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Office of Emergency and
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Washington DC 20460

Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
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Cincinnati OH 45268

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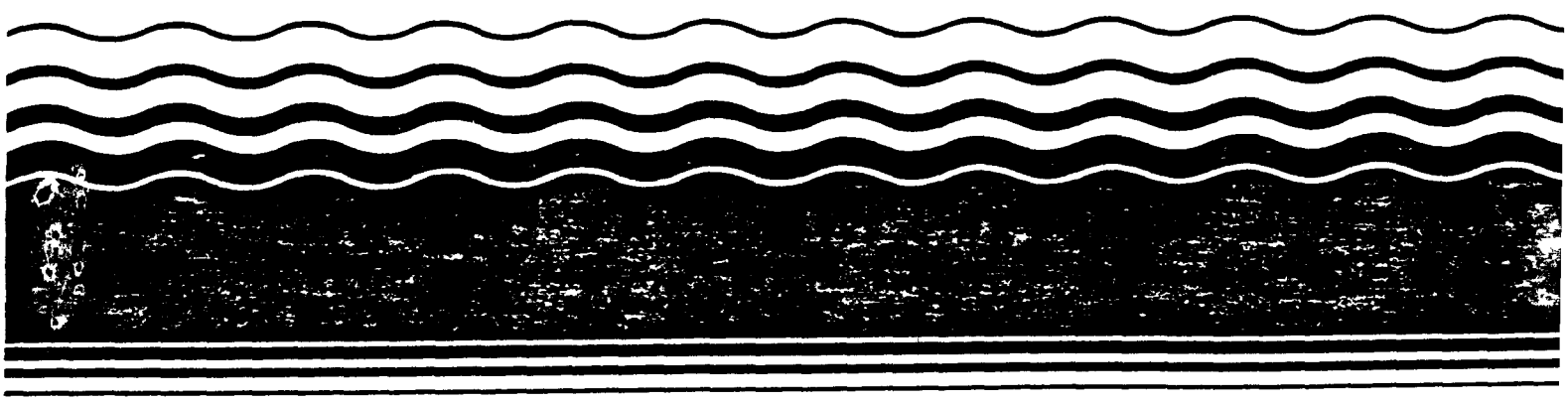
HEALTH EFFECTS ASSESSMENT FOR POLYCHLORINATED BIPHENYLS



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HEALTH EFFECTS ASSESSMENT FOR POLYCHLORINATED BIPHENYLS (PCBS)

U.S. Environmental Protection Agency
Office of Research and Development
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Cincinnati, OH 45268

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Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with polychlorinated biphenyls. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Polychlorinated Biphenyls. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-068. NTIS PB 81-117798.

U.S. EPA. 1985. Drinking Water Criteria Document for Polychlorinated Biphenyls. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final Draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Limited human data are available suggesting a relationship between PCB exposure and cancer. *In vitro* mutagenicity evaluations have been primarily negative. PCBs have been shown to be carcinogenic in rats and mice when administered orally. Using data for hepatocellular carcinoma and neoplastic nodules in female rats, a carcinogenic potency (q_1^*) of 4.34 $(mg/kg/day)^{-1}$ has been estimated for oral exposure of humans to PCBs. Data were inadequate to develop a quantitative estimate for the inhalation route.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
FEL	Frank-effect level
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
mol.wt.	Molecular weight
NOEL	No-observed-effect level
PCBs	Polychlorinated biphenyls
PCDFs	Polychlorinated dibenzofurans
ppm	Parts per million
RNA	Ribonucleic acid
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. ENVIRONMENTAL CHEMISTRY AND FATE

PCBs consist of a mixture of chlorinated biphenyls that contain a variable number of substituted chlorine atoms on the aromatic rings. The commercial PCBs manufactured in the United States are known as Aroclors followed by a 4-digit number. The first two digits indicate the type of mixture (e.g., those with "12" as the first two digits are chlorinated biphenyls; those with "25" are blends of 75% biphenyls and 25% triphenyls; and those with "54" are chlorinated triphenyls), and the last two digits represent the approximate weight percent of chlorine in the product. The approximate compositions of the commercially available Aroclors and Kanechlors are shown in Table 1-1. The relevant physical and chemical properties and identification numbers of the Aroclors are presented in Table 1-2.

The mobility of different Aroclors in soils as it pertains to leaching has been studied by Pal et al. (1980). The two most important factors that determine the leachability of Aroclors in soils are the characteristics of the soils and the nature of the Aroclors. For example, as the chlorine content of an Aroclor increases, it may increase the adsorption characteristics in soils, thereby decreasing its rate of leaching. Similarly, soils with more organic matter content may tend to increase the adsorption and decrease the leaching rate. Therefore, maximum leaching of Aroclors is expected in sandy soils and with Aroclors having lower chlorine content, such as Aroclor 1221 and Aroclor 1232. Incorporation of 1 ppm dichlorobiphenyl in a sandy loam soil showed that no detectable amounts (<0.001 ppm) of the compound leached beyond 30 cm soil layer after 1 year of incorporation (Pal et al., 1980).

Bioconcentration factors have not been determined for all the individual Aroclors. The potential for bioaccumulation of Aroclors is related to the

TABLE 1-1

Approximate Compositions of the Commercially Available Aroclors*

Molecular Formula	No. of Chlorine Atoms	No. of Isomers	mol. wt.	wt. % Cl	Aroclor							Kanechlor		
					1221	1232	1242	1248	1254	1260	1016	300	400	500
$C_{12}H_{10}$	0	1	154	0	11	<0.1	<0.1	ND	<0.1	ND	<0.1	ND	ND	ND
$C_{12}H_9Cl$	1	3	189	18.8	51	31	1	ND	<0.1	ND	1.0	ND	ND	ND
$C_{12}H_8Cl_2$	2	12	223	31.8	32	24	16	2	0.5	ND	20	17	3	ND
$C_{12}H_7Cl_3$	3	24	258	41.3	4	28	49	18	1.0	ND	57	60	33	5
$C_{12}H_6Cl_4$	4	42	292	48.6	2	12	25	40	21	1	21	23	44	27
$C_{12}H_5Cl_5$	5	46	326	54.3	<0.5	4	8	36	48	12	1	0.6	16	55
$C_{12}H_4Cl_6$	6	42	361	58.9	ND	<0.1	1	4	23	38	<0.1	ND	5	13
$C_{12}H_3Cl_7$	7	24	395	62.8	ND	ND	<0.1	ND	6	41	ND	ND	ND	ND
$C_{12}H_2Cl_8$	8	12	430	66	ND	ND	ND	ND	ND	8	ND	ND	ND	ND
$C_{12}HCl_9$	9	3	464	68.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Average mol. wt.					201	232	267	300	328	376	258	NA	NA	NA

*Source: Callahan et al., 1979; IARC, 1978

ND = Not detected; NA = not available

TABLE 1-2

Identification Numbers and Selected Physical and Chemical Properties of Aroclors[a]

Properties	Identification Numbers						
	1221	1232	1016	1242	1248	1254	1260
Vapor pressure mm Hg at 25°C	[6.7×10^{-3}]	[4.06×10^{-3}]	[4×10^{-4}]	4.06×10^{-4}	4.94×10^{-4}	7.71×10^{-5}	4.05×10^{-5}
Water solubility mg/ℓ	0.59[b] at 24°C	NA	0.42 at 25°C	0.24[c] at 25°C	0.054 at 25°C	0.012[c] at 25°C	0.0027[c] at 25°C
Log octanol/water partition coefficient	[2.8] 4.09	[3.2] >4.54	4.38 >5.58	4.11 >5.58	[5.75] >6.11	[6.03]	[7.14] >6.11
CAS Registry Number	11104-28-2	11141-16-5	12674-11-2	53469-21-9	12672-29-6	11097-69-1	11096-82-5

[a]All values are taken from Callahan et al., 1979, except where noted; the bracketed data are estimated.

[b]Verschueren, 1983

[c]Mackay and Leinonen, 1975

NA = Not available

number of chlorines, with the BCF value increasing with higher chlorine content (Callahan et al., 1979). The BCF value in freshwater species may vary from 3000 for the muscle of a brook trout, Salvelinus fontinalis, to 274,000 for the whole body of a fathead minnow, Pimephales promelas, (U.S. EPA, 1980b).

