosis (Jonsson et al., 1981). Porphyria was observed by both Kimbrough et al. (1972) and Zinkl (1977) after exposure of female Sherman rats for 8 months to 20 ppm Aroclor 1254 (1 mg/kg bw/day) or CD rats for 16 weeks to 10 ppm of Aroclor 1254 (0.5 mg/kg bw/day). In a dietary study of Aroclor 1254 employing near lifetime exposure (2 years), Morgan et al. (1981) reported an increase in mortality (17% as compared with 8% in controls) in Fischer 344 rats at the lowest dose tested (25 ppm; 1.25 mg/kg bw/day). In summary, the subchronic studies demonstrated increasing liver pathology over the dose ranges studied, 0.5-5 mg/kg bw/day; while in the only chronic study, the lowest dose tested (1.25 mg/kg bw/day) resulted in early deaths.

In mice dietary exposure levels to Kanechlor-300, -400, or -500 or Aroclor 1254 of between 100 and 500 ppm (13-65 mg/kg bw/day) for periods from 23 weeks to 11 months produced hepatomegaly (Ito et al., 1973; Bell, 1983; Kimbrough and Linder, 1974). The only study that defined a NOAEL in mice was the study by Koller (1977). Groups of BALB/CJ mice were maintained for 9 months on diets containing 0, 3.75, 37.5 or 375 ppm of the Aroclors 1221, 1242 or 1254 (0.45, 4.57 or 45.7 mg/kg bw/day). Aroclor 1221, with the lowest chlorine content (21%), produced no liver lesions, while exposure to Aroclor 1242 (42% chlorine) resulted in increased liver weight in the high-dose group. In mice exposed to Aroclor 1254, increased mortality was observed in the high-dose group with mild hepatopathology being observed in the median-dose group, and no liver lesions detected in the low-dose group. The NOEL observed in this study in mice of 0.45 mg/kg bw/day is nearly identical to the LOELs of 0.5 mg/kg bw/day associated with porphyria in rats (Zinkl, 1977), or 0.25 mg/kg bw/day associated with ultrastructural evidence suggesting increased thyroid gland activity (Collins and Capen, 1980b).

The only other species tested in chronic bioassays was the monkey and it proved to be highly sensitive to the toxic effects of PCBs. The most common observation in monkeys exposed to Aroclor 1248 in the diet for a period of from 8-39 months was skin lesions, edema and erythema (Barsotti and Allen, 1975; Allen and Barsotti, 1976; Allen et al., 1980; Becker et al., 1979). These effects were observed at the lowest doses tested [2.5-3 ppm in the diet (0.095-0.126 mg/kg bw/day)]. In addition, Becker et al. (1979) reported that monkeys fed diets containing 3 ppm of PCBs had gastric lesions, body weight loss and reduced hemoglobin and leukocytes.

PCBs have been demonstrated to be animal teratogens following oral exposure, and have been demonstrated to adversely affect reproduction. In an early study, Villeneuve et al. (1971a) reported no adverse effects when Aroclor 1254 was administered to pregnant Wistar rats at a dose of 100 mg/kg bw/day on days 6-15 of gestation. More recently, Spencer (1982) reported a decrease in the average fetal weight/ litter in Holtzman rats that received Aroclor 1254 at 100 ppm in the diet (5 mg/kg bw/day) from days 6 through 15 of pregnancy. A decrease in fetal survival rate was observed at exposure $\geq$300 ppm (15 mg/kg bw/day), while dietary exposure to Aroclor 1254 at 50 ppm (2.5 mg/kg bw/day) was found to be the NOEL (Spencer, 1982). Rabbits exposed to Aroclor 1254 had resorptions, abortions and dead fetuses at similar dose levels of 12.5 mg/kg bw/day administered on days 0-28 of gestation; however, slightly lower doses of 10 mg/kg bw/day were reported to be the NOEL (Villeneuve et al., 1971a). The Hartley guinea pig, which has been shown to have greater sensitivity to the toxicity of PCBs than most other species, had macerated fetuses after receiving 2.2 mg/day (6.5 mg/kg bw/day) of Clophen A-50 on days 10-60 of gestation (Brunstroem et al., 1982).

