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PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures

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PREFACE

This report updates the cancer dose-response assessment for PCBs and shows how information on toxicity, disposition, and environmental processes can be considered together to evaluate health risks from PCB mixtures in the environment. Intended to be brief, it focuses on analysis and interpretation rather than a compilation of study results. More detailed information on PCB toxicity has been compiled by the Agency for Toxic Substances and Disease Registry (ATSDR, 1993, 1995), Safe (1994), Silberhorn et al. (1990), and the U.S. Environmental Protection Agency (U.S.EPA) (1988a).

Although not covered by this report, PCBs also have significant ecological and human health effects other than cancer, including neurotoxicity, reproductive and developmental toxicity, immune system suppression, liver damage, skin irritation, and endocrine disruption. Toxic effects have been observed from acute and chronic exposures to PCB mixtures with varying chlorine content. These toxic effects should be included along with cancer in future assessments of PCBs.

This report is to be used to support risk-based decisions within the general policy framework provided by applicable EPA statutes and does not alter such policies. It does not imply that one kind of information or another is a prerequisite for action. Not every risk assessment based on this dose-response assessment will have the same scope or depth; the level of detail of an assessment is a matter of management policy.

This report is being made available to the public and the U.S. Congress, responding to the report of the House of Representatives Appropriations Committee, which specifies:

> By December 31, 1995, the Administrator shall submit to the Congress, and make available to the public, a draft report providing an assessment of the risk of each of the polychlorinated biphenyl (PCB) mixtures that has been the subject of laboratory animal cancer bioassays, and a proposed methodology for assigning cancer risk numbers to mixtures of PCB's found in the environment. By September 1, 1996, the Committee directs that EPA shall have completed, by a panel of independent experts on the carcinogenicity of PCB's, a peer review of the draft report, and shall submit a final report to the Congress and make it available to the public.

A new laboratory animal study of four commercial mixtures will soon be made public. Because this study will provide the most comprehensive information for dose-response modeling, this report makes use of preliminary information obtained through July 1996. Although some of this information is still under review and additional information may soon become available, updating the dose-response assessment at this time allows current decisions to reflect current science and provides a framework for incorporating new information.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

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A draft report was made available to the public in January 1996. The following people or organizations provided written comments:

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The draft report was considered at a public, external peer review workshop in May 1996. A workshop report was written by the review panel, which included the following experts on the carcinogenicity of PCBs:

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This report has been approved by EPA's consensus review panel for inclusion on EPA's Integrated Risk Information System (IRIS).

The author is grateful for the contributions of the review panel and all who commented on the draft report. Their efforts truly improved the final product.

1. INTRODUCTION

1.1. PCB MIXTURES

PCBs (polychlorinated biphenyls) are mixtures of synthetic organic chemicals.[1] Different mixtures can take on forms ranging from oily liquids to waxy solids. Although their chemical properties vary widely, different mixtures can have many common components. Table 1–1 shows the overlapping composition of some commercially manufactured mixtures. Because of their inflammability, chemical stability, and insulating properties, commercial PCB mixtures had been used in many industrial applications, especially in capacitors, transformers, and other electrical equipment. These chemical properties, however, also contribute to the persistence of PCBs after they are released into the environment. Because of evidence that PCBs persist in the environment and cause harmful effects, domestic manufacture of commercial mixtures was stopped in 1977; existing PCBs, however, continue in use. Table 1–2 shows some commercial mixtures as a percentage of domestic production.

Some notes on chemical structure and nomenclature: Each PCB molecule consists of two 6-carbon rings, with one chemical bond joining a carbon from each ring (imagine sunglasses with hexagonal frames). Chlorine can attach to any of the other 10 carbons; these positions are said to be substituted. There are 209 possible arrangements, called congeners; congeners with the same number of chlorines are called isomers. The number and position of chlorines determine a molecule's physical and chemical properties. The 10 positions are numbered 2–6 on one ring and 2'–6' on the other. For example, the congener 2,4,2',5'-tetrachlorobiphenyl has chlorines in positions 2 and 4 of one ring and 2 and 5 of the other. (Standard chemical notation for this congener is 2,2',4,5'-tetrachlorobiphenyl; instead, this assessment lists chlorines on one ring, then the other, to emphasize each ring's chlorination pattern.) Positions 2, 6, 2', and 6', adjacent to the bond, are called ortho positions; 3, 5, 3', and 5', meta positions; 4 and 4' (the outermost), para positions. The International Union of Pure and Applied Chemists (IUPAC) has adopted an alternative system for numbering congeners sequentially from 1 to 209; numbers assigned to congeners named in this assessment are listed in table 3–3. A molecule's two rings can twist on the bond joining them; they are coplanar if aligned in the same plane. Chlorine in ortho positions inhibits a coplanar alignment. Coplanar molecules have dioxin-like properties (Safe, 1990, 1994; U.S. EPA, 1994b). PCB mixtures manufactured in the United States carried the trademark "Aroclor" followed by a four-digit number; the first two digits are "12," and the last two digits indicate the percent chlorine content by weight. For example, Aroclor 1260 contains approximately 60 percent chlorine by weight. Aroclor 1016 is an exception to this scheme; it contains approximately 41 percent chlorine. "Clophens" and "Kanechlors" are PCB mixtures manufactured in Germany and Japan, respectively; these series have their own numbering schemes.

Table 1–1. Typical composition (%) of some commercial PCB mixtures

	Aroclor					Clophen		Kanechlor		
	1016	1242	1248	1254	1260	A 30	A 60	300	400	500
Mono-CBs	2	1	—	—	—	—	—	—	—	—
Di-CBs	19	13	1	—	—	20	—	17	3	—
Tri-CBs	57	45	21	1	—	52	—	60	33	5
Tetra-CBs	22	31	49	15	—	22	1	23	44	26
Penta-CBs	—	10	27	53	12	3	16	1	16	55
Hexa-CBs	—	—	2	26	42	1	51	—	5	13
Hepta-CBs	—	—	—	4	38	—	28	—	—	—
Octa-CBs	—	—	—	—	7	—	4	—	—	—
Nona-CBs	—	—	—	—	1	—	—	—	—	—
Deca-CB	—	—	—	—	—	—	—	—	—	—

Columns may not total 100% due to rounding; "—" signifies less than 1%.
Lot-to-lot variability exists but has not been quantified.
Impurities include chlorinated dibenzofurans and naphthalenes; see World Health Organization (WHO) (1993) for sample concentrations.
Sources: Adapted from Silberhorn et al. (1990), ATSDR (1995).

Table 1–2. Domestic production (%) of commercial PCB mixtures, 1957–1977

Mixture	Percent of production
Aroclor 1016	13
Aroclor 1221	1
Aroclor 1232	< 1
Aroclor 1242	52
Aroclor 1248	7
Aroclor 1254	16
Aroclor 1260	11
Aroclor 1262	1
Aroclor 1268	< 1

Column does not total 100% due to rounding.
Source: Adapted from Brown (1994).

In the environment, PCBs also occur as mixtures of congeners, but their composition differs from the commercial mixtures. This is because after release into the environment, the composition of PCB mixtures changes over time, through partitioning, chemical transformation, and preferential bioaccumulation.

Partitioning refers to processes by which different fractions of a mixture separate into air, water, sediment, and soil. PCBs adsorb to organic materials, sediments, and soils; adsorption tends to increase with chlorine content of the PCBs and organic content of the other material (Callahan et al., 1979). PCBs can volatilize or disperse as aerosols, providing an effective means of transport in the environment (Callahan et al., 1979). Congeners with low chlorine content tend to be more volatile and also more soluble in water (Callahan et al., 1979). Vaporization rates and water solubility of different Aroclors and individual congeners vary over several orders of magnitude (Hutzinger et al., 1974; Erickson, 1986).

Biodegradation transforms the chemical composition of PCB mixtures in the environment. Anaerobic bacteria in sediments selectively remove chlorines from meta and para positions, appearing to reduce the toxicity and bioaccumulation potential of residues; the occurrence and extent of these dechlorinations can be limited by sediment PCB concentrations (Abramowicz, 1990; Brown and Wagner, 1990; Lake et al., 1992). (Dechlorination is not synonymous with detoxication, as congeners having carcinogenic activity can be formed through dechlorination.) Aerobic bacteria remove chlorines from PCBs with low chlorine content (1–4 chlorines) and break open the carbon rings through oxidation (Abramowicz, 1990). PCBs with higher chlorine content are extremely resistant to oxidation and hydrolysis (Callahan et al., 1979). Photolysis can slowly break down congeners with high chlorine content (Callahan et al., 1979). Overall, dechlorination processes are slow and altered PCB mixtures can persist in the environment for many years.

PCBs can accumulate selectively in living organisms. PCBs are highly soluble in lipids and are absorbed by fish and other animals. Rates of metabolism and elimination are slow and vary by congener (Matthews and Anderson, 1975). Bioaccumulation through the food chain tends to concentrate congeners of higher chlorine content, producing residues that are considerably different from the original Aroclors (Schwartz et al., 1987; Oliver and Niimi, 1988; Lake et al., 1995). PCB residues in fish and turtles, changed through environmental or metabolic alteration,

could not be characterized by Aroclor 1242, 1248, 1254, or 1260 standards (Schwartz et al., 1987). Congener distributions in several species, including humans, do not resemble any Aroclor (McFarland and Clarke, 1989). Because, in general, some toxic congeners are preferentially retained, bioaccumulated PCBs appear to be more toxic than commercial PCBs (Aulerich et al., 1986; Hornshaw et al., 1983).

PCBs are widespread in the environment, and humans are exposed through multiple pathways. Levels in air, water, sediment, soil, and foods vary over several orders of magnitude, often depending on proximity to a source of release into the environment (ATSDR, 1993; WHO, 1993). Average daily intake by humans via ambient air is about 100 ng, and about an order of magnitude higher if indoor concentrations are considered (ATSDR, 1993). Average daily intake via drinking water is less than 200 ng (ATSDR, 1993). Estimates of average daily intake via diet vary widely depending on geographic area, food habits, and sampling methodology; 5–15 μg is considered a good estimate of average daily intake via diet in industrialized countries (WHO, 1993). For nursing infants, average daily intake was estimated at 1.5–27 μg/kg (ATSDR, 1993); another study estimated 3–11μg/kg (WHO, 1993). Using the narrower range, average daily intake for a 5-kg nursing infant would be 15–55 μg, about triple the average adult intake, and approximately 50-fold higher when adjusted for body weight. Nursing infants are, therefore, an important potentially highly exposed population. Another is people whose diet is high in game fish, game animals, or products of animals contaminated through the food chain.

Although environmental mixtures are often characterized in terms of Aroclors, this can be both imprecise and inappropriate. Qualitative and quantitative errors can arise from judgments in interpreting gas chromatography/mass spectrometry (GC/MS), which reveals a spectrum of peaks that are compared with characteristic patterns for different Aroclors. For environmentally altered mixtures, an absence of these characteristic patterns can suggest the absence of Aroclors, even though some congeners are present in high concentrations. Large differences have been found in

results reported by laboratories analyzing the same sediment samples (Alford-Stevens et al., 1985; Alford-Stevens, 1986).

1.2. CANCER POTENTIAL OF PCB MIXTURES

Occupational studies show some increases in cancer mortality in workers exposed to PCBs. Bertazzi et al. (1987) found significant excess cancer mortality at all sites combined and in the gastrointestinal tract in workers exposed to PCBs containing 54 and 42 percent chlorine. Brown (1987) found significant excess mortality from cancer of the liver, gall bladder, and biliary tract in capacitor manufacturing workers exposed to Aroclors 1254, 1242, and 1016. Sinks et al. (1992) found significant excess malignant melanoma mortality in workers exposed to Aroclors 1242 and 1016. Some other studies, however, found no increases in cancer mortality attributable to PCB exposure (ATSDR, 1993). The lack of consistency overall limits the ability to draw definitive conclusions from these studies. Incidents in Japan and Taiwan where humans consumed rice oil contaminated with PCBs showed some excesses of liver cancer, but this has been attributed, at least in part, to heating of the PCBs and rice oil, causing formation of chlorinated dibenzofurans (ATSDR, 1993; Safe, 1994).

A new study of rats fed diets containing Aroclors 1260, 1254, 1242, or 1016 found statistically significant, dose-related, increased incidences of liver tumors from each mixture (Brunner et al., 1996). Earlier studies found high, statistically significant incidences of liver tumors in rats ingesting Aroclor 1260 or Clophen A 60 (Kimbrough et al., 1975; Norback and Weltman, 1985; Schaeffer et al., 1984). Partial lifetime studies found precancerous liver lesions in rats and mice ingesting PCB mixtures of high or low chlorine content.

Several mixtures and congeners test positive for tumor promotion (Silberhorn et al., 1990). Toxicity of some PCB congeners is correlated with induction of mixed-function oxidases; some congeners are phenobarbital-type inducers, some are 3-methylcholanthrene-type inducers, and some have mixed inducing properties

(McFarland and Clarke, 1989). The latter two groups most resemble 2,3,7,8-tetrachlorodibenzo-p-dioxin in structure and toxicity.

Overall, the human studies have been considered to provide limited (IARC, 1987) to inadequate (U.S. EPA, 1988a) evidence of carcinogenicity. The animal studies, however, have been considered to provide sufficient evidence of carcinogenicity (IARC, 1987; U.S. EPA, 1988a). Based on these findings, some commercial PCB mixtures have been characterized as probably carcinogenic to humans (IARC, 1987; U.S. EPA, 1988a). There has been some controversy about how this conclusion applies to PCB mixtures found in the environment.

1.3. APPROACH TAKEN BY THIS ASSESSMENT

Previous assessments developed a single dose-response slope (7.7 per mg/kg-d average lifetime exposure) for evaluating PCB cancer risks (U.S. EPA, 1988a). With no agreed-on basis for reflecting differences among environmental mixtures, this slope was used by default for any mixture. Different alternatives have been suggested that would make some distinctions about cancer risks from different PCB mixtures. One alternative would assume there is no cancer hazard from environmental mixtures unless the mixture is highly chlorinated, for example, an overall chlorine content of approximately 60 percent or greater (Delaware Department of Natural Resources and Environmental Control, 1994). Another alternative would develop a separate assessment for each commercial mixture that has been studied. These alternatives begin to distinguish among PCB mixtures, but they do not address how the environmental processes of partitioning, transformation, and bioaccumulation diminish the similarity of environmental mixtures to any of the commercial mixtures.

This new assessment adopts a related approach that distinguishes among PCB mixtures by using information on environmental processes. Environmental processes have profound effects that can decrease or increase toxicity, so toxicity of an environmental mixture is only partly determined by the original commercial mixture. This new assessment, therefore, considers all cancer studies (which used commercial

mixtures only) to develop a range of dose-response slopes, then uses information on environmental processes to provide guidance on choosing an appropriate slope for representative classes of environmental mixtures and different exposure pathways.

Different kinds of information, many not typically considered in dose-response assessments, are used in this approach. Other innovative features include:

- A range of upper-bound potency estimates for PCB mixtures, plus a range of central estimates, with guidance for choosing estimates from these ranges to reflect the effect of environmental processes on a mixture's toxicity. Sources of uncertainty in these estimates are identified and discussed.
- A tiered approach that can use site-specific congener information when available, but can be adapted if information is limited to total PCBs encountered through each exposure pathway.
- Application of EPA's proposed cancer guidelines (U.S. EPA, 1996a) in the quantitative dose-response assessment, including the interagency consensus cross-species scaling factor (U.S. EPA, 1992b) and discussion of circumstances affecting cancer risk.

A new rat study (Brunner et al., 1996), with parallel experiments for Aroclors 1260, 1254, 1242, and 1016, will soon be made public. Each experiment tested both sexes at several dose levels. Because this study will provide the most comprehensive information for dose-response modeling, this assessment makes use of preliminary information that could be obtained through July 1996. To ensure the scientific quality of this information, the laboratory report was reviewed by four members of the external peer review panel (Koller, 1996).

Section 2 briefly summarizes the studies used in developing the dose-response assessment and applying it to environmental mixtures. For a comprehensive discussion of PCB toxicity, including many other studies, see ATSDR (1993), Safe (1994), Silberhorn et al. (1990), or U.S. EPA (1988a). Section 3 uses the studies summarized in section 2 to develop a new dose-response assessment. Section 4

discusses application of the dose-response assessment to environmental mixtures, to different exposure routes, to less-than-lifetime and early-life exposure, and in combination with dioxin toxic equivalence factors. Section 5 characterizes the results of this assessment, lists research needs, and gives specific guidance for risk assessors.

2. SUMMARY OF STUDIES USED IN THE DOSE-RESPONSE ASSESSMENT

2.1. CANCER STUDIES IN HUMANS

EPA's cancer guidelines (U.S. EPA, 1986a, 1996a) favor basing dose-response assessments on human studies. This requires quantitative information on both exposure and response. This limited review focuses on the suitability of the human studies for dose-response assessment. More detailed information on these studies and on other studies not amenable to dose-response assessment has been compiled by ATSDR (1993).