The half-life of PCBs in air is not known. Although photolysis of PCBs in the atmosphere is a likely process, it is expected to be slow (Pal et al., 1980). The removal of PCBs from the atmosphere by physical removal processes, such as wet and dry deposition, may not be significant (Cupitt, 1980). The half-life of PCBs as a result of chemical reactions with OH radicals and O^3 in air has been estimated to be >8 days (Cupitt, 1980).

The half-life of a PCB in aqueous media will depend on both the nature of the PCB and the characteristics of the body of water. PCBs with increasing chlorine content, because of their lower volatility and biodegradation and higher sorption characteristics, will have longer half-lives. Based on published reports, PCBs containing less than three chlorines may be degraded in aquatic media (Callahan et al., 1979; Pal et al., 1980), although no estimation of half-lives in natural bodies of water is available. PCBs with four chlorines appear to be somewhat degradable, while those with five or more appear to be recalcitrant.

The half-life of PCBs in soils is expected to follow the same pattern as in water. Both volatility and biodegradation may destroy PCBs containing one or two chlorine atoms; the half-lives of such PCBs may be a few days. PCBs containing three or four chlorine atoms will have longer half-lives, whereas PCBs containing five or more chlorine atoms may be refractory (Pal et al., 1980).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

One of the problems associated with understanding the toxicokinetics of PCB products is that they are mixtures of many different isomers, each with its own characteristic kinetics of behavior in the animal body. In one of the early studies of oral absorption, Albro and Fishbein (1972) administered 5, 50 or 100 mg of 19 "pure" PCB isomers and the totally unchlorinated biphenyl by gavage to male CD rats (number not reported). Feces were collected for 4 days; the total amount excreted in the feces and the amount absorbed or metabolized in the gut were determined. The results are presented in Table 2-1. For all compounds tested at all dosage levels, absorption was >90%. The authors recognized that this study did not investigate the possibility of intestinal metabolism, enterohepatic recirculation or the effects of dietary status on retention of PCBs, all of which would be required for full elucidation of the PCB absorption process.

Gavage administration of 1.5 or 3.0 g Aroclor 1248/kg bw to adult rhesus monkeys resulted in uptake of >90% of the total dose (Allen et al., 1974), confirming the data of Albro and Fishbein (1972). These investigators subsequently administered a single 18 mg dose of 2,5,2',5'-tetra PCB/kg bw to seven adult male rhesus monkeys. Excreta were collected and analyzed for 14 days. Over 12% of the total dose was recovered unmodified in the feces (Allen et al., 1975). Norback et al. (1978) administered one dose of ^{3}H-labeled 2,4,5,2',4',6'-hexa PCB to two young monkeys with bile duct and duodenal cannulae. The authors reported that 59.3-87% of the total dose passed unmodified through the intestinal tract within the first week. It was unclear why relatively little of this isomer was absorbed.

TABLE 2-1

Uptake of PCBs by Rats[a]

Compound	Percentage Retained[b]					
	5 mg/kg	± S.D.	50 mg/kg	± S.D.	100 mg/kg	± S.D.
Biphenyl	99.5	0.11	98.8	0.25	98.2	0.30
2-Cl	98.9	0.45	98.0	0.30	98.4	0.15
3-Cl	98.0	1.01	96.6	0.10	97.3	0.40
4-Cl	97.3	1.73	96.3	0.40	96.4	0.42
2,6-Cl_2	NR	NR	95.0	0.96	94.9	0.75
2,2'-Cl_2	95.0	2.42	97.4	0.20	98.2	2.10
2,4-Cl_2	NR	NR	95.7	0.40	97.1	0.35
2,3'-Cl_2	NR	NR	96.8	0.51	97.9	0.28
2,4'-Cl_2	97.2	3.38	95.5	1.20	96.6	0.78
3,4'-Cl_2	95.7	3.45	94.3	0.86	97.1	0.63
4,4'-Cl_2	95.4	3.05	95.6	1.12	97.4	1.10
2,5,2'-Cl_3	NR	NR	95.1	3.00	94.3	3.18
2,3,5'-Cl_3	NR	NR	95.6	1.05	95.0	1.12
3,4,3'-CL_3	NR	NR	93.5	2.85	90.3	3.58
2,4,4'-Cl_3	NR	NR	92.6	0.86	94.0	1.50
2,5,2',5'-Cl_4	96.0	1.75	NR	NR	NR	NR
2,3,4,5-Cl_4	97.3	0.86	NR	NR	NR	NR
3,4,3',4'-Cl_4	98.8	0.57	NR	NR	NR	NR
2,4,5,2',5'-Cl_5	95.1	0.57	NR	NR	NR	NR
2,4,5,2',4',5'-Cl_6	95.3	1.11	NR	NR	NR	NR

[a]Source: Albro and Fishbein, 1972

[b]Each value is the average of three determinations on each of two rats:

$$\text{Percentage Retained} = \frac{\text{(amount fed) - (amount excreted)}}{\text{amount fed}} \times 100\%$$

NR = Not reported; S.D. = standard deviation

2.2. INHALATION

One brief report concerning inhalation absorption of PCBs was located. Benthe et al. (1972) exposed male Wistar rats once to Pydranil A200 (number of rats, concentration of Pydranil A200 and length of exposure time not specified). Animals were killed and examined at 15 minutes, 2 hours, 24 hours and 2 days post-exposure. At the end of 15 minutes, liver concentrations were >50% of the maximum concentrations attained after 2 hours. During the first 24 hours, rapid increase in brain and fat levels of PCBs was noted. At the end of 2 days, liver and brain levels of PCBs had fallen, and levels in adipose tissue had reached a maximum, indicating very good absorption; however, absorption factors were not quantitated.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Subchronic oral exposure of experimental animals to PCBs has been investigated in detail in several species, and PCB toxicity in rats appears to have been studied most extensively. The details of protocol and results of these studies are summarized in Tables 3-1, 3-2 and 3-3. In an early study, Kimbrough et al. (1972) compared the effects of Aroclor 1254 and Aroclor 1260 on groups of 10 male and 10 female Sherman rats. Aroclor 1254 was included in the diet at 0, 20, 100 or 500 ppm (mg/kg/diet), and Aroclor 1260 was included in the diet at 0, 20, 100, 500 or 1000 ppm (mg/kg/diet). The duration of exposure was 8 months. Aroclor 1260 appeared to be more toxic to female than to male rats, since none of the male rats fed Aroclor 1260-containing diets died, but 1/10, 2/10 and 8/10 females fed diets containing 100, 500 and 1000 ppm Aroclor 1260, respectively, died. Aroclor 1254 at dietary levels of 500 ppm resulted in the death of two male rats and one female rat.

Dietary levels $\geq$500 ppm Aroclor 1260 or Aroclor 1254 seemed to reduce rate of weight gain severely in treated rats, although statistical analysis was not performed to substantiate that observation. There was, however, a statistically significant increase in relative liver weight (liver weight expressed as percent of body weight) in all rats at dietary levels $\geq$20 ppm of either of the Aroclors tested, except for females exposed to 20 ppm Aroclor 1260 in the diet. Because the diets with 20 ppm of either Aroclor 1260 or Aroclor 1254 were set up at a different time from the diets containing other levels, they had their own simultaneous female and male control groups. These control females had unusually high liver weights (no

TABLE 3-1

Effects of Subchronic and Chronic Oral Exposure of PCBs to Rats and Mice

Species/ Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
Rat/F344	M,F/191	Aroclor 1254	diet	0, 25, 50, 100 mg/kg diet for 2 years	2 years	Reduced body weight. Stomach: "Intestinal" metaplasia, dose-related; adenocarcinoma of glandular stomach.	Morgan et al., 1981
Rat/ Sherman	F/400	Aroclor 1260	diet	0 or 100 mg/kg diet for 21 months	21 months	No effect on food intake; reduced body weight. Elevated tan liver modules (170/184), hepatocellular carcinoma (26/184). Other areas: hepatic disruption.	Kimbrough et al., 1975
Rat/Wistar	M/290	Kanechlor-300, -400 or -500	diet	0, 500 or 1000 mg/kg diet for 27-52 weeks	1 year	Heavy mortality. Hepatomegaly, oval cell and bile duct proliferation, fatty liver infiltration. Cholangiofibrosis at 1000 mg/kg level of all 3 Kanechlors, nodular hyperplasia. Depressed final body weight.	Ito et al., 1974
Rat/ Sprague-Dawley	M/6/group	Aroclor 1242	diet	0, 5 or 25 mg/kg diet 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 mg/kg.	Bruckner et al., 1974
Rat/ Sprague-Dawley	M/96	Aroclors 1248, 1254 or 1262	diet	0 or 100 mg/kg diet 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
Rat/CD	F/300	Aroclor 1254	diet	0, 10, 30 or 100 mg/kg diet for up to 20 weeks	20 weeks	Serum cholesterol, beta globulin increased; gamma globlin decreased (dose-related). $\geq$30 mg/kg: Reduced rate of gain, hepatomegaly, cardiomegaly (dose-related). $\geq$10 mg/kg: Hepatic porphyrinic fluorescence. $\geq$10 mg/kg: Erythema, crustiness, hyperkeratosis, perikeratosis on ears, dorsum of nose and feet, tail.	Zinkl, 1977
Rat/Donryu	M/15, F/15	Kanechlor-400	diet	total intake 450-1500 mg 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 intracranial abscesses suggested impaired resistance to infection.	Kimura and Baba, 1973

TABLE 3-1 (cont.)