Toxic doses of PCBs were lower when exposure occurred before and during gestation. In a 2-generation reproduction study, Sherman rats maintained on diets containing 20 ppm Aroclor 1254 (1 mg/kg bw/day) had reduced litter size, and at 100 ppm (5 mg/kg bw/day) the pups that were born exhibited a significant increase in mortality (Linder et al., 1974). In this study, 5 ppm (0.25 mg/kg bw/day) was the NOEL. Complete loss of fertility was observed in male and female Wistar rats caged together for 9 weeks while ingesting 6.4 mg/kg bw/day of Aroclor 1254 emulsified in their drinking

water (Baker et al., 1977). Males regained normal fertility after removal from treatment for 2 weeks. When Aroclor 1254 was administered to lactating Holtzman rats at 32 mg/kg bw/day on days 3, 5 and 7 of lactation, the future mating behavior of nursing male pups was adversely affected (Sager, 1983). A lower dose of 8 mg/kg bw/day was a NOEL.

The mink and the monkey are the most sensitive species tested to the reproductive toxicity of the PCBs. Bleavins et al. (1980) maintained mink on diets containing 5 ppm Aroclor 1242 or 20 ppm Aroclor 1016 (doses of 0.75 and 3 mg/kg bw/day, assuming a mink consumes 15% of its body weight per day) for 8 months and observed complete reproductive failure in the Aroclor 1242 group and 25% mortality and infertility in the Aroclor 1016 group. In a limited study (8 animals/group), Barsotti et al. (1976) maintained rhesus monkeys on diets containing 2.5 or 5 ppm (0.1 or 0.2 mg/kg bw/day) of Aroclor 1248 for 18 months. In the low-dose group, all eight females conceived, but only five delivered viable infants. In the high-dose group, the mothers showed overt signs of toxicity. In the 5.0 ppm group, 6 of 8 females conceived, but only one live birth occurred. After removal from exposure for 1 year, reproductive capabilities appeared to return to normal; however, an increase in abortion rate and infant mortality was observed for both PCB treatment groups (Allen et al., 1980). It is apparent that frank effects in reproduction were observed in monkeys at lower doses than the NOEL in rats, rabbits and guinea pigs following repeated exposure to PCBs. Little data are available for the toxicity of specific congeners. Dietary exposure to as little as 1 ppm of pure 3,4,5,3',4',5'-hexa-CB for 28 days caused liver microabscesses and an increased liver weight in 18-20 g 5-week-old C57Bl/6J mice (Biocca et al., 1981). In this study, dietary exposure at

a concentration of 0.3 ppm resulted in increased liver weight with no other adverse effects (Biocca et al., 1981). This dose could be considered a NOAEL for 3;3',4,4',5,5'-hexa-CB, which is one of the most potent PCBs.

Quantification of Noncarcinogenic Effects

Studies of PCB toxicity in experimental animals have demonstrated a progression of toxicologic responses correlated with dose for studies of 1-30 days. Villeneuve et al. (1971a) found increased incidences of fetal death, resorptions and abortions at 12.5 mg/kg bw/day of Aroclor 1254 in rabbits when exposed on days 1 through 28 of pregnancy. A dose of 1.0 mg/kg bw/day appeared to be without effect. Collins and Capen (1980a,b,c), in a series of studies on thyroid effects in rats, determined that 50 ppm of diet (2.5 mg/kg bw/day) for 4 weeks was associated with clearly defined adverse effects but that doses of 5 ppm of diet (0.25 mg/kg bw/day) produced only ultrastructural evidence suggesting increased thyroid gland activity. Carter (1983) demonstrated liver hepatomegaly in rats at doses of 20 ppm Aroclor 1254 of diet (1 mg/kg bw/day) for 4, 8 and 14 days; such an effect in the absence of other signs of toxicity (that is, fatty infiltration of the liver) might not be considered adverse. Grant and Phillips (1974) observed increased liver weights at doses as low as 5 mg/kg bw/day Aroclor 1254 given in corn oil for 7 consecutive days. Collectively these studies indicate that the experimental threshold for adverse effects of Aroclor 1254 in studies of 30 days duration or less is at or near a dose of 1 mg/kg bw/day. Thus, it seems reasonable to use this latter dose as a basis for health risk assessments for Aroclor 1254-contaminated soil for short duration human exposure situations.

Utilizing a dose of 1 mg/kg bw as a no-adverse-effect dose, a 10-day exposure level to PCB-contaminated soil may be calculated as follows (U.S. EPA, 1986b):

$$\text{10-day exposure level} = \frac{1 \text{ mg/kg/day} \times 10 \text{ kg}}{100} = 0.1 \text{ mg/day}$$

where:

10 kg = assumed body weight of a child

100 = uncertainty (safety) factors; this uncertainty factor was chosen in the accordance with the National Academy of Sciences guidelines in which a NOAEL from an animal study is employed.