Bertazzi et al. (1987). This cohort study analyzed cancer mortality among workers at a capacitor manufacturing plant in Italy. PCB mixtures with 54, then 42 percent chlorine were used through 1980. The cohort included 2100 workers (544 males and 1556 females) employed at least 1 week. At the end of follow-up in 1982, there were 64 deaths, 26 from cancer.

In males, there was a statistically significant increase in death from gastrointestinal tract cancer, compared with national and local rates (6 observed, 1.7 expected using national rates, SMR=346, CI=141–721; 2.2 expected using local rates, SMR=274, CI=112–572).[2] In females, there was a statistically significant excess risk of death from hematologic cancer compared with local, but not national, rates (4 observed, 1.1 expected, SMR=377, CI=115–877). Analyses by exposure duration, latency, and year of first exposure revealed no trend; however, the numbers are small.

Standardized mortality ratio (SMR) = 100 × observed / expected.
CI = 95% confidence interval.

Brown (1987). This cohort study analyzed cancer mortality among workers at two capacitor manufacturing plants in New York and Massachusetts. At both plants the Aroclor mixture being used changed twice, from 1254 to 1242 to 1016. The cohort included 2588 workers (1270 males and 1318 females) employed at least 3 months in areas of the plants considered to have potential for heavy exposure to PCBs. At the end of follow-up in 1982, there were 295 deaths, 62 from cancer.

Compared with national rates, there was a statistically significant increase in death from cancer of the liver, gall bladder, and biliary tract (5 observed, 1.9 expected, SMR=263, $p<0.05$). Four of these five occurred among females employed at the Massachusetts plant. Analyses by time since first employment or length of employment revealed no trend; however, the numbers are small.

Sinks et al. (1992). This cohort study analyzed cancer mortality among workers at a capacitor manufacturing plant in Indiana. Aroclor 1242, then 1016, had been used. The cohort included 3588 workers (2742 white males and 846 white females) employed at least 1 day. At the end of follow-up in 1986, there were 192 deaths, 54 from cancer. Workers were classified into five exposure zones based on distance from the impregnation ovens.

Compared with national rates, there was a statistically significant excess risk of death from skin cancer (8 observed, 2.0 expected, SMR=410; CI=180–800); all were malignant melanomas. A proportional hazards analysis revealed no pattern of association with exposure zone; however, the numbers are small.

Other occupational studies. Other studies (NIOSH, 1977; Gustavsson et al., 1986; Shalat et al., 1989) looked for an association between occupational PCB exposure and cancer mortality. Because of small sample sizes, brief follow-up periods, and confounding exposures to other potential carcinogens, these studies are inconclusive and not amenable to dose-response analysis.

Accidental ingestion. Serious adverse health effects, including liver cancer and skin disorders, have been observed in humans who consumed rice oil contaminated with PCBs in the "Yusho" incident in Japan or the "Yu-Cheng" incident in

Taiwan. These effects have been attributed, at least in part, to heating of the PCBs and rice oil, causing formation of chlorinated dibenzofurans, which have the same dioxin-like mode of action as some PCB congeners (ATSDR, 1993; Safe, 1994).

2.2. LIFETIME CANCER STUDIES IN ANIMALS

Because of their controlled exposures and absence of confounding factors, animal studies are often used for dose-response analysis. A new study compared several commercial mixtures over a range of dose levels; earlier studies had focused on mixtures with high chlorine content. This limited review focuses on the information that would be used in a dose-response assessment. More detailed information on these studies has been compiled by ATSDR (1993).

Kimbrough et al. (1975). Groups of 200 female Sherman rats were fed diets with 0 or 100 ppm Aroclor 1260 for about 21 months. Six weeks later the rats were killed and their tissues were examined. Hepatocellular carcinomas and neoplastic nodules were significantly increased in rats fed Aroclor 1260 (see table 2–1).

Table 2–1. Liver tumor incidences in rats from lifetime exposure studies, 1975–1985

Study, sex and strain, mixture	Dose	Original[a]	Reevaluation[a,b]
Kimbrough et al. (1975)	Control	** 1/173 (1%)	** 1/187 (1%)
F Sherman, 1260	100 ppm	170/184 (92%)	138/189 (73%)
NCI (1978)	Control	** 0/24 (0%)	** 0/24 (0%)
M Fischer, 1254	25 ppm	0/24 (0%)	1/24 (4%)
	50 ppm	1/24 (4%)	1/24 (4%)
	100 ppm	3/24 (12%)	3/23 (13%)
NCI (1978)	Control	** 0/23 (0%)	0/23 (0%)
F Fischer, 1254	25 ppm	0/24 (0%)	1/24 (4%)
	50 ppm	1/22 (5%)	2/24 (8%)
	100 ppm	2/24 (8%)	1/24 (4%)
Schaeffer et al. (1984)	Control[c]	** 2/120 (2%)	8/120 (7%)
M Wistar, Clophen A 30	100 ppm	42/130 (32%)	16/128 (12%)
Schaeffer et al. (1984)	Control[c]	** 2/120 (2%)	** 8/120 (7%)
M Wistar, Clophen A 60	100 ppm	123/129 (95%)	114/125 (91%)
Norback and Weltman (1985)	Control	** 0/32 (0%)	0/31 (0%)
M Sprague-Dawley, 1260	100/50/0 ppm[d]	7/46 (15%)	5/40 (12%)
Norback and Weltman (1985)	Control	** 1/49 (2%)	** 1/45 (2%)
F Sprague-Dawley, 1260	100/50/0 ppm[d]	45/47 (96%)	41/46 (89%)

**Statistically significant (p<0.05) by Cochran-Armitage trend test (for experiments with more than one dosed group) or Fisher exact test (for experiments with one dosed group).
[a]Hepatocellular adenomas or carcinomas
[b]Decreases between original and reevaluated denominators are due to lost slides; increases, to slides that were excluded originally but could not be specifically identified for exclusion in the reevaluation.
[c]One control group supported both experiments.
[d]Dosing was decreased twice during the study.
Source: Adapted from Moore et al. (1994).

National Cancer Institute (NCI, 1978). Groups of 24 male or female Fischer 344 rats were fed diets with 0, 25, 50, or 100 ppm Aroclor 1254 for 104–105 weeks (24 months). Then the rats were killed and their tissues were examined. The combined incidence of leukemia and lymphoma in males was significantly increased by the Cochran-Armitage trend test; however, since Fisher exact tests were not also significant, NCI did not consider this result clearly related to

Aroclor 1254. Hepatocellular adenomas and carcinomas were increased (see table 2–1).

Morgan et al. (1981) and Ward (1985) reevaluated gastric lesions from this study and found 6 adenocarcinomas in 144 exposed rats. This result is statistically significant, as gastric adenocarcinomas had occurred in only 1 of 3548 control male and female Fischer 344 rats in the NCI testing program. Intestinal metaplasia in exposed rats differed morphologically from controls, suggesting Aroclor 1254 can act as a tumor initiator.

Schaeffer et al. (1984). Male weanling Wistar rats were fed a standard diet for 8 weeks, then were divided into three groups. One group was fed the basic diet; for the other groups 100 ppm Clophen A 30 or A 60 was added. Rats were killed at 801–832 days (26.3–27.3 months) and were examined for lesions in the liver and some other tissues. For both mixtures, preneoplastic liver lesions were observed after 500 days (16.4 months) and hepatocellular carcinomas after 700 days (23 months) in rats dying before the end of the study (see table 2–1). The investigators concluded, "Clophen A 60 had a definite, and Clophen A 30 a weak, carcinogenic effect on rat liver."

Norback and Weltman (1985). Groups of male or female Sprague-Dawley rats were fed diets with 0 or 100 ppm Aroclor 1260 for 16 months; the latter dose was reduced to 50 ppm for 8 more months. After 5 additional months on the control diet, the rats were killed and their livers were examined. Partial hepatectomy was performed on some rats at 1, 3, 6, 9, 12, 15, 18, and 24 months to evaluate sequential morphologic changes. In males and females fed Aroclor 1260, liver foci appeared at 3 months, area lesions at 6 months, neoplastic nodules at 12 months, trabecular carcinomas at 15 months, and adenocarcinomas at 24 months, demonstrating progression of liver lesions to carcinomas. By 29 months, 91 percent of females had liver carcinomas and 95 percent had carcinomas or neoplastic nodules; incidences in males were lower, 4 and 15 percent, respectively (see table 2–1).

Vater et al. (1995) obtained individual animal results to determine whether the partial hepatectomies, which exert a strong proliferative effect on the remaining tissue,

affected the incidence of liver tumors. They reported that the hepatectomies did not increase the tumor incidence. Among females fed Aroclor 1260, liver tumors developed in 4 of 7 with hepatectomies and 37 of 39 without hepatectomies; no liver tumors developed in controls or males with hepatectomies.

Moore et al. (1994); Institute for Evaluating Health Risks (IEHR) (1991). The preceding rat liver findings were reevaluated using criteria and nomenclature that had changed to reflect new understanding of mechanisms of toxicity and carcinogenesis. The reevaluation found somewhat fewer tumors than did the original investigators. The apparent increase for Clophen A 30 (Schaeffer et al., 1984) is no longer statistically significant. Original and revised rat liver tumor incidences are given in table 2–1.

Brunner et al. (1996). This new study compared carcinogenicity across different Aroclors, dose levels, and sexes. Groups of 50 male or female Sprague-Dawley rats were fed diets with 25, 50, or 100 ppm Aroclor 1260 or 1254; 50 or 100 ppm Aroclor 1242; or 50, 100, or 200 ppm Aroclor 1016. There were 100 controls of each sex. The animals were killed at 104 weeks, after which a complete histopathologic evaluation was performed for control and high-dose groups; histopathologic evaluations of liver, brain, mammary gland, and male thyroid gland were also performed for low- and mid-dose groups.

Statistically significant increased incidences of liver adenomas or carcinomas were found in female rats for all Aroclors and in male rats for Aroclor 1260 (see table 2–2). Several of these tumors were hepatocholangiomas, a rare bile duct tumor seldom seen in control rats. Hepatocholangiomas occurred in three females and two males fed 100 ppm Aroclor 1260, in two, six, and one female fed Aroclor 1254 at 25, 50, and 100 ppm, respectively, and in one and two females fed Aroclor 1242 at 50 and 100 ppm, respectively; there was a hepatocholangiocarcinoma in one female fed 50 ppm Aroclor 1242.

Table 2–2. Liver tumor incidences in rats from 1996 lifetime exposure study

Mixture	Dose	Females[a]	Males[a]
Aroclor 1260	Control[b]	****** 1/85 (1%)	****** 7/98 (7%)
	25 ppm	10/49 (20%)	3/50 (6%)
	50 ppm	11/45 (24%)	6/49 (12%)
	100 ppm	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control[b]	****** 1/85 (1%)	7/98 (7%)
	25 ppm	19/45 (42%)	4/48 (8%)
	50 ppm	28/49 (57%)	4/49 (8%)
	100 ppm	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control[b]	****** 1/85 (1%)	7/98 (7%)
	50 ppm	11/49 (24%)	1/50 (2%)
	100 ppm	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control[b]	****** 1/85 (1%)	7/98 (7%)
	50 ppm	1/48 (2%)	2/48 (4%)
	100 ppm	6/45 (13%)	2/50 (4%)
	200 ppm	5/50 (10%)	4/49 (8%)

******Statistically significant (p<0.05) by Cochran-Armitage trend test.
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.
[b]One control group supported all experiments.
Source: Adapted from Brunner et al. (1996), Keenan and Stickney (1996).

To investigate tumor progression after exposure stops, groups of 24 female rats were exposed for 52 weeks, then exposure was discontinued for an additional 52 weeks before the rats were killed. For Aroclors 1254 and 1242, tumor incidences from the stop study were approximately half those of the lifetime study; that is, nearly proportional to exposure duration. In contrast, stop-study tumor incidences were zero for Aroclor 1016, while for Aroclor 1260 they were generally greater than half those of the lifetime study (see table 2–3). For 100 ppm Aroclor 1260, the stop study incidence was greater than that of the lifetime study, 71 vs. 48 percent. (This 48 percent lifetime study incidence was also low compared with incidences of 73, 91, and 89 percent from the earlier studies of 100 ppm Aroclor 1260 or Clophen A 60.)

Table 2–3. Liver tumor incidences in female rats from 1996 stop study

Mixture	Dose	Stop study[a]	Lifetime study[b]
Aroclor 1260	Control[c]	****** 1/85 (1%)	****** 1/85 (1%)
	25 ppm	4/24 (17%)	10/49 (20%)
	50 ppm	3/24 (12%)	11/45 (24%)
	100 ppm	17/24 (71%)	24/50 (48%)
Aroclor 1254	Control[c]	****** 1/85 (1%)	****** 1/85 (1%)
	25 ppm	5/24 (21%)	19/45 (42%)
	50 ppm	7/24 (29%)	28/49 (57%)
	100 ppm	6/24 (25%)	28/49 (57%)
Aroclor 1242	Control[c]	****** 1/85 (1%)	****** 1/85 (1%)
	50 ppm	3/24 (12%)	11/49 (22%)
	100 ppm	6/24 (25%)	15/45 (33%)
Aroclor 1016	Control[c]	1/85 (1%)	****** 1/85 (1%)
	50 ppm	0/24 (0%)	1/48 (2%)
	100 ppm	0/24 (0%)	6/45 (13%)
	200 ppm	0/24 (0%)	5/50 (10%)

******Statistically significant (p<0.05) by Cochran-Armitage trend test.
[a]Hepatocellular adenomas, carcinomas, or cholangiomas in female rats dosed for 52 weeks and killed at 104 weeks.
[b]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in female rats dosed for 104 weeks and killed at 104 weeks (comparison from table 2–2).
[c]One control group supported all experiments.
Source: Adapted from Brunner et al. (1996).

Thyroid gland follicular cell adenomas or carcinomas were increased in males for all Aroclors (see table 2–4); significant dose trends were noted for Aroclors 1254 and 1242. The increases did not continue proportionately above the lowest dose. No trends were apparent in females.

Table 2–4. Thyroid gland tumor incidences in male rats from 1996 lifetime exposure study

Mixture	Dose	Males[a]
Aroclor 1260	Control[b]	2/100 (2%)
	25 ppm	7/50 (14%)
	50 ppm	5/50 (10%)
	100 ppm	4/50 (8%)
Aroclor 1254	Control[b]	****** 2/100 (2%)
	25 ppm	7/50 (14%)
	50 ppm	7/50 (14%)
	100 ppm	6/50 (12%)
Aroclor 1242	Control[b]	****** 2/100 (2%)
	50 ppm	7/50 (14%)
	100 ppm	6/50 (12%)
Aroclor 1016	Control[b]	2/100 (2%)
	50 ppm	4/50 (8%)
	100 ppm	3/50 (6%)
	200 ppm	1/50 (2%)

******Statistically significant (p<0.05) by Cochran-Armitage trend test.
[a]Follicular cell adenomas or carcinomas in male rats dosed for 104 weeks.
[b]One control group supported all experiments.
Source: Adapted from Brunner et al. (1996).

In female rats, the incidence of mammary tumors was decreased with lifetime exposure to Aroclor 1254 and, to a lesser extent, to 1260 or 1242; this result was not observed for Aroclor 1016. Decreases did not occur for any Aroclor in the stop study. The first mammary tumor was observed at a later age in the dosed groups.

Studies of structurally related agents. Studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin and a polybrominated biphenyl (PBB) mixture are summarized here because the pattern of tumors found by Brunner et al. (1996) mimics the tumors induced in rats by these structurally related agents.

The National Toxicology Program (NTP, 1982) exposed groups of 50 male or female Osborne-Mendel rats by gavage to 0, 1.4, 7.1, or 71 ng/kg-d 2,3,7,8-tetrachlorodibenzo-p-dioxin for 2 years. Similar to the Brunner et al. (1996) study, liver tumors were increased in female rats and thyroid gland follicular cell tumors were

increased in male rats. Mammary tumors were not, however, decreased in dosed female rats.

NTP (1983) exposed groups of 51 male or female Fischer 344/N rats by gavage to 0, 0.1, 0.3, 1, 3, or 10 mg/kg-d of a PBB mixture ("Firemaster FF–1") for 6 months, then exposure was discontinued for 23 months before the animals were killed. Statistically significant increased incidences of liver tumors were found in male and female rats. Dose-related increased incidences of cholangiocarcinomas were found in male and female rats. The Firemaster FF–1 mixture comprised an anticaking agent blended with a PBB mixture containing 56 percent 2,4,5,2',4',5'-hexabromobiphenyl, 27 percent 2,3,4,5,2',4',5'-heptabromobiphenyl, and other unspecified penta-, hexa-, and heptabromobiphenyls. The analogous PCB congeners are noted for their high toxicity and abundance in environmental samples (McFarland and Clarke, 1989); 2,4,5,2',4',5'-hexachlorobiphenyl is highly persistent in the body (Matthews and Anderson, 1975) and comprises 21.5 and 12.0 percent, respectively, of PCB residues in human fat and milk (McFarland and Clarke, 1989).