Species/ Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
Rat/ Sprague-Dawley	F/6/group	Aroclor 1242	diet	0, 75 or 150 mg/kg diet for 8 or 36 weeks	36 weeks	Both levels: massive venous engorgement of liver with characteristic darkening; marked focal necrosis 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 smooth ER proliferation; deposits of iron; granular degeneration of mitochondria; many hepatocytes contained whorl-like membranous bodies.	Jonsson et al., 1981
Rat/ Sherman	M/10, F/10 in each group	Aroclor 1254	diet	0, 20, 100, 500 mg/kg diet for 8 months	8 months	Mortality (3/20) and reduced rate of gain at 500 mg/kg. Hepatomegaly, enlarged hepatocytes with foamy cytoplasm-containing inclusions at ≥20 mg/kg. Adenofibrosis and pigment accumulation at ≥100 mg/kg.	Kimbrough et al., 1972
	M/10, F/10 in each group	Aroclor 1260	diet	0, 20, 100, 500, 1000 mg/kg diet for 8 months	8 months	Mortality 1/10, 2/10, 8/10 of females in 100, 500, 1000 mg/kg groups. Decreased rate of gain at ≥500 mg/kg. Hepatomegaly, M&F at ≥20 mg/kg, discolored livers with UV fluorescence, enlarged hepatocytes with foamy cytoplasm-containing inclusions. Increased lipid content at ≥100 mg/kg. Pigment accumulations at 500 mg/kg. Adenofibrosis at ≥100 mg/kg.	
Rat/ Sprague-Dawley	M/96	Aroclors 1248, 1254 or 1262	diet	0 or 100 mg/kg diet 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 <controls by 65 weeks. Hepatomegaly: focal degeneration and necrosis by 13 weeks.	Allen et al., 1976
Mice/dd	M/114	Kanechlor-300, -400, or -500	diet	0, 100, 250, or 500 mg/kg diet for 32 weeks	32 weeks	Hepatomegaly in all treatment groups. No effect on final bw. Oval cell formation and bile duct proliferation at mid- and high-dose levels of Kanechlor-400 and -500. Hepatocellular hypertrophy in all exposed groups except low-dose Kanechlor-300. Amyloidosis in all exposed groups except high-dose Kanechlor-400 and -500 groups; greater incidence associated with lower doses of lower-chlorinated Kanechlors.	Ito et al., 1973

TABLE 3-1 (cont.)

Species/ Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
Mice/ BALB/C	M/25/group	Aroclor 1221, 1242 or 1254	diet	0, 3.75, 37.5, or 375 mg/kg diet for 6 months	9 months	375 mg/kg 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 mg/kg Aroclor 1242 and 37.5 mg/kg Aroclor 1254-exposed groups after 3-month recovery period. Aroclor 1254: 375 mg/kg: mortality and severe hepatopathology; 37.5 mg/kg: mild hepatopathology; 3.75 mg/kg: Aroclor 1242: 375 mg/kg: moderate hepatopathology. Aroclor 1221: no liver lesions.	Koller, 1977
Mice/Swiss Albino	F/63	Aroclor 1254	diet	200 mg/kg diet for 23 weeks	23 weeks	Thickening and erythemia of pinna of ear; changes in microvasculature.	Bell, 1983
Mice/BALB/ CJ	M/200	Aroclor 1254	diet	0 or 300 mg/kg diet for 6 or 11 months	11 months	Both 11- and 6-month exposure: Hepatomegaly, hepatomas, liver degeneration and elevated porphyrin.	Kimbrough and Linder, 1974
Mice/ddN	F/60	"PCB"	olive or rice bran oil	0, 0.5% V/V PCB in olive oil, or 1600 mg/kg PCB 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

A/G = Albumin/globulin; ER = endoplasmic reticulum; Hb = hemoglobin; PCV = packed cell volume

TABLE 3-2

Effects of Subchronic and Chronic Oral Exposure of PCBs to Other Species

Species/ Strain	Sex/ Number	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 mg/kg diet	8 months	Mortality of all mink on ≥20 mg/kg diet.	Bleavins et al., 1980
		Aroclor 1016	diet	0 or 20 mg/kg diet		Death of 3/12 (25%) of females. Necropsy: emaciation, complete absence of body fat, gastric ulceration. Aroclor 1242 at 5 or 10 mg/kg diet: complete reproductive failure. Aroclor 1016 at 20 mg/kg diet: reduced reproductive performances.	
Mink/ NR	F/7 or 8/group	Aroclor 1016, 1221, 1242 or 1254	diet	0 or 2 mg/kg diet	≈10 months	Aroclor 1254: interference with reproduction. All Aroclors tested: no significant differences in body weight gains, hemoglobin, PCV.	Aulerich and Ringer, 1977

NR = Not reported; PCV = packed cell volume

TABLE 3-3

Effects of Chronic and Subchronic Exposure of PCBs to Monkeys

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 mg/kg diet, ~18 months	~39.6 months	Males (5.0 mg/kg 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 mg/kg diet	~16 months; total intake 90 or 180 mg/kg by females in 6 months	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., 1979a Barsotti, 1981
	M/10	Aroclor 1248	diet	0 or 5.0 mg/kg diet, ~16 months			
	F/8/group	Aroclor 1248	diet	0.5 or 1.0 mg/kg diet 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 hyperpigmented.	
	F/24	Aroclor 1016	diet	0.025, 0.25 or 1.0 mg/kg diet for unreported length of time	NR	No abnormalities of clinical, gross or reproductive parameters. 1.0 mg/kg: Infants had reduced birth weight.	
Rhesus	NR/7	Aroclor 1248	trans-placental or mother's milk	mothers exposed to PCBs 6 months before gestation, through gestation and 3 to 4 months of nursing	up to infant age of 24 months	Significantly increased locomotor behavior (hyperactivity). Significantly retarded learning ability.	Bowman and Heironimus, 1981; Bowman et al., 1981
		Aroclor 1248	trans-placental or mother's milk	mothers removed from exposure to PCBs for 22-84 weeks before conception		Mothers exposed to $\geq$2.5 mg/kg: hyperactivity.	

TABLE 3-3 (cont.)

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	M/3/group	3,4,3',4'-TCB	diet	3 mg/kg reduced to 1 mg/kg reduced to 0.3 mg/kg	Up to 215 days	Mortality of all three by day 215 in 3,4,3',4'-TCB-exposed groups: emaciation, skin lesions, nail bed hyperplasia, loss of nails, thymus atrophy, gastric lesions as described (Allen, 1975). 2,5,2',5'-TCB: no signs of toxicity, no gross or histologic lesions.	McNulty et al., 1980
		2,5,2',5'-TCB		elevated to 1 mg/kg			
	M/4-5/group	3,4,3',4'-TCB or 2,5,2',5'-TCB	diet	1 mg/kg 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 mg/kg for 133 days 5 mg/kg additional 2 months		No evidence of toxicity.	
Rhesus	M/6	Aroclor 1242	diet	0, 3, 10, 10, 30 or 100 mg/kg 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
Cynomolgus	F/7	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 smooth ER, 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			

[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.
A/G = Albumin/globulin; Hb = Hemoglobin; NR = Not recorded; ER = Endoplasmic reticulum NA = Not available; SRBC = Sheep red blood cells

explanation was given) which undoubtedly accounted for the apparent lack of statistical significance in relative liver weights of the females exposed to 20 ppm Aroclor 1260.