This 10-day exposure level of 0.1 mg/day may be applied for a 10-day HA for drinking water if it is assumed that Aroclor 1254 mixtures are soluble and detected in drinking water. This assumption is probably not correct since the less chlorinated congeners are much more soluble than the highly chlori- nated ones and Aroclor 1254 has not yet been detected in finished drinking water.

The finished water from the Dority Reservoir treatment and distribution system was reported to contain Aroclor 1016 congeners at a level of 86 ng/ℓ (Brinkman et al., 1981). The public water supply system of the village of Fort Edward, located near the township of Moreau of Saratoga County in upstate New York, is obtained from the Dority Reservoir treatment and distribution system. The level of Aroclor 1016 in this finished water corresponded well to the median level of 99 ng/ℓ in the Dority River water. The Brinkman et al. (1981) study was discussed earlier in Chapter IV.

Silkworth and Loose (1978) observed that treatment of male C57Bl/6 mice with 167 ppm Aroclor 1016 in the diet for 3 weeks activates donor lymphocytes as measured by greater graft vs. host response. Loose et al. (1978b) observed that treatment with the same dose (167 ppm) for 6 weeks using male BALB/CJ mice suppresses the immune system as measured by increased mortality to Salmonella typhosa endotoxin and Plasmodium berghei. Since these are single dose studies, no dose-response determination can be done. These studies are not adequate for deriving 10-day or 1-day HAs. No other subchronic studies are available on Aroclor 1016 that can be utilized for deriving HAs. Accordingly, no 10-day or 1-day HA for Aroclor 1016 is estimated.

There are only a few reports on the toxicity associated with chronic exposure to Aroclor 1016. Studies were conducted in mink and rhesus monkeys, species that exhibit a high degree of sensitivity to PCBs. Female mink fed a diet containing 20 ppm Aroclor 1016 for 8 months exhibited 25% mortality compared with 12.5% mortality in the control group. Aroclor 1016 was less toxic than Aroclor 1242, which produced 100% mortality in female mink at the same level of exposure (Bleavins et al., 1980). Dietary exposure to 20 ppm Aroclor 1016 reduced, but did not completely eliminate, reproduction. Four of the nine mated females produced kits in the Aroclor 1016 group compared with 16 of 21 in the control group. Body weight at 4 weeks was significantly lower for the kits nursed by females fed Aroclor 1016 (20 ppm). In addition, higher kit mortality between birth and 4 weeks of age was also noted. Bleavins et al. (1980) also reported that reproductive parameters, kit growth, and adult and kit mortality were not significantly affected in ferrets at a diet containing 20 ppm Aroclor 1016.

In another study, Aulerich and Ringer (1977) exposed female minks through diet containing 2 ppm Aroclor 1016 for 10 months (0.3 mg/kg bw/day, assuming a mink consumes 15% of its body weight per day). This level of exposure produced no effect on reproductive parameters, kit growth, and adult and kit mortality. Thus, chronic exposure to 2 ppm Aroclor 1016 in the diet (0.3 mg/kg bw/day) appears to be a NOAEL in the mink. Barsotti and Van Miller (1984) exposed 24 adult rhesus monkeys to diets containing Aroclor 1016 at levels of 0.025, 0.25 and 1.0 ppm. No abnormalities were noted in clinical, growth and reproductive parameters of the adult monkeys. The infants born to the 1.0 ppm Aroclor 1016 group (0.042 mg/kg bw/day, assuming a monkey consumes 4.2% of its body weight per day) were significantly smaller than the control at a confidence level of 99%. Thus, 0.25 ppm (0.0105 mg/kg bw/day) appears to be a NOAEL for chronic oral exposure to Aroclor 1016 in rhesus monkeys.

Utilizing a dose of 0.01 mg/kg bw/day (0.25 ppm) as the NOAEL, the longer-term HA for Aroclor 1016 may be calculated as follows:

$$\text{RfD} = \frac{0.01 \text{ mg/kg/day}}{100} = 0.0001 \text{ mg/kg/day}$$

where 100 = uncertainty (safety) factor. This uncertainty factor was chosen in accordance with the National Academy of Sciences guidelines in which a NOAEL from an animal study is employed.

Longer-term HA for a 10 kg child:

$$= \frac{0.0001 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ ℓ/day}}$$

$$= 0.001 \text{ mg/ℓ}$$

for a 70 kg adult:

$$= \frac{0.0001 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ ℓ/day}}$$

$$= 0.0035 \text{ mg/ℓ}$$

However, 0.001 mg/ℓ will also be protective for a 70 kg adult.