2.3. PARTIAL LIFETIME STUDIES IN ANIMALS

Although lifetime studies are preferred for dose-response modeling, partial lifetime studies often use experimental designs addressing specific issues in the application of a dose-response assessment. Partial lifetime studies for PCBs have compared different commercial mixtures and the relative sensitivity of the sexes. Some studies examined early-life exposure, which is not covered by most lifetime cancer studies, where exposure starts at age 2–3 months, when the animals are mature. This limited review focuses on the information that pertains to issues in the dose-response assessment. More detailed information on these studies has been compiled by ATSDR (1993).

Kimbrough et al. (1972). Groups of 10 male or female Sherman rats were fed diets with 0, 20, 100, 500, or 1000 ppm Aroclor 1254 or 1260, beginning at 3–4 weeks of age and continuing for 8 months. Incidences of adenofibrosis reached 2/10 in males

and 4/7 in females fed 1000 ppm Aroclor 1260; in contrast, for 100 and 500 ppm Aroclor 1254, incidences were 1/10 and 10/10 in males and 7/10 and 9/9 in females. There was no adenofibrosis in 10 controls of each sex. With regard to differences between sexes, the investigators concluded Aroclor 1260 is more toxic to female rats than males, but such a difference could not be established for Aroclor 1254. With regard to differences between mixtures, the investigators concluded the effect on the liver "is more pronounced with Aroclor 1254 when all morphologic changes of equivalent dietary levels of Aroclor 1254 and 1260 are compared."

Although adenofibromas are not carcinomas, these lesions, particularly in less-than-lifetime studies, are sometimes regarded as indicating a potential for tumor formation over a longer duration. For example, in a subsequent study, most female rats of this strain fed 100 ppm Aroclor 1260 developed hepatocellular carcinomas or neoplastic nodules after 23 months (Kimbrough et al., 1975).

Kimbrough and Linder (1974). Groups of 50 male BALB/cJ mice were fed diets with 300 ppm Aroclor 1254 for 11 months, or for 6 months followed by 5 months without exposure. Hepatomas were found in 9 of 22 surviving mice exposed for 11 months, in 1 of 24 mice exposed for 6 months, and in none of 58 controls. Adenofibrosis was observed in all mice exposed for 11 months, but in none of the others.

Kimura and Baba (1973). Groups of 10 male or female Donryu rats were fed diets that increased from 38 to 462 ppm (time-weighted average, 330 ppm) Kanechlor 400, beginning at 10 weeks of age and continuing for different durations of up to 400 days (13 months). Multiple adenomatous liver nodules were found in the six females exposed for the longest durations. No nodules were found in males or in five controls of each sex.

Ito et al. (1973). Groups of 12 male dd mice were fed diets with 100, 250, or 500 ppm Kanechlor 300, 400, or 500, beginning at 8 weeks of age and continuing for 32 weeks (7.5 months). Among mice fed 500 ppm Kanechlor 500, five had

hepatocellular carcinomas and seven had nodular hyperplasia. No other groups, including six controls, showed these effects.

Ito et al. (1974). Male Wistar rats were fed diets with 0, 100, 500, or 1000 ppm Kanechlor 300, 400, or 500, beginning at 8 weeks of age and continuing for 28–52 weeks (6.5–12 months). Nodular hyperplasia was seen with all three mixtures, highest for Kanechlor 500 and lowest for Kanechlor 300, but not in controls. Histologically, the nodular hyperplasia was similar to that induced by other chemical carcinogens, suggesting the nodular hyperplasia is preneoplastic. The investigators concluded, "Hepatocellular carcinomas could be induced by administration of Kanechlor-500, -400, or -300 for a longer period."

Rao and Banerji (1988). Groups of 32 male Wistar rats were fed diets with 0, 50, or 100 ppm Aroclor 1260, beginning at 5 weeks of age and continuing for 120 days (4 months). Neoplastic nodules with adenofibrosis were found in 24 of 32 rats fed 50 ppm Aroclor 1260 and in 16 of 32 rats fed 100 ppm. None of 32 controls showed these changes. The investigators concluded Aroclor 1260 induces liver tumors when fed to young rats for a short time.

2.4. TUMOR INITIATING AND PROMOTING ACTIVITY

Studies of tumor initiating and promoting activity are available for a few commercial mixtures and congeners. The congener studies are beginning to identify a subset of mixture components that may be significant contributors to cancer induction. As some of these congeners are present in environmental mixtures, these studies provide information about the potential for environmental mixtures to cause cancer. This limited review focuses on identifying congeners with tumor promoting activity to help risk assessors know what to look for in a site-specific congener analysis. More detailed information on these and other studies has been compiled by Silberhorn et al. (1990).

Several commercial PCB mixtures and congeners show tumor promoting activity (Silberhorn et al., 1990). Aroclor 1254 and Kanechlors 400 and 500 promote liver

tumors in initiation-promotion studies; Aroclor 1254 also promotes lung tumors (Anderson et al., 1983, 1994; Beebe et al., 1992, 1993). Aroclor 1254, Clophens A 30 and A 50, four tetrachlorobiphenyls, three pentachlorobiphenyls, and one hexachlorobiphenyl showed promoting activity in studies to identify alterations in adenosine triphosphatase (ATPase), gamma-glutamyl transpeptidase (GGT), or placental glutathione S-transferase (PGST) activity, markers of tumor promoting activity in the liver. One study found the interaction of 2,5,2',5'- and 3,4,3',4'-tetrachlorobiphenyl to produce more alterations than either alone (Sargent et al., 1991). One monochlorobiphenyl and one dichlorobiphenyl showed no promoting activity. Lists of mixtures and congeners tested for promoting activity (with either positive or negative results) appear in table 2–5; references can be found in Silberhorn et al. (1990) and later references cited in the table.

Table 2–5. Mixtures and congeners tested for tumor promoting activity

Mixture	Tumors	Mixture or congener	Altered foci
Aroclor 1254	Liver, lung	Aroclor 1254	GGT+
Kanechlor 400	Liver	Clophen A 30	Marker not reported
Kanechlor 500	Liver	Clophen A 50	ATPase-, GGT+
		4–MCB	Negative
		4,4'–DiCB	Negative
		2,4,2',4'–TeCB	GGT+
		2,4,2',5'–TeCB	ATPase–, GGT+
		2,5,2',5'–TeCB	ATPase–, PGST+
		3,4,3',4'–TeCB	ATPase–, GGT+, PGST+
		2,3,4,3',4'–PeCB	GGT+, PGST+
		2,4,5,3',4'–PeCB	ATPase–, GGT+
		3,4,5,3',4'–PeCB	GGT+, PGST+
		2,4,5,2',4',5'–HxCB	ATPase–, GGT+, PGST+

Compiled from many studies; not all mixtures or congeners were tested in all systems.
Sources: Adapted from Silberhorn et al. (1990), Buchmann et al. (1991), Laib et al. (1991), Sargent et al. (1991), Beebe et al. (1992, 1993), Hemming et al. (1993), Anderson et al. (1994).

Although PCBs are not generally described as tumor initiators, in some studies a small number of ATPase-deficient or GGT-positive foci were initiated by treatment with

Clophen A 50 alone (Silberhorn et al., 1990). Weak initiating activity was found with 2,4,2',5'-tetrachlorobiphenyl, which induced ATPase-deficient, but not GGT-positive, foci (Rose et al., 1985; Laib et al., 1991). Initiation potential had been suggested by the different intestinal metaplasia morphology induced by Aroclor 1254 (Morgan et al., 1981; Ward, 1985). Many other investigators, however, report negative results for tumor initiation by PCB mixtures or congeners (Silberhorn et al., 1990).

The significance of the promotion studies is apparent, as all six ortho-substituted congeners producing altered foci are abundant in commercial mixtures (Schulz et al., 1989) and have been found in environmental samples (Lake et al., 1995; McFarland and Clarke, 1989), though the tetrachlorobiphenyls are not particularly persistent in the environment. Known for its bioaccumulation potential and abundance in environmental samples, 2,4,5,2',4',5'-hexachlorobiphenyl has been found to comprise 21.5 and 12.0 percent, respectively, of PCB residues in human fat and milk; 2,4,5,3',4'-pentachlorobiphenyl constitutes 5.4 and 6.5 percent, respectively, of these residues (McFarland and Clarke, 1989). The coplanar congeners 3,4,3',4'-tetrachlorobiphenyl and 3,4,5,3',4'-pentachlorobiphenyl have lower abundance in commercial mixtures (Kannan et al., 1988) but have been found in a variety of organisms, including humans (Safe, 1994).

2.5. ABSORPTION AND RETENTION

Cancer studies of lifetime and partial lifetime PCB exposure have been by ingestion only. Pharmacokinetic studies provide information about the potential for absorption and a risk of cancer by other exposure routes. Other studies have quantified the retention and persistence of PCBs in the body. This limited review focuses on the information that pertains to applying the dose-response assessment to dermal and inhalation exposure. More detailed information on these studies and on ingestion studies has been compiled by ATSDR (1993).

Humans absorb PCBs from ingestion, inhalation, and dermal exposure (ATSDR, 1993). Once absorbed, PCBs enter the circulation and are transported throughout the

body. Initial distribution is to liver and muscle, which are highly perfused; subsequently, PCBs, being highly lipophilic, accumulate in fat and skin (Matthews and Anderson, 1975).

Inhalation can be a principal absorption route for occupational PCB exposure (Wolff, 1985). In animals, an inhaled PCB aerosol was rapidly absorbed, although rates were not estimated (ATSDR, 1993).

PCBs can cross human skin and increase the body burden. Dermal exposure can contribute significantly to body burdens of workers (Wolff, 1985) and can be a major route of environmental exposure (ATSDR, 1993). In vivo dermal absorption by rhesus monkeys exposed for 24 hours to soil containing 44 ppm Aroclor 1242 or 23 ppm Aroclor 1254 was 14 percent in each case (Wester et al., 1993). Earlier studies found similar absorption rates for PCBs in mineral oil, trichlorobenzene, and acetone (Wester et al., 1990). Subsequent washing did not remove all PCBs, especially if time had elapsed after exposure (Wester et al., 1983). In vitro human skin accumulation of Aroclor 1254 from water was 12 percent after a half hour (Wester et al., 1987) and 44 percent after 24 hours (Wester et al., 1990), suggesting absorption is rapid initially and continues at a slower rate with further contact.

PCBs are eliminated through metabolism, which occurs primarily in the liver (Matthews and Anderson, 1975). Metabolism rates are generally lower with high chlorine content, but chlorine position is also important (Hutzinger et al., 1974; Matthews and Anderson, 1975). Absence of chlorine at two adjacent positions facilitates metabolism (Matthews and Anderson, 1975). Metabolism and elimination can be quite slow; for example, the biological half-life of 2,4,5,2',4',5'-hexachlorobiphenyl exceeds the lifespan of rats (Matthews and Anderson, 1975).

In addition to variability by congener, there is human variability in PCB metabolism and elimination. People with decreased liver function, including inefficient glucuronidative mechanisms in infants, can have less capacity to metabolize and eliminate PCBs (Calabrese and Sorenson, 1977). Additionally, approximately five percent of nursing infants receive a steroid in human milk that inhibits the activity of

glucuronyl transferase, further reducing PCB metabolism and elimination (Calabrese and Sorenson, 1977).

Persistent congeners can retain biological activity long after exposure stops; residual liver enzyme induction was observed in mice 42 weeks after a single dose of Aroclor 1254 (Anderson et al., 1991a). The majority of the retained mixture comprised 2,4,5,3'4'- and 2,3,4,3',4'-pentachlorobiphenyl and 2,4,5,2',4',5'- and 2,3,4,2',4',5'-hexachlorobiphenyl (see tables 2–5, 3–3, and 3–4).

Analysis of 1977 and 1985 serum levels in 58 Indiana workers exposed to PCBs yielded median half-lives of 2.6 years for Aroclor 1242 and 4.8 years for Aroclor 1254[3] (Phillips et al., 1989). Among workers with lowest concentrations (0–30 ppb), median half-lives were higher, 3.1 years for Aroclor 1242 and 6.5 years for Aroclor 1254. In another study in the same Indiana city, from 1977 to 1984 serum levels in five workers exposed to PCBs decreased 89–94 percent (median, 92 percent) for Aroclor 1242 and 14–53 percent (median, 16 percent) for Aroclor 1260; among six others without current occupational exposure, decreases were 23–71 percent (median, 39 percent) for total PCBs (Steele et al., 1986). Analysis of serum levels in the exposed workers yields half-lives of 2 years for Aroclor 1242 and 16 years for Aroclor 1260; in those without current occupational exposure, a half-life of 8 years for total serum PCBs.[4]

A study of people exposed through eating contaminated fish suggests that these mixtures can be more persistent. From 1977 to 1985 mean serum levels (quantified using Aroclor 1260 as a reference standard) from 111 Great Lakes fish eaters decreased only slightly, from 20.5 to 19.0 ppb (Hovinga et al., 1992).

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[3]The workers came from the plant studied by Sinks et al. (1992), where Aroclor 1242, then 1016, had been used. The quantitation of PCBs as Aroclors 1254 and 1242 illustrates both (1) selective retention of congeners with high chlorine content and (2) the imprecision of characterizing altered PCB mixtures as if they were Aroclors.

[4]Serum concentration was modeled as an exponentially decreasing function of time: $c_t = c_0 \exp(-bt)$, where c_t is concentration at time t, c_0 is initial concentration, and b is the rate parameter, estimated by linear regression of $\ln(c_0/c_t)$ on t.

It is important to recognize that ascribing a half-life to a mixture is problematic if half-lives of its components differ widely; more specifically, half-life estimates for a mixture can underestimate its long-term persistence.[5]

2.6. METABOLISM AND MODE OF ACTION IN THE LIVER

Mechanistic information provides insight and understanding of the biological activity of PCBs and their metabolites. The following discussion was contributed by peer reviewers Drs. Larry Robertson and Lucy Anderson.

Although the rate of metabolism is slow (Mills et al., 1985), PCBs may be converted by hepatic enzymes to hydroxylated metabolites. The relative rates of conversion are dependent on the number and placement of the chlorine atoms present. PCBs with fewer chlorines and with adjacent, unsubstituted carbon atoms are more readily susceptible to metabolic attack. Cytochrome P–450 isozymes may catalyze these hydroxylation reactions via an electrophilic arene oxide intermediate or via direct insertion mechanisms. Evidence for the intermediacy of arene oxides during PCB metabolism is found in the identification of (1) NIH-shift products, (2) dihydrodiol metabolites, (3) mercapturic acid products, and (4) sulfone metabolites (Sipes and Schnellman, 1987).

PCB metabolites with multiple hydroxyl groups also have been identified in animals and in microsomal incubations (McLean et al., 1996a). Dihydroxy metabolites may be oxidized in vitro to o- or p-quinones by peroxidases. In vitro studies have demonstrated that adducts of PCBs and nucleotides (dGp and dAp) or exogenous DNA may be formed during the hydroxylation step (from electrophilic arene oxides) and during the peroxidase-catalyzed oxidation of PCB catechol and hydroquinone metabolites to the respective o- and p-quinones (McLean et al., 1996b; Oakley et al.,

[5]To illustrate, consider a mixture of two components in equal parts: one component has a half-life of 1 year; the other, 100 years. If the mixture concentration is sampled after 10 years, the half-life of the total mixture will appear to be approximately 10 years: virtually all the first component will be gone, virtually none of the second, so about half the original mixture will remain. This half-life, however, overestimates the slow rate of decrease in the more persistent mixture fraction that remains.

1996). Hydroxylated PCB metabolites may have estrogenic activity (Gierthy et al., 1995).

Higher halogenated PCBs may be efficacious inducers of xenobiotic-metabolizing enzymes, although they are poor substrates. Several PCBs, possessing no or one ortho chlorine, bind the aryl hydrocarbon receptor with avidity (Bandiera et al., 1982) and induce cytochrome P–450 1A. Several di-ortho substituted PCBs induce cytochrome P–450s as does phenobarbital, while other congeneric PCBs may induce cytochrome P–450s from both subfamilies. Many of these PCBs may also induce epoxide hydrolase, glutathione transferases, and glucuronosyl transferases. Induction of xenobiotic metabolites may be accompanied by an increase in hepatic cell size and number and a proliferation of the endoplasmic reticulum. The persistent induction of hepatic cytochrome P–450s, in the absence of an oxidizable xenobiotic substrate, may provide suitable conditions for generation of reactive oxygen species.