At levels ≥20 ppm, exposure to Aroclor 1254 or 1260 resulted in hepatocellular enlargement with foamy cytoplasm that contained inclusions. Livers, particularly those from rats exposed to Aroclor 1260, were discolored; many fluoresced under UV light, indicating porphyria. Accumulations of pigment were noticed in livers from rats exposed to ≥100 ppm of Aroclor 1254 or 1260. Lipid accumulation and extensive foci of adenofibrosis were also noted in livers from rats exposed to 100 ppm Aroclor 1260. Ultrastructurally, an increase of smooth endoplasmic reticulum, cytoplasmic inclusion of lipid-containing vacuoles and atypical mitochondria were noted. Structures of concentrically arranged membranous whorls surrounding lipid-containing vacuoles were also seen. The most striking difference in livers from rats exposed to these two Aroclors was considerably greater adenofibrosis (synonyms: cholangiofibrosis, bile duct proliferation, fibroadenoma) in livers from Aroclor 1254-exposed rats. Under the conditions of this study, 20 ppm of Aroclor 1254 or 1260 appeared to produce effects such as hepatomegaly and hepatocytic enlargement because of the expanded smooth endoplasmic reticulum, which may be considered adverse effects. Therefore, 20 ppm Aroclor 1260 or 1254 was considered a FEL for this study.

Subsequently, Bruckner et al. (1974) exposed groups of six male Sprague-Dawley rats to 0, 5 or 25 ppm (mg/kg/diet) Aroclor 1242 for 2, 4 or 6 months to evaluate the results of prolonged exposure to relatively low levels. These authors observed no differences in either body weight gain or food consumption resulting from Aroclor 1242 exposure. The high-dose group

(25 ppm) suffered a slight but significantly reduced hematocrit after 2 months of exposure, and both treatment groups suffered slight but significantly reduced hemoglobin levels. These appeared to be temporary phenomena, since both hematocrit and hemoglobin values recovered quickly for the duration of the study.

Microsomal enzyme assays indicated a significant ($p<0.05$) induction of mixed-function oxidase activity after 2 months of exposure to 25 ppm Aroclor 1242 in the diet, and after 4 months of exposure to 5 ppm. N-demethylase activity was significantly ($p<0.001$) induced by 25 ppm Aroclor 1242 after 4 months of exposure. Urinary coproporphyrin levels were elevated after 2 months of exposure to 25 ppm Aroclor 1242 in the diet ($p<0.001$) and after 6 months of exposure to 5 ppm ($p<0.05$). Liver weight expressed as percent of body weight was elevated only at the 25 ppm dietary level ($p<0.02$) and only after 4 months of exposure. Liver lipid expressed as mg/g wet weight was elevated ($p<0.02$) after only 2 months of exposure, but after 6 months, only livers from rats exposed to 25 ppm showed elevated ($p<0.02$) lipid content.

Upon histopathological examination, no hepatic lesions were found in any rat after 2, 4 or 6 months of exposure. Sudan IV staining, however, revealed increased liver lipid in all rats exposed to Aroclor 1242 for 2, 4 or 6 months. Histopathological examination of the kidney revealed a slight vacuolization of convoluted tubules only after exposure to 25 ppm Aroclor 1242 in the diet for 4 or 6 months. In this study, it appeared that dietary exposure of rats to 5 ppm Aroclor 1242 for 2, 4 or 6 months resulted in induction of microsomal hydroxylase activity, increase in urinary coproporphyrin and increase in liver lipid content. These changes are probably reversible and, over a short term, do not appear to threaten life or health, since neither body weight gain nor food consumption was affected. In this study, 5 ppm Aroclor 1242 for 2, 4 or 6 months appeared to be a LOAEL.

Zinkl (1977) exposed 300 female CD rats to diets containing 0, 10, 30 or 100 ppm (mg/kg/diet) Aroclor 1254 for 20 weeks, and reported that there was no change in hematocrit throughout the trial. Serum cholesterol was elevated within 2 weeks in rats exposed to $\geq$30 ppm dietary Aroclor 1254 ($p<0.01$). SGOT was elevated ($p<0.05$) and serum gamma globulin was reduced ($p<0.01$) in rats exposed to 100 ppm Aroclor 1254. A dose-related increase ($p<0.05$) in beta globulin was also noted. Rats exposed to $\geq$30 ppm Aroclor experienced decreased body weight gain ($p<0.01$) and increased relative liver weights ($p<0.01$), which appeared to be dose-related ($p<0.01$).

Liver lesions were similar to those described previously (Kimbrough et al., 1972; Bruckner et al., 1974). Upon gross examination, the livers of 100 ppm-exposed rats were noticeably enlarged and dark in color, often exhibiting an accentuated lobular pattern. Porphyria fluorescence was eventually seen in livers from all groups of Aroclor 1254-exposed rats. Microscopically, focal necrosis was observed, accompanied by inflammation. Kupfer cells were noted to accumulate a brownish, iron-positive pigment. Midzonal and centrilobular degeneration consisting of vacuolated or eosinophilic hepatocytic cytoplasm was noted. Lesions in livers from 30 ppm-exposed groups were similar to but less dramatic than those observed in livers from 100 ppm-exposed rats.

Most striking were skin lesions on the ears, which eventually involved 15/60 of the high-dose (100 ppm) group, 4/60 of the mid-dose (30 ppm) group and 1/60 of the low-dose (10 ppm) group rats. These lesions consisted of alopecia, hyperkeratosis, perikeratosis and deep rete pegs. Keratinous plugging of follicles was noted. Dessicated serum and other blood elements

were observed on the surface of the skin. Subcutaneous tissues were slightly edematous and contained focal areas of polymorphonuclear infiltration and accumulation. Similar lesions were seen on the tail and on the dorsum of the nose. This was the only report found of skin lesions in rats associated with PCBs. Since no mention was made of liver pathology in 10 ppm-exposed rats, and they suffered neither reduced body weight gain, hepatomegaly nor altered blood chemistries, 10 ppm Aroclor 1254 was considered a LOAEL in this study.

Skin lesions on the ears of mice were reported by Bell (1983), who exposed female Swiss Albino mice to a much higher level, 200 ppm (mg/kg diet) Aroclor 1254 for 23 weeks, and observed erythema and thickening of the pinna of the ear. Hyperkeratosis and occlusive cystic degeneration of the pilosebaceous units were seen. Basal layer cells became elongated and markedly thickened. Ultrastructurally, the most striking lesions involved the microvasculature and included gross enlargement of the cells of the basal layer of the capillaries and small venuoles. The resultant lumenar stenosis caused a failure of the microcirculation, which was associated with the skin lesions.

In a large experiment, Koller (1977) fed diets containing 0, 3.75, 37.5 or 375 ppm (mg/kg diet) Aroclor 1221, 1242 or 1254 to groups of 25 male BALB/C mice for 6 months. Groups of mice fed 375 ppm Aroclor 1254 experienced high mortality during the 5th and 6th months. The mice exhibited the hepatic lesions discussed above that were found in rats. No other groups experienced mortality. Hepatomegaly ($p<0.01$) was observed in all Aroclor 1254-exposed groups and in the 375 ppm Aroclor 1242-exposed groups. No lesions other than moderate hepatomegaly were found in livers from 3.75 ppm Aroclor 1254-exposed rats. Liver lesions in Aroclor 1242-exposed rats

occurred only in the 375 ppm group. None of the Aroclor 1221-exposed mice evidenced hepatic lesions. Exposure to Aroclor-containing diets was terminated after 6 months, and all remaining mice were given a control diet without added PCBs for an additional 3-month observation period. Hepatomegaly persisted in the Aroclor 1254-exposed groups and the 375 ppm Aroclor 1242-exposed group. Mild liver lesions persisted only in the 37.5 ppm Aroclor 1254-exposed group.

In this study, Aroclor 1254 was clearly the most toxic substance and Aroclor 1221, the least toxic substance tested. Since the lowest dose of Aroclor 1254, 3.75 ppm, resulted only in reversible hepatomegaly without histologically demonstrated liver lesions, 3.75 ppm may be considered a LOAEL in this study.

Other studies describing subchronic exposure of rats and mice to PCBs are detailed in Table 3-1.

Mink are especially sensitive to the effects of PCBs (see Table 3-2). Bleavins et al. (1980) investigated the toxicity of Aroclor 1242 and Aroclor 1016 to pastel mink. Aroclor 1242 was fed at dietary levels of 0, 5, 10, 20 or 40 ppm (mg/kg diet) and Aroclor 1016 was fed at levels of 0 or 20 ppm. The duration of exposure was 8 months.