Because of their high lipophilic and stable nature, PCBs can rapidly bioaccumulate in human milk, adipose tissues and serum. Only 2,4,4'-tri-CB, one of the constituents of Aroclor 1016, has been found as a major component with the other seven major and four minor components of PCB congeners in human milk samples.

On starvation and stress the PCB components from the adipose-rich tissues can become free in the bloodstream and redistribute to other compartments. This can create additional opportunities for insult by free PCB on different organ and physiologic systems. This can also result in further metabolism of the free PCBs. However, the toxicologic significance of PCB metabolism has not yet been delineated.

It should be noted that during document review several studies indicating potential alteration in postnatal function following exposure during the prenatal or early postnatal period were identified. These studies may impact on the ultimate quantification of noncarcinogenic effects, since: 1) reproductive and developmental effects have been used in establishing exposure levels for noncarcinogenic effects, 2) postnatal deficiencies have been reported/suspected in cases of human exposure (Yusho and Yu Cheng), and

3) postnatal deficiencies could possibly occur at levels of exposure lower than those required for effects on structural development or viability. These and other similar studies will be reviewed for their impact on the assessment of developmental and reproductive effects and will be added to the document where appropriate.

Carcinogenic Effects

There are several studies demonstrating that PCBs cause cancer in laboratory animals. Male dd mice fed Kanechlor 500 developed hepatocellular carcinomas and liver nodules (Ito et al., 1973). Male BALB/CJ mice fed Arochlor 1254 developed hepatomas or liver adenofibrosis (Kimbrough and Linder, 1974). Female Sherman rats fed Arochlor 1260 developed hepatocellular carcinomas and neoplastic nodules (Kimbrough et al., 1975). Male and female Fischer 344 rats fed Arochlor 1254 developed hepatocellular carcinomas (NCI, 1978). Although NCI's results are not statistically significant, they are considered supportive because the small sample sizes limit the study's power to show a significant response and because there is a dose-response trend. Male Wistar rats fed Clophen A60 developed hepatocellular carcinomas (Schaeffer et al., 1984). Male and female Sprague-Dawley rats fed Arochlor 1260 developed hepatocellular carcinomas (Norback and Weltman, 1985).

These studies provide sufficient evidence regarding the carcinogenicity of PCBs. Liver cancer has been induced in several studies in different animal strains fed several commercial PCB products. The contention that these results are due to the PCDF contamination of PCBs is refuted by the

Schaeffer study, which tested its PCB mixtures and found them to be free of furans. This conclusively demonstrates that PCBs alone are capable of causing cancer.

The combination of sufficient evidence from animal studies and inadequate, but suggestive, evidence from human studies leads to a designation of PCBs as probable human carcinogens, Group B2 under EPA's cancer guidelines. This designation is not altered by the ancillary evidence from several mutagenicity, promotion, antitumorigenicity, and cocarcinogenicity studies.

Quantification of Carcinogenic Effects

Although CAG regards the human data at this time to be suggestive of a carcinogenic risk but still inadequate overall, it has recently been learned (Moolenaar, 1987) that the International Agency for Research on Cancer (IARC) has upgraded their weight-of-evidence classification on PCBs to "limited" (i.e., 2A).

The basis for this recent decision by IARC has not yet been ascertained. CAG is now attempting to obtain further information from IARC representatives regarding the rationale for their decision. If there are newer data available to IARC that led to a change in their position, it might necessitate a reconsideration of the CAG position prior to final publishing. CAG has obtained a more recent study by Bertazzi et al. (1986) not included in the current draft. A review of this study is underway at this time and will be included in the final draft.

Data Selection. Human studies, although suggestive of a link between PCBs and certain types of cancer, are not yet suitable for quantitative cancer risk estimation. Consequently, risk estimates must at this time be based on animal studies. The most sensitive animal species tested appears to be the rat. In the past the U.S. EPA has based its risk estimates on a study by Kimbrough et al. (1975) in which chronic dietary administration of Aroclor 1260 was shown to cause hepatocellular carcinomas in female Sherman rats. The following analysis, however, is based on a study by Norback and Weltman (1985) in which chronic dietary administration of Aroclor 1260 was shown to cause hepatocellular carcinomas in male and female Sprague-Dawley rats. This recent study is preferred because the Sprague-Dawley rat has a low incidence of spontaneous hepatocellular neoplasms, because the Norback and Weltman (1985) study spanned the natural life of the animal, and because concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas. Because neoplastic nodules have been shown to precede carcinomas, animals with neoplastic nodules were counted with those developing carcinomas. The tumor incidences for female rats, which were more sensitive than the males, are presented in Table VIII-1. The average levels (in ppm) of PCDFs in Aroclor 1260 are typically: TCDF, 0.2-0.8; PeCDF, 0.3-0.9; hexa-CDF, 0.3-0.5 (see Table II-3). The levels (in ng/g) of 2,3,7,8-substituted toxic isomers are: TCDF, 0.84; PeCDF, 2.1; hexa-CDF, 2.4 (see Table II-5). The toxic PCDFs are analogues of 2,3,7,8-TCDD, which is a known animal carcinogen. The role of the PCDFs in PCB toxicity and carcinogenesis is still unknown. The following dose-response treatment will not consider the contribution of the PCDFs.