Several PCBs tested as promoters in rat two-stage hepatocarcinogenesis were efficacious when they were administered at doses that caused liver hypertrophy and the induction of cytochrome P–450s (Silberhorn et al., 1990). Promoter activity has been observed among groups of PCB congeners that have been characterized as having widely different kinds of biological activity, including congeners that are aryl hydrocarbon agonists, congeners that induce cytochrome P–450 1A and 2B isozymes, and congeners that have a pattern of enzyme induction similar to that of phenobarbital. This may indicate multiple mechanisms of action for promotion (Buchmann et al., 1991). Congeneric PCBs may interfere with gap-junctional intercellular communication via structure-specific mechanisms. Mono- and di-ortho chlorine substituted PCBs were more active (Swierenga et al., 1990).

2.7. MODE OF ACTION IN THE THYROID

Recent mechanistic insights into thyroid carcinogenesis provide a rationale for choosing a dose-response approach for thyroid tumors. The following discussion was contributed by EPA consensus reviewer Dr. Richard Hill.

Thyroid tumors are noted for PCBs (Brunner et al., 1996) and for structurally related 2,3,7,8-tetrachlorodibenzo-p-dioxin (NTP, 1982). These compounds are accompanied by a lack of mutagenic activity in many different test systems. Liver microsomal enzyme inducers of both the AHH and PB types, which include the PCBs, commonly increase the metabolism and excretion of thyroid hormone (McClain, 1989). Depending upon the compound, there may be increased clearance of thyroid hormone from the blood, accentuated binding of the hormone in the liver, increased glucuronidation of the hormone following induction of UDP-glucuronyl transferase (Barter and Klaassen, 1992), increased bile flow and increased excretion of hormone in the bile. Effects are usually more pronounced for thyroxine (T4) than triiodothyronine (T3).

PCBs have effects on thyroid hormone status independent of their influence on thyroid hormone metabolism and excretion. They cause damage to follicular cells (Kasza et al., 1978; Byrne et al., 1987) and bind to and possibly displace thyroid hormone from plasma protein carriers (Rickenbacher et al., 1986). Both of these may contribute to a reduction in effective levels of circulating thyroid hormone.

Decreases in circulating thyroid hormone stimulate the pituitary by negative feedback to increase the output of thyroid stimulating hormone (TSH). TSH is a trophic hormone for the thyroid, resulting in the increased synthesis of thyroid hormone. When thyroid hormone needs cannot be met by existing follicular cells, cells undergo hypertrophy and diffuse hyperplasia. With continuing disruption in thyroid-pituitary status, focal hyperplasia and then benign and malignant neoplasms develop (Hill et al., 1987).

It is not totally clear whether hormonal derangement noted in rodents is a factor in the development of thyroid tumors in humans. Some studies of persons with iodide deficiency or inborn deficiency in the synthesis of thyroid hormone support the contention, while others do not. At this time there is not enough information to dismiss the animal model as not being relevant to human thyroid carcinogenesis. Even if

humans are susceptible to cancer from thyroid-pituitary disruption, existing information indicates that humans are less sensitive than rodents (Hill et al., 1987).

Thyroid cancer risks in rodents exist under conditions of disruption in thyroid-pituitary status. When, however, circulating levels of thyroid hormone and TSH pertain, risks would be expected to be minimal. Such findings are best expressed by nonlinear dose-response relationships. In assessing the risks from thyroid tumors, one would want dose-response and time-action data from repeat dose studies on such things as thyroid weight and morphology, UDP-glucuronyl transferase activity, and thyroid hormone and TSH levels. Points of departure for evaluation of risks could be determined from doses not associated with perturbations in thyroid status. Margin of exposure—the ratio of the point of departure to expected human exposure levels—could be used to express the nonlinear risks.

3. DOSE-RESPONSE ASSESSMENT

3.1. APPROACHES TO DOSE-RESPONSE ASSESSMENT

Dose-response assessment begins with consideration of developing a biologically based model, that is, a model whose mathematical structure reflects the ascertained mode of action and whose parameters are measured in experimental studies. Biologically based models have been developed for 2,4,2',5'- and 3,4,3',4'-tetrachlorobiphenyl; few congeners or mixtures, however, have been tested to measure the rate parameters that would be used in a biologically based model. Further, PCBs can cause cancer through multiple modes of action (Safe, 1990, 1994), indicating a need for multiple models. Consequently, the information available at this time is more suited to empirical modeling, where a flexible default model—allowing either linearity or nonlinearity—is fitted to describe tumor incidence as a function of dose in the experimental range.

Extrapolation to lower doses considers both linear and nonlinear approaches, with a linear default if there is not sufficient information to support a sublinear model

(U.S. EPA, 1986a, 1996a). This policy rests, in part, on some general considerations. Low-dose-linear models are appropriate for extrapolation to lower doses when a carcinogen acts in concert with other exposures and processes that cause a background incidence of cancer (Crump et al., 1976; Lutz, 1990). Further, even when the mode of action indicates a nonlinear dose-response curve in homogeneous animal populations, the presence of genetic and lifestyle factors in a heterogeneous human population tends to make the dose-response curve more linear (Lutz, 1990). This is because genetic and lifestyle factors contribute to a wider spread of human sensitivity, which extends and straightens the dose-response curve over a wider range. Although these considerations provide a reasonable argument for a model that is linear at low doses, the relation of the low-dose slope to one from the experimental range is uncertain; this uncertainty increases with the distance from the experimental range.

PCBs give generally negative results in tests of genetic activity (ATSDR, 1993), implying that PCBs induce tumors primarily through modes of action that do not involve gene mutation. This raises the possibility of a nonlinear dose-response curve. There is, however, no dose-response information on either tumors or tumor precursors to describe the dose range where the curve would be sublinear. At the low end of the experimental range (25–100 ppm), dose-response curves are not sublinear, as tumor incidence declines less than proportionately with dose for Aroclors 1260, 1254, and 1242 (Brunner et al., 1996). At much lower doses, some PCB congeners add to the considerable background of human exposure to dioxin-like compounds and augment processes associated with dioxin toxicity, providing a linear component to the dose-response curve. Between these supralinear and linear dose ranges there is no dose-response information; consequently, the information available at this time is more suited to linear extrapolation.

Environmental PCBs occur as mixtures, prompting consideration of which agents provide the most appropriate basis for an assessment. EPA's mixture guidelines (U.S. EPA, 1986b) favor basing assessments on the effects of the mixture of interest; the

second choice is to use a sufficiently similar mixture; next, to assess the components of the mixture. The guidelines further advise,

> Attention should also be given to the persistence of the mixture in the environment as well as to the variability of the mixture composition over time or from different sources of emissions. If the components of the mixture are known to partition into different environmental compartments or to degrade or transform at different rates in the environment, then those factors must also be taken into account, or the confidence in and applicability of the risk assessment is diminished.

There are no cancer studies of PCB mixtures found in the environment. Studies are available for some commercial mixtures, though their similarity to an environmental mixture can be a matter of considerable uncertainty as mixtures are partitioned, transformed, and bioaccumulated in the environment. Assessing mixture components is not now a viable alternative, because only a few congeners have been tested, none in long-term carcinogenesis studies. Thus assessments of environmental mixtures must use information on commercial mixtures. Partitioning, transformation, and bioaccumulation in the environment, however, must also be taken into account.

Risk estimates can be derived from either human or animal studies; each has strengths and limitations. Estimates derived from human studies reflect an observed association between human exposure and cancer; however, it is difficult to reconstruct reliable estimates of past exposure and separate the effect of confounding exposures to other carcinogens. Estimates derived from animal studies benefit from controlled exposures and absence of confounding factors; however, there is uncertainty in extrapolating dose and response rates across species. EPA's cancer guidelines (U.S. EPA, 1986a, 1996a) favor basing dose-response assessments on human studies. In the absence of adequate human information, assessments use animal species responding most like humans. If this cannot be determined, assessments emphasize long-term animal studies showing the greatest sensitivity, with due regard to biological relevance, exposure route, and statistical considerations; this default is considered to be conservative, tending toward public health protection.

For PCBs, the human studies involve relatively few cancer cases and lack contemporaneous exposure estimates. Some studies report air concentrations, but because skin contact is a major route of occupational exposure, air concentrations would be a poor measure of exposure (Bertazzi et al., 1987; Brown, 1987). Some studies report blood levels, but for relatively few workers at the end of exposure (Bertazzi et al., 1987; Brown, 1987; Taylor, 1988; Sinks et al., 1992). Reconstruction of past exposure is problematic because different mixtures had been in use over the years, the distribution of exposure and absorption by route and congener is unknown, and congener persistence in the body varies greatly from congener to congener (Brown, 1994) and person to person (Steele et al., 1986). Similarly, adjustment for confounding exposures to other potential carcinogens, many of them unidentified, is also problematic. Because of these limitations in quantitative information, the human studies are not well suited to dose-response assessment. Because of their controlled exposures, absence of confounding factors, and ability to provide comparable information on a range of different mixtures, the animal studies will be used for dose-response modeling.

A biologically based model for two congeners is discussed in section 3.2. Empirical models are developed and discussed in section 3.3. Analyses of congener toxicity are discussed in section 3.4.

3.2. BIOLOGICALLY BASED MODELING OF TUMOR PROMOTION

Using a two-stage carcinogenesis model, Luebeck et al. (1991) modeled tumor promoting activity of 2,4,2',5'- and 3,4,3',4'-tetrachlorobiphenyl, based on the study of Buchmann et al. (1991). Female Wistar rats were initiated with 10 mg/kg-d diethylnitrosamine for 10 days, followed by eight weekly injections of 10 or 150 μmol/kg of various compounds. The rats were killed 1 or 9 weeks later, and preneoplastic activity was characterized by changes in ATPase and GGT activity.

Because results are available for two times after dosing stopped, modeling can assess persistence of promoting activity. There was little or no promoting activity by

2,4,2',5'-tetrachlorobiphenyl after dosing stopped, but 3,4,3',4'-tetrachlorobiphenyl continued to promote vigorously (Luebeck et al., 1991).

Modeling can also estimate the probability of altered foci becoming extinct; that is, disappearing after dosing stops. After dosing stops, the probability of extinction is high, as most altered foci do not develop into observable tumors. Those that become large, however, tend to persist, as the probability of extinction decreases as size increases (Luebeck et al., 1991).

3.3. EMPIRICAL MODELING OF TUMOR INCIDENCE

The new feeding study by Brunner et al. (1996), with parallel experiments for four commercial mixtures in both sexes of rats, provides the most comprehensive information for empirical modeling. Each experiment tested several dose levels, providing information about the shape of the dose-response curve in the experimental range. For each mixture and sex, a linear-quadratic multistage model (Howe et al., 1986) was fitted to experimental results.[6] Dose was expressed as a lifetime daily average (U.S. EPA, 1986a, 1992a), calculated from weekly body weight measurements and food consumption estimates (Keenan and Stickney, 1996). Doses were scaled to humans using a factor based on the 3/4 power of relative body weight[7] (U.S. EPA, 1992b). Response was taken as the incidence of hepatocellular adenomas or carcinomas[8]; combining adenomas and carcinomas reflects guidance of the National

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[6]Formerly, EPA guidelines (U.S. EPA, 1986a) called for using the linearized multistage procedure, which fits models where risk is a function of dose d,

$$\text{Risk}(d) = 1 - \exp(-q_1 d - q_2 d^2 - \ldots - q_k d^k);\ q_i \geq 0,\ i=1,\ldots,k$$

The linearized multistage procedure fits several such models, through degree k=6. The peer review panel objected to the polynomial degree exceeding the number of dosed groups (U.S. EPA, 1996b). Consequently, this assessment uses linear-quadratic models (that is, k=2) unless there is only one dosed group, in which case it uses a linear model (k=1).

[7]Equivalent human dose = animal dose × (animal weight / 70 kg human weight)$^{1/4}$.

[8]The tables compiled by Brunner et al. (1996) combined hepatocholangiomas with hepatocellular adenomas and carcinomas, a combination not recommended by McConnell et al. (1986). Individual animal results needed to remove the hepatocholangiomas from the incidences used for modeling were not provided to EPA. The effect, however, is expected to be negligible, as few rats had a hepatocholangioma.

Toxicology Program (McConnell et al., 1986) and the observed progression of hepatocellular adenomas to carcinomas (Norback and Weltman, 1985).

Cancer potency is described by an ED10 (estimated dose associated with 10 percent increased incidence) and its lower bound, LED10. ED10s have been used both for potency ranking and as a starting point for low-dose extrapolation (Cogliano, 1986; U.S. EPA, 1988b, 1994a; National Research Council, 1993). These measures are expressed as equivalent human doses.

For extrapolation to lower doses, an ED10 can be converted to a slope by computing 0.10/ED10.[9] (Note that slopes are inversely proportional to ED10s; high potency is indicated by high slopes, but low ED10s.) Similarly, an upper-bound slope can be obtained by computing 0.10/LED10. Formerly, upper-bound slopes were calculated by the linearized multistage procedure (U.S. EPA, 1980, 1986a); these are reported in the appendix as "q_1*"s. The LED10 method and the linearized multistage procedure give similar upper-bound slopes; for example, for female rats fed Aroclor 1254, the LED10 method and the linearized multistage procedure give upper-bound slopes of 1.5 and 1.6 per mg/kg-d, respectively. Potency and slope estimates are compiled in table 3–1; details supporting the calculations appear in appendix tables A–1 through A–8.

[9]The slope is the change in response divided by the change in dose. Relative to the origin (an increased response of 0 at a dose of 0), the change in response is 0.10 at the dose ED10; thus the slope is 0.10/ED10.

Table 3–1. Human potency and slope estimates derived from rat liver tumors

Study, sex and strain, mixture	ED10[a]	LED10[b]	Central slope[c]	Upper-bound slope[d]	See table
Brunner, F Sprague-Dawley, 1260	0.24	0.19	0.4	0.5	A–1
Brunner, F Sprague-Dawley, 1254	0.086	0.067	1.2	1.5	A–2
Brunner, F Sprague-Dawley, 1242	0.38	0.27	0.3	0.4	A–3
Brunner, F Sprague-Dawley, 1016	2.4	1.4	0.04	0.07	A–4
Brunner, M Sprague-Dawley, 1260	1.0	0.55	0.1	0.2	A–5
Brunner, M Sprague-Dawley, 1254[e]	1.7	0.87	0.06	0.1	A–6
Brunner, M Sprague-Dawley, 1242[e]	2.9	1.2	0.03	0.08	A–7
Brunner, M Sprague-Dawley, 1016[e]	5.9	2.5	0.02	0.04	A–8
Kimbrough, F Sherman, 1260	0.10	0.091	1.0	1.1	A–9
NCI, M Fischer, 1254	1.0	0.55	0.1	0.2	A–10
NCI, F Fischer, 1254[e]	1.2	0.61	0.08	0.2	A–11
Schaeffer, M Wistar, A 30[e]	2.1	1.0	0.05	0.1	A–12
Schaeffer, M Wistar, A 60	0.058	0.047	1.7	2.1	A–13
Norback, M Sprague-Dawley, 1260[e]	1.0	0.53	0.1	0.2	A–14
Norback, F Sprague-Dawley, 1260	0.062	0.046	1.6	2.2	A–15

[a]Estimated dose associated with 10% increased incidence, in mg/kg-d.
[b]95% lower bound on ED10, in mg/kg-d.
[c]Per mg/kg-d, computed as 0.10/ED10.
[d]Per mg/kg-d, computed as 0.10/LED10.
[e]No significant increase; quantities indicate sensitivity of study.

In conjunction with the Brunner et al. (1996) study, the earlier studies provide useful information on the potential for lot-to-lot and strain-to-strain differences. Because these studies did not report body weight and food consumption, administered doses were converted from ppm in the diet to mg/kg-d using default factors based on rats weighing 350 grams and consuming food equal to 5 percent of body weight daily (U.S. EPA, 1980).[10] Potency and slope estimates from the earlier studies are included in table 3–1; details, in tables A–9 through A–15.

[10]Equivalent human dose (mg/kg-d) = (ppm in diet) × 0.05 × (animal weight / 70 kg human weight)$^{1/4}$.
In the studies by Kimbrough et al. (1975) and Norback and Weltman (1985) initial dose levels were later decreased or discontinued. It is likely, however, that tumor development had already begun and internal exposure remained high with release of PCBs stored in fat (Vater et al., 1995). Thus, for these studies, initial dose levels were used without averaging over the study duration; this reduces these potency estimates by up to one-third compared to the default of averaging dose over the study duration.

The range of potency values in table 3–1 is summarized in table 3–2. It is based primarily on the range for Aroclors 1260, 1254, 1242, and 1016 in female Sprague-Dawley rats (Brunner et al., 1996), but considers the other studies, too. For example, the two studies of female Sprague-Dawley rats fed Aroclor 1260 (Brunner et al., 1996; Norback and Weltman, 1985) could reflect, in part, lot-to-lot differences that are pertinent to mixtures altered in the environment; thus the range of upper-bound slopes includes those from the Brunner et al. (1996) study (0.07–1.5 per mg/kg-d) and the Norback and Weltman (1985) study (2.2 per mg/kg-d). The earlier gastric tumors and leukemias and lymphomas in male rats fed Aroclor 1254 (NCI, 1978) are not included in this range, because they were not confirmed by the Brunner study; they would contribute little to the overall estimates since incidences are several-fold less than those of the liver tumors.