Each treatment group consisted of 12 females and 3 males; the control group contained 24 females and 6 males. Aroclor 1242 at $\geq$20 ppm resulted in mortality of all mink. At 10 ppm diet, Aroclor 1242 resulted in mortality of 8/12 of the females and 2/3 of the males. Only one female fed the 5 ppm Aroclor 1242 diet died. Among controls, 3/24 females died. No explanation was given for death of control group mink. Aroclor 1016 resulted in death of 3/12 females exposed to 20 ppm in the diet. Necropsy procedures consisted of gross examination only and revealed emaciation characterized by

almost complete absence of body fat and the presence of gastric ulcers. Reproduction was not possible in mink exposed to ≥5 ppm Aroclor 1242, while 20 ppm Aroclor 1016 seriously interfered with reproduction. Clearly, Aroclor 1242 was more toxic to mink than Aroclor 1016 in this study. The finding of gastric ulceration and severe cachexia (emaciation) had not been reported previously in experimental animals. It was not clear if the one female that died in the 5 ppm Aroclor 1242 group exhibited the lesions associated with PCB-induced mortality at higher dietary levels. Since more sensitive criteria of toxicity were not evaluated, it is not possible to derive a NOEL or LOAEL from this study.

In an earlier study, Aulerich and Ringer (1977) exposed groups of seven or eight female mink to 0 or 2 ppm Aroclor 1016, 1221, 1242 or 1254 in the diet for ~10 months. No overt signs of toxicity involving any of these Aroclors occurred. Body weight gain, hemoglobin and hematocrit remained normal. Aroclor 1254 at 2 ppm in the diet interfered with reproductive performance. For nonreproductive parameters, 2 ppm of the Aroclors tested appeared to be a NOEL in this study.

Monkeys have also been found to be very sensitive to PCBs (see Table 3-3). Barsotti et al. (1976) and Allen et al. (1979a) fed diets containing Aroclor 1248 for 7 months to rhesus monkeys. The control groups consisted of 12 females and 6 males. Treatment groups were as follows: nine females received 200 g/day of a diet containing 2.5 ppm (mg/kg diet) Aroclor 1248 (low-dose group); nine females received 200 g/day of a diet containing 5.0 ppm Aroclor 1248 (high-dose group); and four males received 300 g/day of a diet containing 5.0 ppm Aroclor 1248.

Within 2 months, Aroclor 1248-treated females exhibited frank weight loss, which continued through the 6 months of exposure. Females in both

groups began to show alopecia, acne of the face and neck, and palpebral edema and erythema. These lesions were present to some degree in all females by the end of 6 months. Histologically, keratinization of hair follicles (biopsy specimens) was the prominent finding. Hemograms remained normal, but an increase in SGPT was observed. After 4 months of exposure, menstrual cycle length and duration of menstrual bleeding were both increased, and other disruptions of the menstrual cycle occurred. Conception rate in the high-dose group females was depressed. Animals that conceived in both groups experienced a high level of early fetal mortality (resorptions) and abortions. By 6 months, one of the low-dose group females had died. Major gross findings included generalized alopecia, acne and subcutaneous edema. Epidermal hyperkeratinization, hyperplasia of follicular epithelium and localized inflammation were noted microscopically. Hepatic focal necrosis, enlarged hepatocytes and lipid accumulation resembled the lesions discussed in other species.

By 6 months, only one of the males (high-dose level) exhibited slight periorbital edema and erythema. Male reproduction was not affected by Aroclor 1248 at these dosage levels.

It is clear from this study that monkeys are more sensitive to PCBs then rats and mice, and that no LOEL can be derived for monkeys from these data. Truelove et al. (1982) dosed four cynomolgus monkeys with 0, 100, 100 or 400 µg Aroclor 1254 in apple juice daily for 238-267 days. Since this experiment was directed primarily toward studying effects of Aroclor 1254 on reproduction, treatment began ~100 days prepartum. Both of the 100 µg Aroclor 1254-treated monkeys delivered full-term stillborn male infants. The 400 µg Aroclor 1254-treated monkey delivered an apparently normal female infant, which died of bronchio-pneumonia at 139 days of age;

this was presumed to be evidence of impaired immunological competence. The 400 μg and one of the 100 μg Aroclor 1254-treated monkeys lost their fingernails (indicating severe hyperplastic hyperkeratosis) after ~235 days. No other overt signs of maternal toxicity were reported.

Barsotti (1981) exposed 24 adult female rhesus monkeys to diets containing 1.0, 0.25 or 0.025 ppm (mg/kg/diet) Aroclor 1016, presumably throughout gestation and lactations. Infants born to the 1 ppm Aroclor 1016 groups were significantly smaller at birth. No other manifestations of toxicity were reported. For this study, a dietary level of 0.25 ppm Aroclor 1016 appeared to be a NOEL. It is possible that Aroclor 1016 is less toxic to monkeys than the other Aroclors usually tested, as was demonstrated in mink (Bleavins et al., 1980).

3.1.2. Inhalation. Pertinent data regarding the effects of subchronic inhalation of PCBs were not located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Reports of chronic oral exposure of laboratory species to PCBs are summarized in Tables 3-1 and 3-2. These studies involved laboratory animals exposed to maximally tolerated doses in order to create and investigate the frank effects of PCBs on various target organs or tissues. They do not define LOAELs or NOELs that would be useful in risk assessment; therefore, this discussion will be a brief review of those studies that most clearly elucidated the toxic effects of PCBs.

As was noted in the discussion of subchronic studies, frank mortality in rats occurred at dietary levels $\geq$500 ppm Aroclor 1254, Aroclor 1260 (Kimbrough et al., 1972) or Kanechlor-300, -400 or -500 (Ito et al., 1974). Other signs reported in rats were reduced appetites, reduced rate of body

weight gain and reduced final body weight. Dietary levels of 100 ppm of several Aroclors (Kimbrough et al., 1975; Allen and Abrahamson, 1979; Allen et al., 1976) or ~200-300 ppm Kanechlor-400 (Kimura and Baba, 1973) resulted in severe hepatomegaly in rats; often livers were 3- to 4-fold normal size. Livers frequently exhibited multiple elevated tan or discolored liver nodules (Kimura and Baba, 1973; Kimbrough et al., 1975), oval cell proliferation, bile duct proliferation (cholangiofibrosis) (Ito et al., 1974), fatty liver degeneration (Ito et al., 1974; Kimura and Baba, 1973) and focal necrosis and degeneration (Allen et al., 1976). Hepatocellular carcinomas were also found (Kimbrough et al., 1975) (Chapter 4). Concurrent with these liver changes in rats were elevated serum lipids and cholesterol levels (Allen et al., 1976); increased hepatic protein, RNA and lipid and decreased DNA content; and increased hepatic microsomal total protein and cytochrome P-450 content (Allen and Abrahamson, 1979). Many hepatic microsomal enzyme activities were markedly induced and remained that way for the duration of exposure (Allen and Abrahamson, 1979). Morgan et al. (1981) reported "intestinal" metaplasia and adenocarcinoma in rats exposed to 25 ppm Aroclor 1254 for 2 years.

The only other laboratory species for which chronic PCB exposure data are available is the monkey, which is considerably more sensitive than the rat to PCBs. As reported in Section 3.1., liver pathology in monkeys and associated serum chemistries (Barsotti et al., 1976) resembled those in other species. No reports of liver neoplasia in monkeys were located in the available literature, but no studies were found where exposure to PCBs exceeded 1-1/2 years. Skin lesions were the most consistently reported toxic manifestation of PCBs in monkeys. Dietary levels as low as 2.5 ppm Aroclor

1248 produced erythema and periorbital edema, which progressed to alopecia, acne, facial edema and hyperpigmentation (Barsotti and Allen, 1975).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Several authors have investigated the teratogenicity and fetotoxicity associated with various mixtures of PCBs. Little evidence of teratogenicity was found; most reports concerned fetotoxicity of PCBs. The more relevant studies are summarized in Table 3-4.

Collectively, these studies reveal several aspects of the toxicity of PCBs. First, manifestations of fetotoxicity in mice (Orberg and Kihlstrom, 1973), rats (Linder et al., 1974) and monkeys (Barsotti, 1981) were observed in the absence of overt signs of maternal toxicity. The ability of PCBs or their metabolites to cross the placenta and cause abortions or fetal mortality has been demonstrated in rats (Baker et al., 1977; Spencer, 1982), rabbits (Villeneuve et al., 1971) and mice (Orberg and Kihlstrom, 1973, Marks et al., 1981). Reduced litter size was observed in rats from dams exposed to diets containing 100-500 ppm Aroclor 1254 from 3-4 weeks of age to termination of a 1-2 generation study (Linder et al., 1974).