TABLE VIII-1

Data Used as the Basis for the q_1^* for Aroclor 1260†

Sex, strain, species	Female Sprague-Dawley rat
Exposure route, vehicle	Oral, diet
Tumor site, type	Liver, trabecular carcinoma/adenocarcinoma neoplastic nodule
Nominal Dose	0 100 ppm
Average daily dose	0 3.45 mg/kg/day (5% food rate assumed)
Equivalent human dose	0 0.59 mg/kg/day (surface-area corrected)
Tumor incidence	1/49 45/47
Body weight	350 g (assumed)
Exposure duration	24 months (dose halved during months 17-24)
Study duration	29 months
Animal lifespan	29 months (assumed)
Potency (q_1^*)	7.7 per mg/kg/day

†q_1^* derived from Norback and Weltman (1985) study.

Dose-Response Modeling. Current available evidence on the metabolism and kinetics of PCBs is insufficient to support the existence of nonlinear mechanisms for the development of PCB-induced cancer. In the absence of evidence to the contrary, the U.S. EPA uses the linearized multistage model to estimate increased cancer risks. The dose data are derived through the following sequence of transformations. First the nominal dose level of 100 ppm in the diet is expressed as 5 mg/kg/day, assuming that a rat consumes an amount equal to 5% of its body weight each day. Then this nominal dose is transformed into a TWA daily dose of 3.45 mg/kg/day, which reflects the dosing schedule of 5 mg/kg/day for the first 16 months, half of that for the next 8 months, and none for the last 5 months. Finally, this average daily dose is transformed into an equivalent human dose of 0.59 mg/kg/day, which reflects an equivalence between species on the basis of relative body surface areas.

The U.S. EPA sometimes uses other mathematical dose-response models to provide alternate risk estimates for comparison. This cannot be done with the preferred data set because the number of dosed groups (one) does not permit the estimation of two or more parameters as required by the other models. In particular, with only one dosed group the multi-hit model with one hit and the Weibull model with shape parameter equal to 1 are identical to the multistage model used here.

Potency Estimation. Using the data described above and the linearized multistage model, the human carcinogenic potency of Aroclor 1260 is estimated at 7.7 mg/kg/day. For small exposures (those for which the risk is <10%) the increased cancer risk can be estimated by multiplying the potency

by the exposure rate. Risks computed in this manner are plausible upper bounds on the increased cancer risk from exposure to Aroclor 1260, meaning that the true risk is not likely to be higher.

This potency estimate is intended to be representative of other PCB mixtures as well. At present there is no information about which constituents of Aroclor 1260 or any other PCB mixture are carcinogenic. Given this lack of information about individual constituents, Aroclor 1260 is assumed to be representative of other PCB mixtures. Furthermore, of all the studies of any PCB mixture, the Norback and Weltman (1985) study using Aroclor 1260 has superior characteristics, and is, therefore, the most suitable for quantitative risk estimation.

Drinking Water Criteria. The concentration of Aroclor 1260 in water associated with a particular increased lifetime cancer risk can be calculated from the following formula:

$$\text{Concentration} = \frac{\text{Risk} \times 70\ \text{kg}}{\text{Potency} \times 2\ \text{ℓ/day}}$$

assuming a typical person weighs 70 kg and consumes 2 ℓ of water each day. For risks of 10^{-4}, 10^{-5} and 10^{-6} these concentrations are 0.5, 0.05 and 0.005 µg/ℓ, respectively.