Table 3–2. Range of human potency and slope estimates

	ED10[a]	LED10[b]	Central slope[c]	Upper-bound slope[d]	See table
Highest observed potency	0.086	0.046[e]	1.2	2.2[e]	A–2,15
Lowest observed potency	2.4	1.4	0.04	0.07	A–4

[a]Estimated dose associated with 10% increased incidence, in mg/kg-d.
[b]95% lower bound on ED10, in mg/kg-d.
[c]Per mg/kg-d, computed as 0.10/ED10.
[d]Per mg/kg-d, computed as 0.10/LED10.
[e]Bound from Norback and Weltman (1985).

These ranges reflect experimental uncertainty and variability of commercial mixtures, but not human heterogeneity and differences between commercial and environmental mixtures. Environmental processes have profound effects that can increase or decrease toxicity, so toxicity of an environmental mixture is only partly determined by the original commercial mixture. Potency estimates for an Aroclor tested in the laboratory may not be the best surrogate for assessing that Aroclor as altered in

the environment. Sections 4 and 5 develop specific guidance for applying these potency ranges to environmental mixtures.

The new upper-bound slopes are lower than the previous estimate of 7.7 per mg/kg-d average lifetime exposure (U.S. EPA, 1988a). The previous estimate was derived from female rats in the Norback and Weltman (1985) study; the new estimate from the same study is 2.2 per mg/kg-d. This difference is attributable to three factors, each responsible for reducing the slope by approximately one-third: the rat liver tumor reevaluation (Moore et al., 1994), use of the new cross-species scaling factor (U.S. EPA, 1992b), and not using a time-weighted average dose (see previous footnote). The difference between the highest observed new upper-bound slope (2.2 per mg/kg-d) and the lowest (0.07 per mg/kg-d) is entirely attributable to the available of tests on several commercial mixtures (Brunner et al., 1996). This 30-fold range in potency reflects differences in commercial mixture composition.

The different responses for male and female rats (Brunner et al., 1996) suggest the possibility of developing different potency values for males and females. In view of the 91 percent response in male Wistar rats (Schaeffer et al., 1984), as well as the sensitivity of male mice (Kimbrough and Linder, 1974; Ito et al., 1973), it is premature to conclude that females are always more sensitive.

For the thyroid tumors, no meaningful ED10 or LED10 can be computed. The dose-response curves for each Aroclor are virtually horizontal across the experimental range, so mathematical models cannot determine whether a dose-response curve begins to be sublinear immediately below the experimental range or whether it remains horizontal for several orders of magnitude below the experimental range before becoming sublinear. This difficulty transcends PCBs and thyroid tumors; in general, there would be an unacceptable level of uncertainty in using a sublinear extrapolation approach when study results in the experimental range are not at all sublinear.

3.4. ANALYSES OF CONGENER TOXICITY

McFarland and Clarke (1989) explain how toxicity of some PCB congeners is correlated with induction of mixed-function oxidases. Some congeners are described as phenobarbital-type inducers, others as 3-methylcholanthrene-type inducers, and some as having mixed inducing properties. The latter two groups most resemble 2,3,7,8-tetrachlorodibenzo-p-dioxin in structure and toxicity. Based on potential for toxicity (some forms of toxicity, for example, neurotoxicity, may not be well represented) and frequency of occurrence in environmental samples, 36 congeners of highest concern were identified and classified (see table 3–3).

Table 3–3. PCB congeners of highest concern

Highest toxicity and abundance[a]	High toxicity and abundance[b]	Abundant in environment[c]	Potential for toxicity[d]
3–MC-type inducers:	**PB-type inducers:**	18: 2,5,2'–TrCB	37: 3,4,4'–TrCB
77: 3,4,3',4'–TeCB	87: 2,3,4,2',5'–PeCB	44: 2,3,2',5'–TeCB	81: 3,4,5,4'–TeCB
126: 3,4,5,3',4'–PeCB	99: 2,4,5,2',4'–PeCB	49: 2,4,2',5'–TeCB	114: 2,3,4,5,4'–PeCB
169: 3,4,5,3',4',5'–HxCB	101: 2,4,5,2',5'–PeCB	52: 2,5,2',5'–TeCB	119: 2,4,6,3',4'–PeCB
	153: 2,4,5,2',4',5'–HxCB	70: 2,5,3',4'–TeCB	123: 3,4,5,2',4'–PeCB
Mixed-type inducers:	180: 2,3,4,5,2',4',5'–HpCB	74: 2,4,5,4'–TeCB	157: 2,3,4,3',4',5'–HxCB
105: 2,3,4,3',4'–PeCB	183: 2,3,4,6,2',4',5'–HpCB	151: 2,3,5,6,2',5'–HxCB	158: 2,3,4,3',4',6'–HxCB
118: 2,4,5,3',4'–PeCB	194: 2,3,4,5,2',3',4',5'–OCB	177: 2,3,5,6,2',3',4'–HpCB	167: 2,4,5,3',4',5'–HxCB
128: 2,3,4,2',3',4'–HxCB		187: 2,3,5,6,2',4',5'–HpCB	168: 2,4,6,3',4',5'–HxCB
138: 2,3,4,2',4',5'–HxCB		201: 2,3,4,5,2',3',5',6'–OCB	189: 2,3,4,5,3',4',5'–HpCB
156: 2,3,4,5,3',4'–HxCB			
170: 2,3,4,5,2',3',4'–HpCB			

[a]Pure 3-methylcholanthrene-type inducers and mixed-type inducers reported frequently in environmental samples.
[b]Phenobarbital-type inducers reported frequently in environmental samples.
[c]Weak inducers or noninducers reported frequently in environmental samples.
[d]Mixed-type inducers not reported frequently in environmental samples, but toxicologically active.
Source: Adapted from McFarland and Clarke (1989).

U.S. EPA (1991) examined toxic effects, including cancer, of four structural classes: dioxin-like PCBs, ortho-substituted PCBs, hydroxylated metabolites, and sulfonated metabolites. Different mechanisms were discussed for dioxin-like and other PCBs. It was concluded that congener toxicity could not be characterized by chlorine content alone. Before adopting toxic equivalence factors (TEFs) for PCB congeners, it was recommended to define other classes of PCBs and identify the mechanisms involved. Criteria for developing TEFs were listed as (1) a demonstrated need, (2) a well defined group of chemicals, (3) a broad base of toxicological data, (4) consistency

in the relative toxicity of congeners across toxicological endpoints, (5) demonstrated additivity between the toxicity of individual congeners, (6) a mechanistic rationale, and (7) consensus.

Safe (1990, 1994) characterized dioxin-like PCBs as eliciting a spectrum of biochemical and toxic responses similar to chlorinated dibenzo-p-dioxins and dibenzofurans, all acting through the aryl hydrocarbon receptor. Based on quantitative structure-activity studies, the first conservative TEFs for dioxin-like PCBs were proposed and refined. Use of these TEFs is limited to responses mediated through the aryl hydrocarbon receptor.

Subsequently, WHO derived TEFs for dioxin-like PCBs (Ahlborg et al., 1994). Included were congeners that show structural similarity to chlorinated dibenzo-p-dioxins and dibenzofurans, bind to the aryl hydrocarbon receptor, elicit dioxin-specific biochemical and toxic responses, and persist and accumulate in the food chain. On the basis of these criteria, 13 PCB congeners were assigned TEFs, expressed as a fraction of the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (see table 3–4). As new information is developed, these TEFs could change, or TEFs for additional congeners could be developed. Section 4 gives guidance, and section 5 an example, for applying these TEFs where a congener analysis is available.

Table 3–4. WHO interim TEFs for human intake of dioxin-like PCBs

Non-ortho congeners	TEF	Mono-ortho congeners	TEF	Di-ortho congeners	TEF
77: 3,4,3',4'–TeCB	0.0005	105: 2,3,4,3',4'–PeCB	0.0001	170: 2,3,4,5,2',3',4'–HpCB	0.0001
126: 3,4,5,3',4'–PeCB	0.1	114: 2,3,4,5,4'–PeCB	0.0005	180: 2,3,4,5,2',4',5'–HpCB	0.00001
169: 3,4,5,3',4',5'–HxCB	0.01	118: 2,4,5,3',4'–PeCB	0.0001		
		123: 3,4,5,2',4'–PeCB	0.0001		
		156: 2,3,4,5,3',4'–HxCB	0.0005		
		157: 2,3,4,3',4',5'–HxCB	0.0005		
		167: 2,4,5,3',4',5'–HxCB	0.00001		
		189: 2,3,4,5,3',4',5'–HpCB	0.0001		

Source: Adapted from Ahlborg et al. (1994).

Brown (1994) calculated relative metabolic rates for 146 congeners and combined them into a measure of "relative human accumulability" for each Aroclor, based on congener concentrations in the Aroclors. Assuming a correlation between

relative human accumulability and chronic toxicity or cancer, it was suggested to calculate relative human accumulability (relative to Aroclor 1260) for each environmental mixture. Because environmental processes can alter the relative congener concentrations, this approach can yield cancer slopes outside the range determined previously for commercial mixtures. In premeeting comments on this assessment (U.S. EPA, 1996b), Brown refined this approach to express cancer slope as a function of both relative human accumulability and dioxin toxic equivalents. Congener concentrations for the commercial mixtures in the Brunner et al. (1996) study will be used to evaluate this suggested approach.

4. APPLICATION OF THE DOSE-RESPONSE ASSESSMENT

4.1. APPLICATION TO PCB MIXTURES IN THE ENVIRONMENT

After release into the environment, PCB mixtures change through partitioning, transformation, and bioaccumulation, differing considerably from commercial mixtures. How can toxicity values for commercial mixtures be applied to mixtures in the environment?

A consensus is emerging on the difficulty of assessing environmental mixtures by reference to Aroclors. Safe (1994) wrote, "Regulatory agencies and environmental scientists have recognized that the composition of PCBs in most environmental extracts does not resemble the composition of the commercial products." Along similar lines, ATSDR (1993) advised,

> It is important to recognize that the PCBs to which people may be exposed are likely to be different from the original PCB source because of changes in congener and impurity composition resulting from differential partitioning and transformation in the environment and differential biological metabolism and retention. Because of this concern, current data are considered inadequate to differentiate between the toxicity and carcinogenicity of environmental PCB mixtures with any reasonable degree of confidence.

For these reasons, risks from environmental mixtures are not assessed by characterizing environmental mixtures as if they were Aroclors. This does not mean that all environmental mixtures are regarded as equally potent; environmental mixtures differ from commercial mixtures and from each other. To make distinctions about risks from environmental mixtures, the range of potency observed for commercial mixtures can be considered along with factors that increase or decrease risk.

First among these is persistence and bioaccumulation through the food chain. Each species, in turn, retains persistent congeners that prove resistant to metabolism and elimination (Oliver and Niimi, 1988). Bioaccumulated PCBs appear to be more toxic than commercial PCBs (Aulerich et al., 1986). Mink fed Great Lakes fish contaminated with PCBs showed liver and reproductive toxicity comparable to mink fed Aroclor 1254 at quantities three times greater (Hornshaw et al., 1983). It is crucial to recognize that commercial PCBs tested in laboratory animals were not subject to prior selective retention of persistent congeners through the food chain. For exposure through the food chain, risks can be higher than those estimated in this assessment.

Also important is the presence or absence of congeners and metabolites that contribute to cancer induction. Mechanistic studies are beginning to identify these congeners and describe their modes of action. Several congeners have dioxin-like activity (Ahlborg et al., 1994; Safe, 1994), some promote tumors through different modes of action (Buchmann et al., 1991). Because concentrations of these congeners are altered by partitioning, transformation, and bioaccumulation in the environment, risks from environmental mixtures can differ from those of commercial mixtures. Congener analyses of environmental samples can provide information on the extent of this difference and can be an important tool in risk assessment, particularly when fish consumption is an issue.

Chlorine content was formerly regarded by some scientists as correlated with cancer risk. Recently, however, Aroclor 1254 was found to be more potent than 1260, which was only slightly more potent than 1242 (Brunner et al., 1996). This casts doubt on chlorine content being a useful indicator of cancer potency in this range of chlorine

content; both the number and position of chlorines are important. It is instructive to compare how the Aroclors rank by other measures. With respect to resistance to metabolism and persistence in the body, there is an association with chlorine content, which partially explains the greater experimental potency of commercial mixtures with higher chlorine content. With respect to dioxin toxic equivalents (TEQs), however, several studies have ranked Aroclor 1254, 1248, and 1242 as more potent than 1260 (Harper et al., 1995; Safe, 1994; Harris et al., 1993; Hong et al., 1993; Schulz et al., 1989). The combined effect is difficult to predict, as Aroclor 1260 and mixtures with higher chlorine content have lower dioxin TEQs but persist longer in the environment and in the body.

A key finding is the several-fold lower potency of Aroclor 1016 compared with 1242 (Brunner et al., 1996). Though these mixtures are similar in average chlorine content (41 and 42 percent, respectively), Aroclor 1016 has virtually no congeners with more than four chlorines. This suggests that one way to differentiate less potent mixtures is to verify the absence of congeners with more than four chlorines.

Since mixtures of congeners with more than four chlorines cannot be assessed using chlorine content alone, other determinants of toxicity are used. Two important determinants, persistence and bioaccumulation, can be related to exposure pathway. (Persistence is not synonymous with toxicity; however, in the absence of testing on most congeners, it is reasonable to suppose some correlation between persistence and toxicity.) Evaporated or dissolved congeners tend to be lower in chlorine content than the original mixture; they tend also to be more inclined to metabolism and elimination and lower in persistence and toxicity. On the other hand, congeners adsorbed to sediment or soil tend to be higher in chlorine content and persistence, and bioaccumulated congeners ingested through the food chain tend to be highest of all. Rates of these processes vary over several orders of magnitude (Hutzinger et al., 1974; Erickson, 1986), thus the effect of environmental processes can be greater than the spread in potency or slope estimated from commercial mixtures.

For these reasons, a tiered approach is recommended. The default tier uses exposure pathway to choose appropriate potency values from the ranges described in table 3–2. The highest observed potency from these ranges is appropriate for food chain exposure, sediment or soil ingestion, and dust or aerosol inhalation, pathways where environmental processes tend to increase risk. Lower potencies are appropriate for ingestion of water-soluble congeners or inhalation of evaporated congeners, pathways where environmental processes tend to decrease risk. To the extent that drinking water or ambient air contains contaminated sediment or dust, the higher potency values would be appropriate, as congeners adsorbed to sediment or dust tend to be of high chlorine content and persistence, especially for sediment or dust with high organic content. Since the lowest observed potency, based on studies to date, is derived from Aroclor 1016, its use is most appropriate in the absence of congeners with more than four chlorines. When congeners with more than four chlorines are present, but exposure is by drinking water ingestion or vapor inhalation, potency values derived from the next lowest tested mixture, Aroclor 1242, can be more appropriate.

Thus three reference points can be designated for each range (see table 4–1): a "high risk" point based on studies of Aroclor 1260 and 1254, which give the highest observed potencies; a "low risk" point, based on the study of Aroclor 1242; and a "lowest risk" point, based on the study of Aroclor 1016. The "high risk" point is used for exposure pathways associated with environmental processes that tend to increase risk; the "low risk" point, for exposure pathways that tend to decrease risk; and the "lowest risk" point, for cases where congener or isomer analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs, suggesting that potency is best represented by the least potent tested mixture. This demonstrates a potential use of congener analysis of environmental samples. Section 5 provides a series of examples illustrating this tiered approach.

Table 4–1. Tiers of human potency and slope estimates for environmental mixtures

HIGH RISK AND PERSISTENCE

ED10[a]	LED10[b]	Central slope[c]	Upper-bound slope[d]	Criteria for use
0.086	0.067	1.	2.	▸ Food chain exposure ▸ Sediment or soil ingestion ▸ Dust or aerosol inhalation ▸ Dermal exposure, if an absorption factor has been applied to reduce the external dose ▸ Presence of dioxin-like, tumor-promoting, or persistent congeners in other media ▸ Early-life exposure (all pathways and mixtures)

LOW RISK AND PERSISTENCE

ED10[a]	LED10[b]	Central slope[c]	Upper-bound slope[d]	Criteria for use
0.38	0.27	0.3	0.4	▸ Ingestion of water-soluble congeners ▸ Inhalation of evaporated congeners ▸ Dermal exposure, if no absorption factor has been applied to reduce the external dose

LOWEST RISK AND PERSISTENCE

ED10[a]	LED10[b]	Central slope[c]	Upper-bound slope[d]	Criteria for use
2.4	1.4	0.04	0.07	▸ Congener or isomer analyses verify that congeners with more than 4 chlorines comprise less than 1/2% of total PCBs

[a]Estimated dose associated with 10% increased incidence, in mg/kg-d.
[b]95% lower bound on ED10, in mg/kg-d.
[c]Per mg/kg-d, computed as 0.10/ED10 and rounded to one significant digit.
[d]Per mg/kg-d, computed as 0.10/LED10 and rounded to one significant digit.