Infants from monkeys exposed to $\geq$2.5 ppm Aroclor 1248 in the diet from ~6 months before mating were born with hyperpigmentation, a mild sign of PCB-induced toxicity in monkeys (Allen and Barsotti, 1976; Allen et al., 1979b). Reduced birth weights were observed in infants from monkeys exposed to 1.0 ppm Aroclor 1016 in the diet (Barsotti, 1981). Nursing resulted in loss of facial hair, edema of the eyelids, gastric hyperplasia and vomiting, liver degeneration and other general signs of PCB-induced toxicity, indicating the ability of monkeys to excrete substantial quantities of PCBs and

TABLE 3-4

Summary: Teratogenetic, Fetotoxic 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/day on days 1-28 of pregnancy; 25 mg/kg/day on days 7-28 of pregnancy	dose ≥25 mg/kg: maternal death, weight loss ≥10.0 mg/kg: hepatomegaly 25 mg/kg days 7-28: reduced rate of gain.	dose ≥12.5 mg/kg/day: fetal death, resorptions, abortions	Villeneuve et al., 1971
Rat/Wistar	Aroclor 1254	0, 6.25, 12.5, 25.0, 50, 100 mg/kg/day on days 6-15 of gestation	none reported	none reported	
Rat/Sherman	Aroclor 1254	0, 1, 5, 20, 100, 500 mg/kg diet from 3-4 weeks of age to termination of 1- or 2-generation study	none reported	F_{1a} 500 mg/kg: reduced litter size; 100 mg/kg: reduced litter size; F_{1b} 100 mg/kg: reduced survival at weaning; 20, 100 mg/kg: reduced litter size; F_{2a} 100 mg/kg: reduced litter size and reduced survival at weaning; 20 mg/kg: reduced litter size; F_{2b} 20, 100 mg/kg: reduced litter size.	Linder et al., 1974
	Aroclor 1260	0, 5, 20, 100, 500 mg/kg diet from 3-4 weeks of age to termination of 1- or 2-generation study	none reported	F_{1a} 500 mg/kg: reduced litter size and reduced survival at weaning. F_{1b} 500 mg/kg: reduced litter size.	
	Aroclor 1254	0,10,50,100 mg/kg/day dosed on days 7-15 of gestation	none reported	F_1 100 mg/kg/day: reduced litter size.	
Rat/ Holtzman	Aroclor 1254	0,25,50,100,200,300,600,900 mg/kg diet/day on days 6-15 of pregnancy	≥600 mg/kg: partial anorexia and weight loss	≥30 mg/kg: fetal death at delivery ≥100 mg/kg: reduced litter weight	Spencer, 1982
Mice/CD_1	3,3',4,4',5,5' HCB	0,0.1,1.0,2.0,4.0,8,12 mg/kg/day, on days 6-15 of gestation	≥8 mg/kg/day: reduced rate of gain, lethargy, vaginal bleeding	≥4 mg/kg/day: fetal mortality,resorptions; ≥2 mg/kg/day: increased incidence of cleft palate; ≥4 mg/kg/day: increased incidence of hydronephrosis; ≥1 mg/kg/day: increased incidence of cream colored liver; ≥1 mg/kg/day: increased incidence of undersized renal papillae.	Marks et al., 1981

TABLE 3-4 (cont.)

Species/ Strain	Source of PCBs	Dosage Level and Duration of Treatment	Maternal Response	Progeny Response	Reference
Rat/Sprague-Dawley	Aroclor 1221 1242 or 1260	0 or 30 mg/kg bw, days 14-20 of pregnancy	none	none	Gellert and Wilson, 1979
Rat/Wistar	Aroclor 1254	0 or 70 mg/ℓ drinking water (6.4 mg/kg bw); 9 wks	mortality at 7 wks	fetal resorption	Baker et al., 1977
Mice/NMRI	Clophen A60	0 or 0.025 mg/day; 72-76 days	lengthened estrus cycle	fetal resorption	Orberg and Kihlstrom, 1973
Mice/NR	2,2¹,4,4¹, 5,5¹ hexa-chlorobiphenyl	0 or 0.5 mg/day; 7 or 13 days of pregnancy	hepatomegaly	none	Mattsson 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., 1971
Mink	Aroclor 1242	0-40 mg/kg diet; 8 months	≥10 mg/kg: significantly increasing mortality ≥5 mg/kg: complete reproductive failure	NA NA	Bleavins et al., 1980
	Aroclor 1016	20 mg/kg diet	25% mortality, reduced fertility	increased mortality, decreased body weight by 4 weeks	
Monkey/ cynomolgus	Aroclor 1254	0,100 or 400 mg/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 mg/kg diet; 18 months starting 6 months pregestational	facial edema, cachexia, hair loss, hyperpigmentation	fetal death, infant facial and eyelid edema, loss of facial hair, facial hyperpigmentation, gastric hyperplasia and vomiting, lymphoid degeneration, hypocellular bone marrow, fatty liver	Allen and Barsotti, 1976; Allen et al., 1979b; Allen et al., 1980
	Aroclor 1248	0,2.5 or 5.0 mg/kg diet; off treatment for 1 year	persistent hyperpigmentation	fetal death; reduced neonatal weight hyperpigmentation	
Monkey/ rhesus	Aroclor 1016	0,0.025, 0.25 or 1.0 mg/kg diet for unspecified length of time	none	1.0 mg/kg diet: infants had reduced birth weight	Barsotti, 1981

NA = Not applicable

their toxic metabolites by lactation (Allen and Barsotti, 1976; Allen et al., 1979b, 1980). This phenomenon had been suggested earlier by Linder et al. (1974), who noticed decreased survival at weaning in rats from dams exposed continuously to dietary concentrations >100 ppm Aroclor 1254.

Only one report associating teratogenicity with oral exposure to PCBs has been found. Marks et al. (1981) treated 13-63 pregnant CD_1 mice/group with 0, 0.1, 1.0, 2.0, 4.0, 8 or 12 mg 3,3',4,4',5,5'-hexa CB/kg bw/day by gavage for days 6-15 of gestation. Although no deaths occurred in exposed dams, lethargy and vaginal bleeding were observed in dams exposed to $\geq$8 mg/kg/day. At dosages $\geq$4 mg/kg/day, the average number of live fetuses/dam was reduced. A reduction in the number of implants and an increase in fetal resorptions were observed in mice treated with $\geq$8 mg/kg/day. Possibly because of the greater care used in examining fetuses in this study, terata were found. Significant ($p<0.001$) incidences of cleft palate occurred in groups dosed at $\geq$2 mg/kg/day. The occurrence of cleft palate was 2/247, 4/83, 5/63, 20/117, 69/154, 118/176 and 82/108 in fetuses from dams, respectively, in the groups described above. Hydronephrosis also followed a significantly ($p<0.001$) dose-related trend in fetuses from dams exposed to $\geq$4 mg/kg/day. Cream-colored liver nodes were significantly ($p<0.001$) associated with dosage levels $\geq$1 mg/kg/day. The authors mentioned briefly that they had also found 3,3',4,4'-tetra CB to be teratogenic, but that 3,3',4,4',5,5'-hexa CB was the more potent teratogen.

In these studies, as in the toxicity studies reviewed in Chapter 3, monkeys appeared to be the species most sensitive to fetotoxic effects of PCBs. Barsotti (1981) reported reduced birth weights in infants from monkeys treated with 1.0 ppm Aroclor 1016 in the diet. The observation of fetotoxic effects at levels lower than those reported to cause toxicity in

animals after birth reduces considerably the confidence placed in risk figures derived solely from subchronic and chronic toxicity studies (Section 6.1.1.). The fact that Aroclor 1016 is probably the least toxic of the PCB products in the environment further erodes confidence in risk figures derived from studies using Aroclor 1016.

3.3.2. Inhalation. Pertinent data regarding the fetotoxicity or teratogenicity associated with inhalation exposure to PCBs could be located in the available literature.