Sensitivity Analysis -- Neoplastic Nodules. The U.S. EPA's guidelines for carcinogen risk assessment call for reporting the relative contribution of nonmalignant lesions whenever they are used in a risk estimate. Table VIII-2 gives the incidence of malignant tumors only. The potency using

TABLE VIII-2

Data Used as the Basis for an Alternate Potency Calculation for Aroclor 1260†

Sex, strain, species	Female Sprague-Dawley rat	
Exposure route, vehicle	Oral, diet	
Tumor site, type	Liver, trabecular carcinoma/adenocarcinoma	
Nominal Dose	0	100 ppm
Average daily dose	0	3.45 mg/kg/day (5% food rate assumed)
Equivalent human dose	0	0.59 mg/kg/day (surface-area corrected)
Tumor incidence	0/49	43/47
Body weight	350 g (assumed)	
Exposure duration	24 months (dose halved during months 17-24)	
Study duration	29 months	
Animal lifespan	29 months (assumed)	
Potency (q_1^*)	5.7 per mg/kg/day	

†q_1^* derived from Norback and Weltman (1985) study.

malignant tumors only is 5.7 per mg/kg/day, 26% less than the estimated potency including neoplastic nodules. Using this potency would increase the drinking water criteria concentration by 35%.

Sensitivity Analysis -- Statistical Upper Bounds. The linearized multistage model uses an explicit statistical 95% upper bound to estimate the increased cancer risk. It is not always possible to know the relative contribution of the upper bound risk estimate because the multistage model without an upper bound procedure does not necessarily give estimates that are consistent with the low-dose linear model of carcinogenesis that has been adopted by the U.S. EPA. In this case, however, the (unlinearized) multistage model is consistent with the linear model, because the multistage model with one treated group becomes the one-stage model, which is intrinsically linear at small doses. The maximum likelihood estimate of the potency is 5.3 per mg/kg/day, 31% less than the estimated upper bound potency. Using this potency would increase the drinking water criteria by 45%. Nevertheless, the U.S. EPA does not recommend using maximum likelihood estimates of risk, because these estimates are typically unstable.

Sensitivity Analysis -- Kimbrough et al. (1975) Study. In the past, the U.S. EPA has based its risk estimates on a study by Kimbrough et al. (1975), in which chronic dietary administration of Aroclor 1260 was shown to cause hepatocellular carcinomas in female Sherman rats. Table VIII-3 presents the tumor incidences from this study. The shorter duration of this study means that the observed liver lesions are mostly neoplastic nodules that had not yet progressed to hepatocellular carcinomas. Although the newer Norback and Weltman (1985) study is preferred for its longer duration,

TABLE VIII-3

Data Used as the Basis for the Previous Potency Calculation for Aroclor 1260†

Sex, strain, species	Female Sherman rat	
Exposure route, vehicle	Oral, diet	
Tumor site, type	Liver, hepatocellular carcinoma/neoplastic nodule	
Nominal Dose	0	100 ppm
Average daily dose	0	4.57 mg/kg/day (5% food rate assumed)
Equivalent human dose	0	0.78 mg/kg/day (surface-area corrected)
Tumor incidence	1/173	170/184
Body weight	350 g (assumed)	
Exposure duration	21 months	
Study duration	23 months	
Animal lifespan	23 months (assumed)	
Potency (q_1^*)	3.9 per mg/kg/day	

†q_1^* derived from Kimbrough et al. (1975) study.

it is useful to know how the new risk estimate compares with the previous one. Under the same assumptions as before, the potency using the Kimbrough et al. (1975) study is 3.9 per mg/kg/day, 49% less than the estimated potency using the Norback and Weltman (1985) study. Using this potency would increase the drinking water criteria by 97%.

Consideration was given to estimating the potency from the Schaeffer et al. (1984) study, in which chronic dietary ingestion of Clophen A60 was shown to cause hepatocellular carcinomas in male Wistar rats. As in the Norback and Weltman (1985) study, treated rats received doses of 100 ppm for the major portion of their lifetimes, over 95% of treated rats developed hepatocellular carcinomas or neoplastic nodules, and the incidence in control rats was <10%. For these reasons one would expect similar potency estimates from the two studies. A precise calculation using the Schaeffer et al. (1984) study is not, however, possible at this time, because a discrepancy in the published tables makes it impossible to determine the number of animals at risk. For now the Schaeffer et al. (1984) study can be used to confirm the Norback and Weltman (1985) results, which are used to estimate potency.

Schaeffer et al. (1984) also studied another PCB mixture, Clophen A 30, which appears to be less potent than Clophen A 60. It would be misleading, however, to quantitatively compare the potency that might be calculated from this study with the potency that was calculated from the Norback and Weltman study, because Schaeffer et al. used male Wistar rats and Norback and Weltman showed that female (Sprague-Dawley) rats are more sensitive than males.