This reasoning assumes that the PCB mixture has undergone alteration in the environment for many years and that partitioning into different environmental media has approached equilibrium. Congener or isomer analyses are important to verifying equilibrium. For example, if drinking water samples contain high concentrations of congeners with high chlorine content, this could indicate a recent release of PCBs that has not had sufficient time to partition as expected, a continuing release of PCBs, or

the presence of stirred-up sediment and the subsequent release of adsorbed congeners with high chlorine content. Judgment should be used in assessing these situations, which are most likely not best represented by the "lowest risk" point derived from Aroclor 1016.

4.2. APPLICATION TO DIFFERENT ROUTES OF EXPOSURE

What inferences can be made about dermal or inhalation exposures, two routes for which there are no lifetime cancer studies?

PCBs are absorbed through ingestion, inhalation, and dermal exposure, after which they are transported similarly through the circulation. This provides a reasonable basis for expecting similar internal effects from different routes of environmental exposure. In addition, the capacity of Aroclor 1254 to promote mouse lung tumors (Anderson et al., 1983, 1994; Beebe et al., 1992, 1993) and the observation of skin cancer from occupational exposure (Sinks et al. 1992) suggest a potential for cancer at the point of entry.

Dermal absorption through human skin is rapid initially and continues at a slower rate with further contact (Wester et al., 1987, 1990). Rhesus monkeys exposed to Aroclor 1242 or 1254 in soil for 24 hours absorbed 14 percent through the skin (Wester et al., 1993). Absorption of PCBs from soil involves competition between the lipophilic attraction of PCBs to skin and adsorption to organic soil material. Absorption increases with duration of skin contact and moisture content of soil, but these relationships have not been quantified. Overall, use of the low end of the potency ranges for dermal exposure appears appropriate in light of the substantial but incomplete absorption through the skin. If, however, an estimate of dermal exposure has been reduced by an absorption factor, then the high end of the potency ranges would be appropriate, as the use of an absorption factor converts an external dose to an internal dose.

The lung is also a potential target for cancer risk following PCB exposure. Aroclor 1254 is active as a promoter in the mouse lung initiated with methylating nitrosamines. Relevant mechanistic information includes: (1) persistent induction of

cytochrome P–450 1A in the lung (up to several months after a single PCB dose), (2) promotion by 2,3,4,2',4',5'–HxCB, not by 2,4,5,2',4',5'–HxCB, and partial abrogation of 2,3,4,2',4',5'–HxCB's effects by 2,4,5,2',4',5'–HxCB, (3) correlation of the promotion effect with body burden of 2,4,5,2',4'–PeCB, and (4) selective retention of PCB congeners, especially 2,3,4,3',4'–PeCB, in mouse lung (Anderson, 1991b).

Inhaled PCBs can be rapidly absorbed, although rates have not been quantified (ATSDR, 1993). Rapid absorption, however, suggests potency by inhalation is comparable to potency by ingestion. Because PCBs are slowly metabolized, little uncertainty results from the first-pass effect, where ingested toxicants are subject to metabolism in the liver before entering the circulation, while inhaled toxicants enter the circulation before reaching the liver. As with ingested mixtures, the composition of an inhaled mixture influences its toxicity. Evaporated mixtures tend to have low chlorine content and persistence, mixtures adsorbed to dust and soil tend to be high in this regard, and mixtures suspended in an aerosol can be more diverse.

4.3. APPLICATION TO LESS-THAN-LIFETIME AND EARLY-LIFE EXPOSURES

In assessing cancer risks from less-than-lifetime exposure, the common practice is to prorate cumulative exposure over the lifespan (U.S. EPA, 1986a, 1992a). For example, exposure lasting 7 years of a 70-year lifespan would be assumed to have one-tenth the effect of lifetime exposure. Does the information available for PCBs support this default or suggest an alternative?

Less-than-lifetime exposure induced statistically significant increased incidences of liver tumors in female rats fed Aroclors 1260, 1254, and 1242 (Brunner et al., 1996). This result was most pronounced for Aroclor 1260, where tumor incidences at the highest dose were higher for a 12-month exposure than for a 24-month lifetime exposure. Only Aroclor 1016 showed no significant increases from less-than-lifetime exposure. The earlier less-than-lifetime studies in rats and mice suggest that less-than-lifetime exposure can quickly induce high incidences of early stages of tumor development (Kimbrough et al., 1972; Ito et al., 1973, 1974). With further exposure,

these can progress to malignancy (Kimbrough et al., 1975; Norback and Weltman, 1985). Tumor incidences from less-than-lifetime exposure were sometimes lower (Kimbrough and Linder, 1974), and sometimes similar (Rao and Banerji, 1988), to those from full lifetime exposure.

The strong response for Aroclor 1260, coupled with the lack of response for Aroclor 1016, suggests that these findings may be related to persistence in the body. PCBs entering the body are transported by the circulation to internal organs and fat, where they are stored (Matthews and Anderson, 1975). Equilibrium is maintained among external exposure levels, concentrations in blood, and concentrations in fat and other tissues. When external exposure is reduced, to maintain equilibrium, stored PCBs reenter the circulation and provide a continuing internal source of exposure (Matthews and Anderson, 1975). Thus PCBs from short-term exposure can be stored in the body and emerge as a source of exposure much later.

Persistence in the body can enhance the opportunity for PCB congeners to express tumor promoting activity (Safe, 1994). Persistent congeners can retain biological activity long after exposure stops (Anderson et al., 1991a); some persistent congeners are tumor promoters. The congener 3,4,3',4'-tetrachlorobiphenyl continues to promote tumors vigorously after dosing stops, but not 2,4,2',5'-tetrachlorobiphenyl (Buchmann et al., 1991; Luebeck et al., 1991). Although the probability of liver focus extinction is high after dosing stops, those that become large tend to persist (Luebeck et al., 1991). This would allay concern for short-term exposure but increase concern as exposure duration increases. Further studies of less-than-lifetime exposure, as well as methods for quantifying the differential effects of less-than-lifetime exposure, are needed.

Regarding early-life exposure, infants can be highly exposed to PCBs during pregnancy and lactation (Dewailly et al., 1991, 1994). The accumulation of PCBs in human adipose tissue creates a store for subsequent release of PCBs into the bloodstream and then into the fetal circulation. During the postpartum period, PCBs are mobilized from adipose stores, transferred into human milk, and delivered to the

neonate via nursing (Dewailly et al., 1991). This source of exposure may account for a substantial fraction of chlorinated dibenzo-p-dioxins and dibenzofurans, and the same may be true for dioxin-like and other PCBs. It is, therefore, important to assess the extent of exposure through the human milk pathway; if direct measurement of concentrations in milk are not available, estimates can be derived from maternal exposures (Smith, 1987).

Normal fetal development depends on the timing and rate of release of T3 and T4. Some evidence indicates that PCBs can alter normal T3 and T4 metabolism, thereby disturbing thyroid function and provoking secondary impacts on organogenesis during development. Any estrogenic/anti-estrogenic, androgenic/anti-androgenic, or other hormonal activity of PCB mixtures has the possibility of altering the development of reproductive organs or the urogenital tract, potentially causing cancer or other adverse effects through a mechanism different from those causing liver cancer (U.S. EPA, 1996b).

Few studies, however, have investigated early-life sensitivity. In human infants, glucuronidative mechanisms are not fully developed; additionally, some nursing infants receive a steroid in human milk that inhibits the activity of glucuronyl transferase, further reducing PCB metabolism and elimination (Calabrese and Sorenson, 1977). In animals, Aroclor 1260 induced high incidences of liver tumors when fed to 5-week-old rats for a short time (Rao and Banerji, 1988). On the other hand, acute perinatal dosing with Aroclor 1254 promoted nitrosamine-initiated lung and liver tumors in mice but did not induce cancer in the offspring when administered alone (Anderson et al., 1983, 1986, 1994). A study of polybrominated biphenyls (PBBs) found that perinatal exposure enhanced susceptibility to liver tumors for female rats also exposed as adults and increased the incidence of liver tumors in male and female mice not further exposed as adults (NTP, 1993). Because of the potential magnitude of early-life exposures, the possibility of greater perinatal sensitivity, and the likelihood of interactions among thyroid and hormonal development, it is reasonable to conclude that early-life exposures may be associated with increased risks; this would indicate

using the "high-risk" potency estimates for early-life exposure. A method for quantifying the differential effects of early-life exposure is needed.

4.4. APPLICATION WITH DIOXIN TOXIC EQUIVALENCE FACTORS

TEFs have been proposed for some dioxin-like PCB congeners, while this assessment develops potency values for overall concentrations of mixtures. How can the TEF approach supplement the mixture-based approach?

When assessing PCB mixtures, it is important to recognize that both dioxin-like and nondioxin-like modes of action contribute to overall PCB toxicity (Safe, 1994; McFarland and Clarke, 1989; Birnbaum and DeVito, in press). Because relatively few PCB congeners are dioxin-like, dioxin equivalence explains only part of a PCB mixture's toxicity. (This applies to cancer and other forms of toxicity, for example, neurotoxicity and endocrine disruption; Birnbaum and DeVito, in press.) Hence, PCB assessments should begin with the mixture-based approach developed in this report.

At the same time, it is possible that concentrations of dioxin-like congeners are increased in an environmental mixture. When congener concentrations are available, the mixture-based approach can be supplemented by analysis of dioxin TEQs to evaluate dioxin-like toxicity. Section 5 gives an example for calculating dioxin TEQs when a congener analysis is available.

When assessing mixtures of dioxin and related compounds, it is important to consider the contribution of dioxin-like PCBs to total dioxin equivalents (U.S. EPA, 1994b). TEQs for dioxin-like PCBs (Ahlborg et al., 1994) can be added to those for other dioxin-like compounds. In some situations, PCBs can contribute more dioxin-like toxicity than chlorinated dibenzo-p-dioxins and dibenzofurans (Schecter et al., 1994; Dewailly et al., 1991, 1994). The congener 2,4,5,3',4'-pentachlorobiphenyl, shown to have tumor-promoting activity, is a major contributor to total dioxin equivalents in the United States (Patterson et al., 1994) and maritime Quebec (Dewailly et al., 1994).

Exposure to dioxin-like PCBs adds to background exposure of dioxin-like compounds and augments processes associated with dioxin toxicity. There is support

for using low-dose-linear dose-response models for incremental doses that add to existing background exposure (Crump et al., 1976; Lutz, 1990). Thus confidence in this assessment's use of low-dose-linear models is enhanced for the dioxin-like portion of a PCB mixture.

5. CHARACTERIZATION AND GUIDANCE FOR RISK ASSESSORS

5.1. DOSE-RESPONSE CHARACTERIZATION

Joint consideration of cancer studies and environmental processes leads to a conclusion that environmental PCB mixtures are highly likely to pose a risk of cancer to humans. Although environmental mixtures have not been tested in cancer assays, this conclusion is supported by several complementary sources of information. Statistically significant, dose-related, increased incidences of liver tumors were induced in female rats by Aroclors 1260, 1254, 1242, and 1016 (Brunner et al., 1996). These mixtures contain overlapping groups of congeners that, together, span the range of congeners most frequently found in environmental mixtures. Several congeners promote tumors or have dioxin-like activity; these congeners are found in environmental samples and in a variety of organisms, including humans.

The range of potency observed for commercial mixtures is used to represent the potency of environmental mixtures. The range reflects experimental uncertainty and variability of commercial mixtures, but not human heterogeneity or differences between commercial and environmental mixtures. Environmental processes alter mixtures through partitioning, transformation, and bioaccumulation, thereby decreasing or increasing toxicity. The overall effect can be considerable, and the range observed for commercial mixtures may underestimate the true range for environmental mixtures. Limiting the potency of environmental mixtures to the range observed for commercial mixtures reflects a decision to base potency estimates on experimental results, however uncertain, rather than apply safety factors to compensate for lack of information (U.S. EPA, 1996b).

A tiered approach allows use of different kinds of information in estimating the potency of environmental mixtures. When congener information is limited, exposure pathway is used to indicate whether environmental processes have decreased or increased a mixture's potency. Partitioning, transformation, and bioaccumulation have been extensively studied and can be associated with exposure pathway, thus the use of exposure pathway to represent environmental processes increases confidence in the risks inferred for environmental mixtures. When available, congener information is an important tool for refining a potency estimate that was based on exposure pathway.

Extrapolation to environmental levels is based on models that are linear at low doses. Low-dose-linear models are appropriate when a carcinogen acts in concert with other exposures and processes that cause a background incidence of cancer. Even when the mode of action indicates a nonlinear dose-response curve in homogeneous animal populations, the presence of genetic and lifestyle factors in a heterogeneous human population tends to make the dose-response curve more linear.

Depending on the specific application, either central estimates or upper bounds can be appropriate. Central estimates describe a typical individual's risk, while upper bounds provide assurance that this risk is not likely to be underestimated if the underlying model is correct. The upper bounds calculated in this assessment reflect study design and provide no information about sensitive individuals or groups. Central estimates are useful for estimating aggregate risk across a population. Central estimates are used for comparing or ranking environmental hazards, while upper bounds provide information about the precision of the comparison or ranking. Comparing a central estimate with its upper bound indicates whether the central estimate is stable enough to support credible risk estimates. In this assessment, the less-than-twofold difference between central estimates and upper bounds indicates that these estimates are stable.

Uncertainty around these estimates extends in both directions. The slope factor ranges primarily reflect mixture variability, and so are not necessarily appropriate for probabilistic analyses that attempt to describe model uncertainty and parameter

uncertainty. Several sources of uncertainty are inherent in the experimental information used in this assessment:

- **Experimental design and conduct:** The new rat study (Brunner et al., 1996) is quite extensive in design and conduct, going beyond standard designs for cancer studies in many respects.
- **Variability in commercial mixture composition:** For the four Aroclors tested in female Sprague-Dawley rats (Brunner et al., 1996; Norback and Weltman, 1985), there is a 30-fold range in potency. This whole range is used to represent environmental mixtures.
- **Variability across strains:** In the four rat strains tested, sensitivity varies up to 15-fold. Potency and slope estimates were derived from a strain covering the middle of this range.
- **Variability between sexes:** Potency and slope estimates were derived from female rats, whose liver response was usually greater than that of males. The greatest response in the liver, however, was in male rats. Greater sensitivity of females was not seen in mice, nor in the thyroid.
- **Variability across experiments:** For the same Aroclor, sex, and strain, differences up to four-fold were observed. To reflect this lot-to-lot variability, both estimates were included.
- **Experimental uncertainty (sample size):** Central and upper-bound potency estimates differ by no more than about two-fold. This is a minor source of uncertainty.
- **Potential for other carcinogenic effects:** The new rat study reported small increases in thyroid tumor incidence for male rats, suggesting a potential for a hormonal mode of action. These results have not yet been publicly discussed or peer reviewed.

Other sources of uncertainty arise in the methods for assessing this experimental information and applying it to human environmental exposure:

- **Animal-to-human extrapolation:** The use of default cross-species scaling factors is intended as an unbiased projection not expected to provide conservatism (U.S. EPA, 1992b). Information is lacking to evaluate whether humans are more or less sensitive than rats.
- **High-to-low-dose extrapolation:** The use of models that are linear at low doses can potentially overestimate potency by an unknown amount. The rat studies, however, show no evidence of sublinearity in the experimental range.
- **Route-to-route extrapolation:** Information on relative absorption rates suggests that differences in toxicity across exposure routes are small.
- **Difference between commercial and environmental mixtures:** Commercial mixtures released into the environment are altered by environmental processes. Qualitatively, exposure pathway is a reasonably good indicator of whether potency has been decreased or increased. Quantitatively, the percentage change in toxicity is unknown, though the 30-fold range in potency observed for commercial mixtures likely underestimates the range for environmental mixtures.
- **Persistence and exposure duration:** Some PCBs persist in the body and retain biological activity after exposure stops (Anderson et al., 1991a). Compared with the current default practice of assuming that less-than-lifetime effects are proportional to exposure duration, rats exposed to the persistent mixture Aroclor 1260 had more tumors, while rats exposed to the less persistent Aroclor 1016 had fewer tumors (Brunner et al., 1996). Thus the current default practice can underestimate risks for persistent mixtures.
- **Human variability in sensitivity:** People with decreased liver function can have less capacity to metabolize and eliminate PCBs. Approximately five percent of nursing infants receive a steroid in human milk that further inhibits PCB metabolism and elimination (Calabrese and Sorenson, 1977).
- **Human variability in exposure:** Blood concentrations vary over a 100-fold range (ATSDR, 1993). Highly exposed populations include nursing infants, consumers of game animals contaminated through the food chain, and workers

with occupational exposure. There is greater confidence in risk estimates for highly exposed groups.