3.4. TOXICANT INTERACTIONS

Many of the interactive effects between PCBs and other xenobiotics can be predicted from an understanding of the microsomal enzyme-inducing capabilities of PCBs. For example, PCB pretreatment of rats resulted in increased rate of metabolism and excretion of pentobarbital, and in reduced pentobarbital-induced sleeping times (Chu et al., 1977; Villeneuve et al., 1972). Hepatotoxicity induced by vinylidene fluoride (Conolly et al., 1979) and halothane anesthesia (Sipes et al., 1978) was increased in rats by pretreatment with PCBs. Cadmium, however, appeared to have an antagonistic effect on the biochemical changes that result from PCB-induced hepatic enzymes (Suzuki, 1980; Horio et al., 1981). The exact nature of this protective effect has not been elucidated, but the effect appears to be additive (Suzuki, 1980).

3.5. HUMAN EFFECTS

Several reports of human effects resulting from occupational or accidental exposure are available. Meigs et al. (1954) reported seven cases of chloracne among 14 workers intermittently exposed to Aroclor vapors. The mean length of exposure was 14.3 months for affected and 11.4 months for

unaffected workers, but no significant correlation between duration of exposure and effects occurred. Apparently, a one-time measurement revealing an Aroclor concentration of 0.1 mg/m³ was made 19 months after exposure began.

Fischbein et al. (1979) reported a cross sectional clinical field survey of 326 workers in two capacitor-manufacturing plants who were exposed to Aroclors 1254, 1242, 1016 and 1221. Air levels (8-hour TWA) of PCBs in these plants were 0-11.0 mg/m³. Dermatologic symptoms reported in 76/168 (45%) male and 87/168 (55%) female workers were rash, pruritus, acne, hyperpigmentation, and thickening and discoloration of the fingernails. Respiratory complaints were made by 3.4-13.8% of these workers, and 48.2% complained of eye irritation (Warshaw et al., 1979). Gastrointestinal symptoms (18%) and neurological symptoms (39% of males and 58% of females) were also reported (Fischbein et al., 1979). The authors performed extensive biochemical and hematological studies on these workers and concluded that there was no correlation between any symptoms and duration of employment but that a positive association between plasma PCB level and serum SGOT level (indicating extent of liver damage) existed.

Ouw et al. (1976) compared dermatologic and hepatic function parameters of 34 electrical industry workers exposed to electrical grade ("no" impurities) Aroclor 1242 with those of 30 control volunteers. Control volunteers had no history of occupational exposure to PCBs, and PCBs were not detected in their blood. Exposed workers had hepatic function tests that yielded scattered abnormal values: one worker had chloracne and five had eczematous rashes on hands and legs. These effects were associated with air levels of <1 mg Aroclor 1242/m³.

Accidental ingestion of PCBs occurred in >1000 persons in Japan in 1968 as a result of contamination of rice oil with Kanechlor-400, a PCB product

used as a heat transfer agent. The average total PCB consumption by affected individuals was estimated to be ~2 g, with 0.5 g being the smallest total amount consumed by a group of 325 people (Kuratsune et al., 1972). The contaminated rice oil also contained ~5 ppm PCDFs, presumably formed from continual reheating of PCBs. PCDFs are thought to be several times more toxic than PCBs. The dermal and respiratory symptoms reported in this case of "Yusho" poisoning were similar to those reported in occupationally exposed workers but were considerably more severe. Additionally, palmar sweating and muscular weakness were common complaints (Kuratsune et al., 1969). Yamashita (1977) reported premature delivery, reduced birth weight and height, hyperpigmentation of skin and mucous membranes, precocious dental eruption and decreased calcification of the cranium in infants of Yusho women. In addition to these findings, Kuratsune et al. (1969) also reported delivery of 3 stillborn and 10 live infants from 11 Yusho women.

By 1979, 31 Yusho patients had died, 11 (35.4%) of these from malignant neoplasms (Urabe et al., 1979). These 11 malignancies included 2 stomach cancers, 1 stomach and liver cancer (possibility of metastasis not discussed), 2 liver cancers in cirrhotic livers, 2 lung cancers, 1 lung tumor, 1 breast tumor and 2 malignant lymphomas.

In 1979, ~2000 persons in central western Taiwan developed symptoms practically identical to those observed in Yusho patients (Chen et al., 1981). These persons had also consumed rice oil contaminated by PCBs used as a heat transfer agent in the manufacturing process. Samples of contaminated rice oil were obtained and were found to contain 53-405 ppm PCB; no estimates of total PCB intake or duration of exposure were reported.

4. CARCINOGENICITY

4.1. HUMAN DATA

There are few data regarding the carcinogenicity of PCBs in humans. Urabe et al. (1979) reported that 11/33 deaths (35.4%) among Yusho patients who had died by 1979 resulted from malignancies. These malig- nancies involved various body sites, and expected incidences based on unexposed populations were not available; therefore, the significance of these data is uncertain. Bahn et al. (1976, 1977) reported 2 cases of malignant melanoma among 31 workers "heavily exposed" and 1 case of malignant melanoma among 41 workers "less heavily exposed" to Aroclor 1254. IARC (1978) estimated that only 0.04 cases would be expected in an unexposed population of this size and concluded that this was suggestive evidence that PCBs are human carcinogens. Davidorf and Knupp (1979) examined the incidence of ocular melanoma in several counties of Ohio during 1967-1977, attempting to associate higher incidences with areas known to have higher concentrations of PCBs because of industrial contamination. No significant associations were found.

4.2. BIOASSAYS

Protocol and results of the major carcinogenicity bioassays are summarized in Table 4-1. Early carcinogenicity bioassays involving dietary administration of PCBs to rats and mice either involved too few animals or had too short a duration to generate statistically or biologically significant data. Kimura and Baba (1973) fed diets containing levels of Kanechlor-400 that varied from 38.5-616 ppm to 10 male and 10 female Donryu rats for 22-80 weeks. The study was inconclusive because of early mortality from a number of unrelated causes. Hyperplastic liver nodules, which the authors suggested were precancerous lesions, occurred in all female rats

TABLE 4-1

Summary of Carcinogenic Effects of Orally Administered PCBs

Species/ Strain	Sex	PCB Source	Dietary Level (ppm)	Number Treated	Exposure (days)	Hepatopathology: No. Affected/No. Necropsied				Reference
						Neoplastic Nodules	Adenofibrosis	Hepatoma	Hepatocellular Carcinoma	
Rats/ Donryu	M	control	0	5	NA	0/10	0/10	NR	0/10	Kimura and Baba, 1973
	F	control	0	5	NA	0/10	0/10	NR	0/10	
	M	Kanechlor-400	38.5	10	159-530	0/10	0/10	NR	0/10	
	F	Kanechlor-400	38.5	10	244-560	6/10	0/10	NR	0/10	
Mice/ dd	M	control	0	6	224	0/6	NR	NR	0/6	Ito et al., 1973
		Kanechlor-500	500	12	224	0/12	NR	NR	5/12	
		Kanechlor-500	250	12	224	0/12	NR	NR	0/12	
		Kanechlor-500	100	12	224	0/12	NR	NR	0/12	
		Kanechlor-400	500	12	224	0/12	NR	NR	0/12	
		Kanechlor-400	250	12	224	0/12	NR	NR	0/12	
		Kanechlor-400	100	12	224	0/12	NR	NR	0/12	
		Kanechlor-300	500	12	224	0/12	NR	NR	0/12	
		Kanechlor-300	250	12	224	0/12	NR	NR	0/12	
		Kanechlor-300	100	12	224	0/12	NR	NR	0/12	

TABLE 4-1 (cont.)

Species/ Strain	Sex	PCB Source	Dietary Level (ppm)	Number Treated	Exposure (days)	Hepatopathology: No. Affected/No. Necropsied				Reference
						Neoplastic Nodules	Adenofibrosis	Hepatoma	Hepatocellular Carcinoma	
Rats/ Wistar	M	control	0	18	378	0/18	0/18	NR	0/18	Ito et al., 1974
		Kanechlor-500	1000	290 rats total in 1 control, 9 treatment groups	378	5/13	4/13	NR	0/13	
		Kanechlor-500	500		378	5/16	0/16	NR	0/16	
		Kanechlor-500	100		378	3/25	0/25	NR	0/25	
		Kanechlor-400	1000		378	3/10	2/10	NR	0/10	
		Kanechlor-400	500		0/8	0/8	NR	0/8		
		Kanechlor-400	100		378	2/16	0/16	NR	0/16	
		Kanechlor-300	1000		378	0/15	2/15	NR	0/15	
		Kanechlor-300	500		378	0/19	0/19	NR	0/19	
		Kanechlor-300	100		378	1/22	0/22	NR	0/22	
Mice/ CJ Balb	M	control	0	100	330	NR	0/58	0/58	NR	Kimbrough and Linder, 1974
		Aroclor 1254	300	50	330	NR	22/22	9/22	NR	
		Aroclor 1254	300	50	180	NR	0/24	1/24	NR	
Rats/ Sherman	F	control	0	200	630	0/173	NR	NR	1/173	Kimbrough et al., 1975
		Aroclor 1260	100	200	630	144/184	NR	NR	26/184	

TABLE 4-1 (cont.)