Cancer Potency Estimates for AroclorR 1254 and other PCB mistures

Because exposure assessments sometimes find PCB mixtures that resemble PCB products other that Aroclor● 1260, it is often asked whether separate cancer potency estimates can be made for other PCB mixtures. Although the best data base for estimating the cancer potency is on Aroclor● 1260, it is appropriate to ask whether existing data on other PCB mixtures are adequate for making separate cancer potency estimates.

A natural candidate for a separate cancer potency estimate is Aroclor● 1254. An estimate can be based on the 1978 National Cancer Institute (NCI) study of Aroclor● 1254, in which statistically significant, dose-related increases in liver nodules, benign tumors, and malignant tumors combined were seen in Fischer 344 rats fed a diet containing Aroclor● 1254. Preliminary calculations would indicate a cancer potency of 2.6 per mg/kg/day continuous lifetime exposure to Aroclor● 1254. This estimate is a plausible upper bound, meaning that the true cancer potency is not likely to exceed this estimate and may be lower. Details of the study and the potency calculation are given in Table VIII-4.

Several sources of uncertainty deserve mention:

1. NCI used only 24 rats per group (50 is considered standard today), so the potency estimate is rather imprecise.

TABLE VIII-4

Data Used for the Preliminary Cancer Potency
Estimate for Aroclor® 1254

Substance	Aroclor(R) 1254
Reference	NCI, 1978
Sex, Strain, Species	Female Fischer 344 rats
Exposure Route, Vehicle	Oral diet
Tumor Site, Type	Liver nodular hyperplasia and adenomas
Nominal Dose	0 25 50 100 ppm
	0 1.25 2.50 5.00 mg/kg/day (5% food factor)
Average Daily Dose	0 1.16 2.32 4.65 mg/kg/day (105/113 weeks)
Equivalent Human Dose	0 0.17 0.33 0.64 mg/kg/day (surf-area adj)
Tumor Incidence	0/24 6/24 10/22 19/24
Tumor Percentage	0% 25% 45% 79%
Statistical Significance	-- 1E-02 2E-04 1E-08
Trend Significance	<0.001, linearity OK
Animal Weight	250 220 200 180 g (at end of study)
Exposure Period	105 week
Study Length	113 week
Animal Lifespan	113 week (assumed)
Potency (q1*)	2.6 per mg/kg/day

2. The NCI study lasted 24 months. Although this is today's standard, Norback and Weltman demonstrated that PCB-fed rats (but not control rats) develop many tumors after 24 months. EPA considers the Norback and Weltman study more appropriate for estimating a lifetime cancer potency.

3. NCI's female rats developed only benign liver tumors and nodules, so some may argue that there was no cancer. Norback and Weltman, however, demonstrated that nodules progress to benign tumors, which in turn progress to malignant tumors. Under EPA's cancer guidelines it is, therefore, appropriate to consider benign tumors and nodules. Furthermore, some male rats in the NCI study did develop malignant liver tumors.

EPA's cancer potency for Aroclor● 1260, which is presumed to apply to other PCB mixtures as well, is 7.7 per mg/kg/day continuous lifetime exposure. Although it appears that the cancer potency of Aroclor● 1254 may be slightly less than that of Aroclor● 1260, this difference may not be real in light of the uncertainties cited above. Larger differences are commonly seen between different sexes and animal strains. For example, a comparison of the NCI and Norback and Weltman studies suggests that Aroclor● 1254 may be more potent in male Fischer 344 rats than Aroclor● 1260 is in male Sprague-Dawley rats. For these reasons, the current data are inadequate to differentiate between these PCB mixtures with any reasonable degree of confidence.

Further investigation, perhaps taking into consideration potency differences between PCB mixtures for other toxic effects, is needed before there can be separate cancer potency estimates for each PCB mixture. At the present time, though, the data are inadequate for calculating separate cancer potency estimates for each PCB mixture.

Existing Guidelines, Recommendations and Standards

Manufacture, sales and distribution of PCBs have been restricted under Section 6(e) of the Toxic Substances Control Act (TSCA) (P.L. 94-469). PCBs were restricted to sealed systems as of 1977, manufacture and distribution were banned in 1979. Rules for the disposal of PCBs were proposed in 1978 (43 FR 7150). Mansanto voluntarily suspended production of Aroclors before the ban.