When exposure involves the food chain, uncertainty extends principally in one direction: through the food chain, living organisms selectively bioaccumulate persistent congeners, but commercial mixtures tested in laboratory animals were not subject to prior selective retention of persistent congeners. Bioaccumulated PCBs appear to be more toxic than commercial PCBs (Aulerich et al., 1986; Hornshaw et al., 1983) and appear to be more persistent in the body (Hovinga et al., 1992). For exposure through the food chain, risks can be higher than those estimated in this assessment. Two highly exposed populations, nursing infants and consumers of contaminated game animals, are exposed through food.

The dioxin-like nature of some PCBs raises a concern for cumulative exposure, as dioxin-like congeners add to background exposure of other dioxin-like compounds and augment processes associated with dioxin toxicity. This weighs against considering PCB exposure in isolation or as an increment to a background exposure of zero. Confidence in this assessment's use of low-dose-linear models is enhanced when there is additivity to background exposures and processes.

To gauge the distance of an extrapolation, human exposures can be compared with the LED10. For mixtures that are altered in the environment, however, this simple comparison of relative exposure is of limited value as some congeners increase in concentration while others decrease. Additionally, for exposures that augment processes leading to a background incidence of cancer, identifying and quantifying background human exposures are necessary for a true measure of total exposure.

5.2. INFLUENCE OF PROPOSED CANCER GUIDELINES

This assessment demonstrates several ideas from EPA's proposed cancer guidelines (U.S. EPA, 1996a). Most prominent is development of a range of potency estimates, using studies for a range of mixtures, instead of focusing on the highest-potency mixture. For low-dose extrapolation, an LED10 approach replaces the

linearized multistage procedure. An ED10 approach provides a statistically stable method for deriving central estimates of low-dose slopes. Dose calculations use the interagency consensus cross-species scaling factor, based on the 3/4 power of relative body weight (U.S. EPA, 1992b).

Also evident is the proposed guidelines' encouragement to use different kinds of information. It is reflected in the tiered approach that uses site-specific congener or isomer analyses when available, but can differentiate among environmental mixtures using exposure pathway when mixture information is limited. It is also found in this assessment itself, which combines information on toxicity and environmental processes.

The proposed guidelines' emphasis on discussing circumstances that affect cancer risks, especially exposure route considerations, is found throughout this assessment. There is extensive discussion of how environmental processes alter the composition and toxicity of PCB mixtures. Exposure circumstances are addressed in a framework that distinguishes different exposure pathways as lower risk or higher risk.

None of these features, however, is inconsistent with previous guidelines (U.S. EPA, 1986a), whose intent is "to permit sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge." Each new feature of this assessment can be viewed in this spirit.

5.3. RESEARCH NEEDS

This dose-response assessment has tried to make the best use of the available information. For some questions it has stopped short because information or methods are needed to resolve an important issue. Research that would enable this assessment to proceed further includes:

- Cancer studies comparing commercial and environmental mixtures, especially those found in the food chain. This assessment warns that food chain risks can be underestimated, but the extent is not quantified.

- A method for using lifetime studies to assess less-than-lifetime exposure to persistent agents. This assessment warns that assuming risk and exposure duration are proportional can underestimate risks for persistent mixtures, but the extent is not quantified.
- Relative cancer potency factors for congeners identified by McFarland and Clarke (1989). This will improve evaluations of mixtures where carcinogenic potential has been increased or decreased beyond the range of tested commercial mixtures. To help determine such factors, 2-year studies in female rats are recommended for 3,4,5,3',4'-pentachlorobiphenyl and 3,4,5,3',4',5'-hexachlorobiphenyl, the two congeners with the highest dioxin TEFs, and 2,4,5,2',4',5'-hexachlorobiphenyl and 2,3,4,5,2',4',5'-heptachlorobiphenyl, the two persistent congeners whose PBB analogues constitute over 80 percent of the PBB mixture that caused hepatocellular adenomas, carcinomas, and cholangiocarcinomas in rats.
- Studies to test the hypothesis that the carcinogenic activity of Aroclor 1016 is due to its tetrachlorobiphenyls only, with no contribution from congeners with 1–3 chlorines. Current information is inadequate to evaluate this hypothesis.

At the peer review workshop, the panel identified other areas where research could help resolve important questions. These can be grouped broadly into exposure methods research, effects research, and risk assessment methods development. Research needs in exposure methods include:

- Standard analytical methods, including sample preparation, for measuring PCB congeners in environmental samples.
- Database of congener levels in environmental samples.

Research needs on effects include:

- Epidemiologic studies focused on tumor promotion. If PCBs act as tumor promoters, they would increase cancer mainly in humans with already-initiated cancer cells. For common cancers with complex etiologies, promotional effects will be seen only if specifically looked for.

- Mechanism-oriented dose-response data for environmental mixtures, including promotional, hormonal, sex-specific effects.
- Mechanisms of PCB-induced liver cancer in rats, its similarity to the mechanism(s) of rat liver cancer induced by "nongenotoxic" carcinogens, its activities at low dose levels, and its relevance to humans.
- Identifying the most significant congeners in commercial and environmental mixtures, describing their modes of action, and conducting studies to quantify their slope factors.
- Dose-response studies in a broader range of test animals.
- Determine sensitivity of fetuses and newborns to the carcinogenic effects of environmental mixtures.
- Determine risks for thyroid and urogenital/reproductive tract cancers in newborns and adults.

Methods development needs for risk assessment include:

- Developing an appropriate dose metric for PCBs.
- Exploring structure-activity methods for predicting pharmacokinetic parameters for PCB mixtures.
- Verifying the appropriateness, for PCBs, of the new cross-species scaling factor.
- Evaluating the consistency of human and animal studies.
- Developing quantitative uncertainty distributions for key sources of uncertainty.

Work in progress includes using congener compositions of the tested Aroclors from the Brunner et al. (1996) study to evaluate the "relative human accumulability" approach (Brown, 1994; U.S. EPA, 1996b). Congener compositions of the Aroclors and the rat tissues can also be used in a factor analysis that would identify a subset of congeners most associated with tumor induction. Field analyses can then reduce uncertainty by quantifying a small number of critical congeners.

Elsewhere, new epidemiologic information is being analyzed. The National Institute for Occupational Safety and Health is updating its study of the Indiana cohort, and is expanding and updating its studies of the cohorts in Massachusetts and New

York. Additionally, the females in these three cohorts are being pooled for a study of breast cancer.

Finally, future risk assessments of PCBs in the environment should consider more than the risk of cancer. Although the purpose of this report was to evaluate cancer risks, the emerging scientific literature indicates that toxicological endpoints other than cancer may also be important to human health. These toxic effects should be included along with cancer in future assessments of PCBs.

5.4. SUMMARY OF GUIDANCE FOR RISK ASSESSORS

Joint consideration of cancer studies and environmental processes leads to a conclusion that environmental PCB mixtures are highly likely to pose a risk of cancer to humans. The cancer potency of PCB mixtures is determined using a tiered approach that depends on the information available (see table 4–1).

Upper-bound slope factors, derived by linear extrapolation from LED10s, are described by a range of estimates with three reference points.

Upper-bound slope factors: 0.07 – 0.4 – 2 per mg/kg-d

Slope factors are multiplied by lifetime average exposure levels to estimate the risk of cancer. The upper bounds reflect study design and provide no information about sensitive individuals or groups. Although PCB exposures are often characterized in terms of Aroclors, this can be both imprecise and inappropriate. Total PCBs or congener or isomer analyses are recommended.

The first (default) tier is invoked when information on the mixture of interest is limited. The upper reference point (2 per mg/kg-d) is appropriate for food chain exposure, sediment or soil ingestion, and dust or aerosol inhalation; these are exposure pathways for which environmental processes are likely to increase risk. Due to potential for higher sensitivity early in life, the upper reference point is also used for all early-life exposure. The middle reference point (0.4 per mg/kg-d) is appropriate for drinking water ingestion and vapor inhalation; these are exposure pathways for which

environmental processes are likely to decrease risk. The lowest reference point (0.07 per mg/kg-d) should not be used without specific information on the congener composition of the mixture.

The second tier is invoked when there are congener or isomer analyses for the mixture of interest. The lowest reference point (0.07 per mg/kg-d) can be used if these analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs, as well as the absence of dioxin-like, tumor-promoting, and persistent congeners. When congener concentrations are available, the slope-factor approach can be supplemented by analysis of dioxin TEQs to evaluate dioxin-like toxicity.

Central-estimate slope factors, derived by linear extrapolation from ED10s, can be described by a similar range with three reference points.

Central-estimate slope factors: 0.04 – 0.3 – 1 per mg/kg-d

Central estimates describe a typical individual's risk, while upper bounds provide assurance that this risk is not likely to be underestimated if the underlying model is correct. Central estimates are useful for estimating aggregate risk across a population.

Highly exposed populations include nursing infants and consumers of game fish, game animals, or products of animals contaminated through the food chain. Highly sensitive populations include people with decreased liver function and infants.

A few limitations of this assessment should be noted:

- It is crucial to recognize that commercial PCBs tested in laboratory animals were not subject to prior selective retention of persistent congeners through the food chain. Bioaccumulated PCBs appear to be more toxic than commercial PCBs and appear to be more persistent in the body. For exposure through the food chain, risks can be higher than those estimated in this assessment.
- PCBs persist in the body, providing a continuing source of internal exposure after external exposure stops. There may be greater-than-proportional effects

from less-than-lifetime exposure, especially for persistent mixtures and for early-life exposures.

5.5. EXAMPLES

Example 1. Consider a release of PCBs onto the ground near a river or lake. Potential pathways of human exposure include vapor inhalation, drinking water, fish ingestion, and skin contact with ambient water and contaminated soil. The population of interest includes anglers who consume an average of two 105-g portions of local fish each week. They spend most of their time in the area, breathing 20 m^3 air and drinking 2 L water, on average, each day. Skin contact with ambient water and soil is negligible for this population. A 30-year exposure duration is to be considered, with a representative lifespan of 70 years and body weight of 70 kg. Environmental samples indicate long-term average concentrations of 0.01 μg/m^3 in ambient air, 5 μg/L in drinking water, and 110 μg/kg in the edible portion of local fish. Dust in ambient air and sediment in drinking water are negligible.

Because of partitioning, transformation, and bioaccumulation, different fractions of the original mixture are encountered through these pathways, hence different potency values are appropriate. Vapor inhalation is associated with "low risk" in table 4–1 (evaporating congeners tend to have low chlorine content and be inclined to metabolism and elimination), so the low end of the range (upper-bound slope of 0.4 per mg/kg-d) is used for vapor inhalation. Similarly, ingestion of water-soluble congeners is associated with "low risk" (dissolved congeners tend to have low chlorine content and be inclined to metabolism and elimination), so the low end is also used for drinking water. (If ambient air or drinking water had contained significant amounts of contaminated dust or sediment, the high-end potency values would be appropriate, as adsorbed congeners tend to be of high chlorine content and persistence.) Food chain exposure appears is associated with "high risk" (aquatic organisms and fish selectively accumulate congeners of high chlorine content and persistence that are resistant to

metabolism and elimination), so the high end of the range (upper-bound slope of 2 per mg/kg-d) is used for fish ingestion.

The lifetime average daily dose (*LADD*) is calculated as the product of concentration *C*, intake rate *IR*, and exposure duration *ED* divided by body weight *BW* and lifetime *LT* (U.S. EPA, 1992a)(table 5-1):

Table 5–1. Sample lifetime average daily dose calculations (examples 1 and 2)

Pathway	*C*	*IR*	*ED*	*BW*	*LT*	*LADD*[a]
Vapor inhalation	0.01 μg/m^3	20 m^3/d	30 yr	70 kg	70 yr	1.2×10^{-6} mg/kg-d
Drinking water	5. μg/L	2 L/d	30 yr	70 kg	70 yr	6.1×10^{-5} mg/kg-d
Fish ingestion	110 μg/kg	30 g/d	30 yr	70 kg	70 yr	2.0×10^{-5} mg/kg-d

[a]$LADD = C \times IR \times ED / (BW \times LT)$

For each pathway, the lifetime average daily dose is multiplied by the appropriate slope to estimate risk (table 5-2):

Table 5–2. Sample risk calculations (example 1)

Pathway	*LADD*	Slope	Risk[a]
Vapor inhalation	1.2×10^{-6} mg/kg-d	0.4 per mg/kg-d	4.8×10^{-7}
Drinking water	6.1×10^{-5} mg/kg-d	0.4 per mg/kg-d	2.4×10^{-5}
Fish ingestion	2.0×10^{-5} mg/kg-d	2 per mg/kg-d	4.0×10^{-5}
Sum	**8.2×10^{-5} mg/kg-d**		**6.4×10^{-5}**

[a]Risk = *LADD* × Slope

It is important to remember that this specific site exposure adds to a background level of exposure from other sources.

Example 2. To show how additional, better information can improve the risk assessment, suppose an analysis of PCB congeners in drinking water is performed in the previous example. Suppose this analysis confirms that congeners with more than four chlorines comprise less than a half-percent of total PCBs. Then it would be

plausible to treat PCBs in drinking water as similar to Aroclor 1016. The slope derived from the Aroclor 1016 study could be used for this pathway(see table 5-3):

Table 5–3. Sample risk calculations (example 2)

Pathway	***LADD***	**Slope**	**Risk**[a]
Vapor inhalation	1.2×10^{-6} mg/kg-d	0.4 per mg/kg-d	4.8×10^{-7}
Drinking water	6.1×10^{-5} mg/kg-d	0.07 per mg/kg-d	4.3×10^{-6}
Fish ingestion	2.0×10^{-5} mg/kg-d	2 per mg/kg-d	4.0×10^{-5}
Sum	**8.2×10^{-5} mg/kg-d**		**4.5×10^{-5}**

[a]Risk = *LADD* × Slope

The additional information leads to a conclusion that fish ingestion is the principal pathway contributing to risk, and that drinking water and vapor inhalation are of lesser consequence. It would be advisable to examine variability in fish consumption rates and fish tissue concentrations to determine whether some individuals are at much higher risk.

Example 3. Next, suppose an analysis of PCB congeners in the edible portion of the fish is performed in the previous example, and it shows that concentrations of dioxin-like congeners are greatly enhanced (see table 5-4):

Table 5–4. Sample congener concentrations and dioxin toxic equivalents (TEQs) in edible portion of fish (example 3)

Congener	Conc.	TEF[a]	TEQ[b]
77: 3,4,3',4'–TeCB	2.1 μg/kg	0.0005	0.0011 μg/kg
105: 2,3,4,3',4'–PeCB	14.	0.0001	0.0014
114: 2,3,4,5,4'–PeCB	1.8	0.0005	0.0009
118: 2,4,5,3',4'–PeCB	54.	0.0001	0.0054
123: 3,4,5,2',4'–PeCB	1.4	0.0001	0.0001
126: 3,4,5,3',4'–PeCB	0.14	0.1	0.0140
156: 2,3,4,5,3',4'–HxCB	5.0	0.0005	0.0025
157: 2,3,4,3',4',5'–HxCB	1.1	0.0005	0.0006
167: 2,4,5,3',4',5'–HxCB	7.7	0.00001	0.0001
169: 3,4,5,3',4',5'–HxCB	0.0068	0.01	0.0001
170: 2,3,4,5,2',3',4'–HpCB	<4.2[c]	0.0001	0.0002
180: 2,3,4,5,2',4',5'–HpCB	<4.2[c]	0.00001	0.0000
189: 2,3,4,5,3',4',5'–HpCB	0.28	0.0001	0.0000
Others[d]	18.85	0.	0.0000
Sum	**111. μg/kg**		**0.0264 μg/kg**

[a]From Ahlborg et al. (1994)
[b]TEQ = Conc. × TEF
[c]Not detected, treated as half the detection limit of 4.2 μg/kg
[d]Nondioxin-like PCB congeners

The lifetime average daily dose would be recalculated separately for the dioxin-like and nondioxin-like portions of the mixture (table 5-5):

Table 5–5. Sample lifetime average daily dose calculations (example 3)

Pathway	*C*	*IR*	*ED*	*BW*	*LT*	*LADD*[a]
Vapor inhalation	0.01 μg/m^3	20 m^3/d	30 yr	70 kg	70 yr	1.2×10^{-6} mg/kg-d
Drinking water	5. μg/L	2 L/d	30 yr	70 kg	70 yr	6.1×10^{-5} mg/kg-d
Fish ingestion						
Dioxin TEQ	0.0264 μg/kg	30 g/d	30 yr	70 kg	70 yr	4.8×10^{-9} mg/kg-d
Nondioxin-like	19 μg/kg	30 g/d	30 yr	70 kg	70 yr	3.5×10^{-6} mg/kg-d

[a]$LADD = C \times IR \times ED / (BW \times LT)$

Using 150,000. per mg/kg-d as the slope for dioxin, the cancer risk would be calculated as follows (table 5-6):

Table 5–6. Sample risk calculations (example 3)

Pathway	*LADD*	Slope	Risk[a]
Vapor inhalation	1.2×10^{-6} mg/kg-d	0.4 per mg/kg-d	4.8×10^{-7}
Drinking water	6.1×10^{-5} mg/kg-d	0.07 per mg/kg-d	4.3×10^{-6}
Fish ingestion			
Dioxin TEQ	4.8×10^{-9} mg/kg-d	150,000 per mg/kg-d	7.2×10^{-4}
Nondioxin-like PCBs	3.5×10^{-6} mg/kg-d	2 per mg/kg-d	7.0×10^{-6}
Sum			**7.3×10^{-4}**

[a]Risk = *LADD* × Slope

This example, although perhaps extreme, shows how it is possible for a total-PCB approach to underestimate the toxicity of a mixture when concentrations of a few dioxin-like or highly toxic congeners are enhanced through environmental and metabolic processes. This shows the importance of obtaining congener analyses and of continuing to develop quantitative methods for incorporating congener information into risk assessments.