Species/ Strain	Sex	PCB Source	Dietary Level (ppm)	Number Treated	Exposure (days)	Hepatopathology: No. Affected/No. Necropsied				Reference
						Neoplastic Nodules	Adenofibrosis	Hepatoma	Hepatocellular Carcinoma	
Rats/ Fischer 344	M	control	0	24	735	NR	0/24	NR	0/24	NCI, 1978
	M	Aroclor 1254	25	24	735	NR	0/24	NR	0/24	
	M	Aroclor 1254	50	24	735	NR	0/24	NR	1/24	
	M	Aroclor 1254	100	24	735	NR	1/24	NR	2/24	
	F	control	0	24	735	NR	0/23	NR	0/23	
	F	Aroclor 1254	25	24	728-735	NR	0/24	NR	0/24	
	F	Aroclor 1254	50	24	728-735	NR	1/22	NR	0/22	
	F	Aroclor 1254	100	24	735	NR	2/24	NR	0/24	

NA=Not applicable; NR=not reported

that survived long enough to consume ≥1200 mg Kanechlor-400. Hyperplastic nodules were not found in male rats.

Ito et al. (1973) produced hepatocellular carcinomas in 5/12 male dd mice exposed to 500 ppm Kanechlor-500 for 32 weeks. Lower dietary levels (250, 100 ppm) of Kanechlor-500 and all three levels of Kanechlor-400 and Kanechlor-300 failed to cause hepatocellular carcinoma. These authors surmised that degree of chlorination was important in determining the carcinogenicity of PCB products. A subsequent study by Ito et al. (1974) produced considerable mortality but no cancer in Wistar rats exposed to 100, 500 or 1000 ppm Kanechlor-300, -400 or -500 in the diet for 378 days.

Exposure of 200 female Sherman rats to 100 ppm Aroclor 1260 (similar to the PCBs contained in Kanechlor-500) in the diet for 630 days resulted in 144 livers containing neoplastic nodules from the 184 rats that survived to termination. Hepatocellular carcinomas were found in 26 of the 184 treated survivors. No neoplastic nodules and only one hepatocellular carcinoma were found in the 173 control group survivors (Kimbrough et al., 1975).

The NCI (1978) exposed groups of 24 male and 24 female Fischer 344 rats to dietary levels of 0, 25, 50 or 100 ppm Aroclor 1254 for 728-735 days. No liver tumors were found in any female rats. Among the male groups, 1/24 and 2/24 rats in the 50 ppm and 100 ppm groups, respectively, developed hepatocellular carcinomas. The incidence did not seem to follow a dose-related pattern and was not significant by either the Cochran-Armitage or Fisher exact tests. The NCI (1978) concluded that Aroclor 1254 was not carcinogenic under the conditions of this bioassay.

4.3. MUTAGENICITY

Schoeny et al. (1979) investigated the mutagenicity of Aroclor 1254 to Salmonella typhimurium in the Ames assay. Negative results were obtained in S. typhimurium strains TA1535, TA1539, TA98 and TA100 without hepatic S-9 activation, and with S-9 activation from rats pretreated with Aroclor 1254 as a hepatic enzyme inducer. Schoeny (1982) also obtained negative results in these same four strains with one monoisomer, two separate tetraisomers and one hexaisomer of PCBs. Activation with hepatic S-9 fractions with and without several kinds of induction failed to elicit positive results. The only report of positive response in the Ames assay involved 4-chlorobiphenyl and, to a lesser extent, Aroclor 1221, tested in S. typhimurium strain TA1538 (Wyndham et al., 1976). These authors used rabbit liver microsomal preparation as the metabolic activator; no reason for this choice was mentioned.

PCB products failed to produce positive results in the dominant lethal assay in rats (Green et al., 1975a) or chromosomal changes in D. melanogaster (Nilsson and Ramel, 1974) or in sperm and bone marrow cells of rats (Green et al., 1975b; Garthoff et al., 1977).

4.4. WEIGHT OF EVIDENCE

IARC (1978) has developed and used a method of qualitative risk assessment of potential carcinogens, based upon sufficiency of evidence from human studies and animal bioassays. The degrees of evidence for carcinogenicity in human studies were categorized as sufficient evidence, limited evidence or inadequate evidence. Based upon the studies of PCB-induced cancers in humans, the evidence for a carcinogenic role of PCBs in humans was judged inadequate. As discussed in Section 4.2., Kanechlor-500 has been shown to be carcinogenic in mice (Ito et al., 1973) and Aroclor 1260 has been shown

to be carcinogenic to rats (Kimbrough et al., 1975). There was judged to be sufficient evidence to conclude that PCBs are carcinogenic in laboratory rodents. Applying the criteria for evaluating the overall weight of evidence for carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), PCBs are most appropriately classifed as Group B2 - Probable Human Carcinogens.

5. REGULATORY STANDARDS AND CRITERIA

Under Section 6(e) of the Toxic Substances Control Act (TSCA) (P.L. 94-469), the manufacture, sale and distribution of PCB products have been restricted. PCB products were further restricted to sealed systems as of 1977, and manufacture and distribution were banned in 1979.

The U.S. EPA (1980b) has set ambient water quality criteria for PCBs for the protection of humans from increased lifetime risk of cancer of 10^{-5}, 10^{-6} and 10^{-7} at 0.79, 0.079 and 0.0079 mg/ℓ. Because these compounds have a 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. The FDA has set temporary tolerances for PCBs in food and related products as reported in Table 5-1 (Code of Federal Regulations, 1981.)

Occupational exposure limits recommended by the ACGIH (1980) for Aroclor 1254 are a TLV of 0.5 and a STEL of 1.0 mg/m³. For Aroclor 1242, the recommended TLV is 1 and the STEL is 2 mg/m³. The NIOSH (1977) criterion is 1.0 µg/m³ for an exposure of 10 hours/day, 40 hours/week.

TABLE 5-1

FDA Regulations for PCBs*

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	5.0
Infant and junior foods	0.2
Paper food packaging material	0.0

*Source: Code of Federal Regulations, 1981

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

PCBs have been shown to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIS for PCBs.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

PCBs have been shown to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIC for PCBs.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Data from female rats in the study by Kimbrough et al. (1975) were chosen by the U.S. EPA Carcinogen Assessment Group to quantify the carcinogenic risk from exposure to PCBs (U.S. EPA, 1980b). The TWA dietary level was determined to be 88.4 ppm, equivalent to 4.42 mg/kg bw/day, assuming an adult rat eats food equal to 5% of its body weight/day and weighs 0.4 kg. For statistical analysis, the incidences of hepatocellular carcinoma (26/184 in treated rats and 1/173 in controls) and neoplastic nodules (144/184 in treated rats and 0/173 in controls) were combined to produce total tumor incidences of 170/184 in treated rats and 1/173 in controls, respectively. Using these data, the data in Table 6-1 and the linearized multistage model developed by Crump and adopted by the U.S. EPA (1980a), a q_1^* for human exposure to PCBs of 4.3396 $(mg/kg/day)^{-1}$ was calculated.

6.3.2. Inhalation. No studies of carcinogenicity of PCBs related to inhalation exposure have been located in the available literature, and no carcinogenic risk data for this route can be calculated.

TABLE 6-1

Data Used as the Basis for the q_1^*

Criteria	Details
Species	rat
Strain	Sherman
Sex	female
Body weight (assumed)	0.4 kg
Length of exposure	645 days
Length of experiment	730 days
Tumor site	liver
Tumor type	combined hepatocellular carcinomas and neoplastic nodules
PCB product tested	Aroclor 1260
Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	1/173
4.42	170/184

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APPENDIX

Summary Table for PCBs

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	Unit Risk or q_1^*	Reference
Inhalation	NA	NA	NA	ND	NA
Oral	rat	4.42 mg/kg/day	hepatic tumors	4.34 $(mg/kg/day)^{-1}$	Kimbrough et al., 1975; U.S. EPA, 1980b

NA = Not applicable; ND = not derivable