The U.S. EPA (1980a,b) has set ambient water quality criteria for PCBs for the protection of humans from increased risk of cancer over the lifetime of 10^{-5}, 10^{-6} and 10^{-7}, at 0.79, 0.079 and 0.0079 ng/ℓ, respectively. As a result of the large BCF, these criteria apply regardless of whether exposure occurs through consumption of 2 ℓ of water and 6.5 g of fish/day or through consumption of fish alone. Table IV-6 presents the geometric mean levels in freshwater fish taken around the United States between 1976 and 1981 (Schmitt et al., 1985). The most contaminated fish (22 ng/g wet weight) in 1980 and 1981 were taken from the Hudson, Connecticut and Delaware Rivers in New England; Lakes Michigan, Huron, Erie and Ontario; the Mississippi in Minnesota; the Ohio River; and the Cape Fear River in North Carolina. Fish bioaccumulate the more chlorinated PCB

isomers (Wszolek et al., 1979; Brown et al., 1985). Food chain vectors also are important in the congeners bioaccumulated (Bush et al., 1985a). The Food and Drug Administration (FDA) has set tolerances for PCBs in food and food related products as indicated in Table VIII-5.

Occupational exposure limits have been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 1980), and a recommended criterion set by the National Institute for Occupational Safety and Health (NIOSH, 1977) for PCBs in the workroom air. The TWA and STEL for Aroclor 1254, respectively, are 0.5 and 1.0 mg/m^3; and 1 and 2 mg/m^3 for Aroclor 1242 (ACGIH, 1980). The NIOSH (1977) recommended criterion for PCBs is 1.0 µg/m^3 for all PCBs for a 10 hours/day, 40 hours/week exposure. The OSHA permissible exposure level (PEL) and immediately dangerous to life and health level (IDLH) for Aroclor 1242 are 1 and 10 mg/m^3, respectively, and 1 and 5 mg/m^3 for Aroclor 1254 (NIOSH, 1977).

The NAS (1980) developed a 24-hour SNARL for PCBs of 350 µg/ℓ based on the induction of mixed-function oxidase enzymes in the liver of rats administered Aroclor 1254 at doses of 1-2 mg/kg. For this analysis, an uncertainty factor of 100 was used, since only enzyme induction was reported in this dose range.

Summary

A recommendation was not made at this time for 1-day or 10-day HAs or a DWEL because of a deficient data base on toxicity and exposure to PCBs through drinking water in the United States. A longer-term HA for Aroclor 1016 for a child has been estimated to be 0.001 mg/ℓ and for an adult

TABLE VIII-5

FDA Regulations for PCBs[a]

Commodity	Temporary Tolerances (ppm)
Milk (fat basis)	1.5
Manufactured dairy products (fat basis)	1.5
Poultry (fat basis)	3.0
Eggs	0.3
Finished animal feeds	0.2
Animal feed components of animal origin	2.0
Edible portion of fish and shellfish[b]	2
Infant and junior foods	0.2
Paper food packaging material	10.0

[a]Source: 21 CFR. 109.30. 51,725; 44(127) FR 38330-38340; 49(100) FR 21514-21519.

[b]The edible portion of fish includes heads, scales, viscera and inedible bones.

0.0035 mg/ℓ. A cancer based criterion for Aroclor 1260 was derived and calculated for excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6}. The respective water concentrations are 0.5, 0.05 and 0.005 µg/ℓ (Table VIII-6). If Aroclor 1260 is detected in the finished drinking water then the cancer based criterion may be applied. A decision to utilize the cancer potency estimate from Aroclor 1260 to characterize the upper limit risks and or calculate specific drinking water criteria for other PCB mixtures is risk assessment option (policy choice).

TABLE VIII-6

Summary of Calculated Health Advisories for PCBs

Health Advisory	NOEL or NOAEL	Species/ Route	Effect	Calculated Level for Safe Exposure		Reference
				Child	Adult	
1-Day	No data available*					
10-Day	1 mg/kg/day	rabbit/diet	reproductive effect	100 µg/ℓ		Villeneuve et al., 1971
Longer-term	0.01 mg/kg/day	monkey/diet	reproductive effect	1 µg/ℓ	3.5 µg/ℓ	Barsotti and Van Miller, 1984
Lifetime DWEL		SD-rat/diet	carcinogenic effect	NA	excess cancer risks at levels 10^{-4} = 0.5 µg/ℓ 10^{-5} = 0.05 µg/ℓ 10^{-6} = 0.005 µg/ℓ	Norback and Weltman, 1985

*Recommended that the 10-day HA of 100 µg/ℓ for 10 kg child be used as the 1-day HA for the 10 kg child

NA = Not applicable

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