6. REFERENCES

Abramowicz, D.A. (1990) Aerobic and anaerobic biodegradation of PCBs: a review. Biotechnology 10(3):241–251.

Ahlborg, U.G.; Becking, G.C.; Birnbaum, L.S.; Brouwer, A.; Derks, H.J.G.M.; Feeley, M.; Golor, G.; Hanberg, A.; Larsen, J.C.; Liem, A.K.D.; Safe, S.H.; Schlatter, C.; Wærn, F.; Younes, M.; Yrjånheikki, E. (1994) Toxic equivalency factors for dioxin-like PCBs. Chemosphere, 28(6):1049–1067.

Alford-Stevens, A.L.; Budde, W.L.; Bellar, T.A. (1985) Interlaboratory study on determination of polychlorinated biphenyls in environmentally contaminated sediments. Anal. Chem. 57:2452–2457.

Alford-Stevens, A.L. (1986) Analyzing PCBs. Environ. Sci. Technol. 20(12):1194–1199.

Anderson, L.M.; van Havere, K.; Budinger, J.M. (1983) Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by *N*-nitrosodimethylamine. J. Natl. Cancer Inst. 71(1):157–163.

Anderson, L.M.; Ward, J.M.; Fox, S.D. et al. (1986) Effects of a single dose of polychlorinated biphenyls to infant mice on N-nitrosodimethylamine-initiated lung and liver tumors. Int. J. Cancer 18:109–116.

Anderson, L.M.; Fox, S.D.; Dixon, D.; Beebe, L.E.; Issaq, H.J. (1991a) Long-term persistence of polychlorinated biphenyl congeners in blood and liver and elevation of liver aminopyrine demethylase activity after a single high dose of Aroclor 1254 to mice. Environ. Toxicol. Chem. 10:681–690.

Anderson, L.M.; Beebe, L.E.; Fox, S.D.; Issaq, H.J.; Kovatch, R.M. (1991b) Promotion of mouse lung tumors by bioaccumulated polychlorinated aromatic hydrocarbons. Exp. Lung Res. 17:455–471.

Anderson, L.M.; Logsdon, D.; Ruskie, S.; Fox, S.D.; Issaq, H.J.; Kovatch, R.M.; Riggs, C.M. (1994) Promotion by polychlorinated biphenyls of lung and liver tumors in mice. Carcinogenesis 15(10):2245–2248.

ATSDR (Agency for Toxic Substances and Disease Registry) (1993) Toxicological profile for polychlorinated biphenyls. Atlanta: ATSDR, TP–92/16, update.

ATSDR (Agency for Toxic Substances and Disease Registry) (1995) Toxicological profile for polychlorinated biphenyls. Atlanta: ATSDR, draft for public comment.

Aulerich, R.J.; Ringer, R.K.; Safronoff, J. (1986) Assessment of primary vs. secondary toxicity of Aroclor 1254 to mink. Arch. Environ. Contam. Toxicol. 15:393–399.

Bandiera, S.; Safe, S.; Okey, A.B. (1982) Binding of polychlorinated biphenyls classified as either phenobarbitone-, 3-methylcholanthrene- or mixed-type inducers to cytosolic *Ah* receptor. Chem.-Biol. Interactions 39:259–277.

Barter, R.A.; Klaassen, C.D. (1992) UDP-glucuronosyltransferase inducers reduce thyroid hormone levels in rats by an extrathyroidal mechanism. Toxicol. Appl. Pharmacol. 113:36–42.

Beebe, L.; Fox, S.D.; Riggs, C.W.; Park, S.S.; Gelboin, H.V.; Issaq, H.J.; Anderson, L.M. (1992) Persistent effects of a single dose of Aroclor 1254 on cytochromes P450IA1 and IIB1 in mouse lung. Toxicol. Appl. Pharmacol. 114:16–24.

Beebe, L.E.; Kim, Y.E.; Amin, S.; Riggs, C.W.; Kovatch, R.M.; Anderson, L.M. (1993) Comparison of transplacental and neonatal initiation of mouse lung and liver tumors by *N*-nitrosodimethylamine (NDMA) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and promotability by a polychlorinated biphenyls mixture (Aroclor 1254). Carcinogenesis 14(8):1545–1548.

Bertazzi, P.A.; Riboldi, L.; Pesatori, A.; Radice, L.; Zocchetti, C. (1987) Cancer mortality of capacitor manufacturing workers. Am. J. Ind. Med. 11:165–176.

Birnbaum, L.S.; DeVito, M.J. (in press) Use of toxic equivalency factors for risk assessment for dioxins and related compounds. Toxicology.

Brown, D.P. (1987) Mortality of workers exposed to polychlorinated biphenyls—an update. Arch. Environ. Health 42(6):333–339.

Brown, J.F., Jr.; Wagner, R.E. (1990) PCB movement, dechlorination, and detoxication in the Acushnet Estuary. Environ. Toxicol. Chem. 9:1215–1233.

Brown, J.F., Jr. (1994) Determination of PCB metabolic, excretion, and accumulation rates for use as indicators of biological response and relative risk. Environ. Sci. Technol. 28(13):2295–2305.

Brunner, M.J.; Sullivan, T.M.; Singer, A.W.; Ryan, M.J.; Toft, II, J.D.; Menton, R.S.; Graves, S.W.; Peters, A.C. (1996) An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats. Columbus, OH: Battelle Study No. SC920192., Chronic toxicity and oncogenicity report.

Buchmann, A.; Ziegler, S.; Wolf, A.; Robertson, L.W.; Durham, S.K.; Schwarz, M. (1991) Effects of polychlorinated biphenyls in rat liver: correlation between primary subcellular effects and promoting activity. Toxicol. Appl. Pharmacol. 111:454–468.

Byrne, J.J.; Carbone, J.P.; Hanson, E.A. (1987) Hypothyroidism and abnormalities in the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyl and polybrominated biphenyl. Endocrinology 121:520–527.

Calabrese, E.J.; Sorenson, A.J. (1977) The health effects of PCBs with particular emphasis on human high risk groups. Rev. Environ. Health 2:285–304.

Callahan, M.A.; Slimak, M.W.; Gabel, N.W.; May, I.P.; Fowler, C.F.; Freed, J.R.; Jennings, P.; Durfee, R.L.; Whitmore, F.C.; Maestri, B.; Mabey, W.R.; Holt, B.R.; Gould, C. (1979) Water-related environmental fate of 129 priority pollutants, vol. I, ch. 36. Washington: U.S. EPA, Report No. EPA–440/4–79–029a.

Cogliano, V.J. (1986) The U.S. EPA's methodology for adjusting the reportable quantities of potential carcinogens. Proceedings of the 7th National Conference on Management of Uncontrolled Hazardous Wastes (Superfund '86). Washington: Hazardous Materials Control Research Institute, pp. 182–185.

Crump, K.S.; Hoel, D.G.; Langley, C.H.; Peto, R. (1976) Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res. 36:2973–2979.

Delaware Department of Natural Resources and Environmental Control (1994) Summary and assessment of polychlorinated biphenyls and selected pesticides in striped bass from the Delaware Estuary. Delaware, Project No. AFC–5; Grant No. NA26FA0148–01.

Dewailly, É.; Weber, J.-P.; Gingras, S.; Laliberté, C. (1991) Coplanar PCBs in human milk in the province of Québec, Canada: are they more toxic than dioxin for breast fed infants? Bull. Environ. Contam. Toxicol. 47:491–498.

Dewailly, É.; Ryan, J.J.; Laliberté, C.; Bruneau, S.; Weber, J.-P.; Gingras, S.; Carrier, G. (1994) Exposure of remote maritime populations to coplanar PCBs. Environ. Health Perspect. 102(Suppl. 1):205–209.

Erickson, M.D. (1986) Analytical chemistry of PCBs. Boston: Butterworth Publishers.

General Electric Company (1995) Letter from Stephen B. Hamilton, Jr., to U.S. Environmental Protection Agency Section 8(e) Coordinator, October 10, 1995.

Gierthy, J.F.; Arcaro, K.F.; Floyd, M. (1995) Assessment and implications of PCB estrogenicity. Organo-Halogen Compounds 25:419-423

Gustavsson, P.; Hogstedt, C.; Rappe, C. (1986) Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am. J. Ind. Med. 10:341–344.

Harper, N.; Connor, K.; Steinberg, M.; Safe, S. (1995) Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: nonadditive (antagonistic) interactions. Fund. Appl. Toxicol. 27:131–139.

Harris, M.; Zacharewski, T.; Safe, S. (1993) Comparative potencies of Aroclors 1232, 1242, 1248, 1254, and 1260 in male Wistar rats—assessment of the toxic equivalency factor (TEF) approach for polychlorinated biphenyls (PCBs). Fund. Appl. Toxicol. 20:456–463.

Hemming, H.; Flodström, S.; Wärngard, L.; Bergman, Å.; Kronevi, T.; Nordgren, I.; Ahlborg, U. (1993) Relative tumour promoting activity of three polychlorinated biphenyls in rat liver. Eur. J. Pharmacol. 248:163–174.

Hill, R.N.; Erdreich, L.S.; Paynter, O.E.; Roberts, P.A.; Rosenthal, S.L.; Wilkinson, C.F. (1987) Thyroid follicular cell carcinogenesis. Fund. Appl. Toxicol. 12:627–697.

Hong, C.-S.; Bush, B.; Xiao, J.; Qiao, H. (1993) Toxic potential of non-ortho and mono-ortho coplanar polychlorinated biphenyls in Aroclors, seals, and humans. Arch. Environ. Contam. Toxicol. 25:118–123.

Hornshaw, T.C.; Aulerich, R.J.; Johnson, H.E. (1983) Feeding Great Lakes fish to mink: effects on mink and accumulation and elimination of PCBs by mink. J. Toxicol. Environ. Health 11:933–946.

Hovinga, M.E.; Sowers, M.; Humphrey, H.E.B. (1992) Historical changes in serum PCB and DDT levels in an environmentally-exposed cohort. Arch. Environ. Contam. Toxicol. 22:362–366.

Howe, R.B.; Crump, K.S.; Van Landingham, C. (1986) Global 86: a computer program to extrapolate quantal animal toxicity data to low doses. Prepared for U.S. EPA under contract 68–01–6826.

Hutzinger, O.; Safe, S.; Zitko, V. (1974) The chemistry of PCB's. Boca Raton, FL: CRC Press.

IARC (International Agency for Research on Cancer) (1987) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42. Lyon, France.

Institute for Evaluating Health Risks (1991) Reassessment of liver findings in five PCB studies in rats. Washington, DC, dated July 1. Report submitted to U.S. EPA.

Ito, N.; Nagasaki, H.; Arai, M.; Makiura, S.; Sugihara, S.; Hirao, K. (1973) Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. J. Natl. Cancer Inst. 51(5):1637–1646.

Ito, N.; Nagasaki, H.; Makiura, S.; Arai, M. (1974) Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann 65:545–549.

Kannan, N.; Tanabe, S.; Tatsukawa, R. (1988) Toxic potential of non-*ortho* and mono-*ortho* coplanar PCBs in commercial PCB preparations: "2,3,7,8–T_4CDD toxicity equivalence factors approach." Bull. Environ. Contam. Toxicol. 41:267–276.

Kasza, L.; Weinberger, M.A.; Hinton, D.E.; Trump, B.J.; Patel, C.; Friedman, L.; Garthoff, L.H. (1978) Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat liver: Light and electron microscopic alterations after subacute dietary exposures. J. Envir. Pathol. Toxicol. 1:241-257.

Keenan, R.E.; Stickney, J.A. (1996) Letter dated June 24 to J. Cogliano, U.S. EPA, Washington.

Kimbrough, R.D.; Linder, R.E.; Gaines, T.B. (1972) Morphological changes in livers of rats fed polychlorinated biphenyls: light microscopy and ultrastructure. Arch. Environ. Health 25:354–364.

Kimbrough, R.D.; Linder, R.E. (1974) Induction of adenofibrosis and hepatomas of the liver in BALB/cJ mice by polychlorinated biphenyls (Aroclor 1254). J. Natl. Cancer Inst. 53(2):547–552.

Kimbrough, R.D.; Squire, R.A.; Linder, R.E.; Strandberg, J.D.; Montali, R.J.; Burse, V.W. (1975) Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyls Aroclor 1260. J. Natl. Cancer Inst. 55:1453–1459.

Kimura, N.T.; Baba, T. (1973) Neoplastic changes in the rat liver induced by polychlorinated biphenyl. Gann 64:105–108.

Koller, L.D. (1996) Letter dated July 3 to E.V. Ohanian, U.S. EPA, Washington.

Laib, R.J.; Rose, N.; Brunn, H. (1991) Hepatocarcinogenicity of PCB congeners. Toxicol. Environ. Chem. 34:19–22.

Lake, J.L.; Pruell, R.J.; Osterman, F.A. (1992) An examination of dechlorination processes and pathways in New Bedford Harbor sediments. Marine Environ. Res. 33:31-47.

Lake, J.L.; McKinney, R.; Lake, C.A.; Osterman, F.A.; Heltshe, J. (1995) Comparisons of patterns of polychlorinated biphenyl congeners in water, sediment, and indigenous organisms from New Bedford Harbor, Massachusetts. Arch. Contam. Toxicol. 29:207–220.

Luebeck, E.G.; Moolgavkar, S.H.; Buchmann, A.; Schwarz, M. (1991) Effects of polychlorinated biphenyls in rat liver: quantitative analysis of enzyme-altered foci. Toxicol. Appl. Pharmacol. 111:469–484.

Lutz, W.K. (1990) Dose-response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis 11(8):1243–1247.

Matthews, H.B.; Anderson, M.W. (1975) Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. Drug Metab. Dispos. 3(5):371–380.

McClain, R.M. (1989) The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: implications for thyroid gland neoplasia. Toxicol. Pathol. 17:294–306.

McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76(2):283–289.

McFarland, V.A.; Clarke, J.U. (1989) Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ. Health Perspect. 81:225–239.

McLean, M.R.; Bauer, U.; Amaro, A.R.; Robertson, L.W. (1996a) Identification of catechol and hydroquinone metabolites of 4-monochlorobiphenyl. Chem. Res. Toxicol. 9:158–164.

McLean, M.R.; Robertson, L.W.; Gupta, R.C. (1996b) Detection of PCB adducts by the ^{32}P-postlabeling technique. Chem. Res. Toxicol. 9:165–171.

Mills, R.A.; Millis, C.D.; Dannan, G.A.; Guengerich, F.P.; Aust, S.D. (1985) Studies on the structure-activity relationships for the metabolism of polybrominated biphenyls by rat liver microsomes. Toxicol. Appl. Pharmacol. 78:96–104.

Moore, J.A.; Hardisty, J.F.; Banas, D.A.; Smith, M.A. (1994) A comparison of liver tumor diagnoses from seven PCB studies in rats. Regul. Toxicol. Pharmacol. 20:362–370.

Morgan, R.W.; Ward, J.M.; Hartman, P.E. (1981) Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res. 41:5052–5059.

National Cancer Institute (1978) Bioassay of Aroclor 1254 for possible carcinogenicity. Carcinogenesis Tech. Rep. Ser. No. 38.

National Institute for Occupational Safety and Health (1977) Criteria for a recommended standard. Occupational exposure to polychlorinated biphenyls (PCBs). Rockville, Md: U.S. Department of Health, Education and Welfare, Public Health Sevice, Centers for Disease Control. NIOSH Publ 77-225.

National Research Council (1993) Issues in risk assessment. Washington: National Academy Press.

National Toxicology Program (1982) Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS no. 1746–01–6) in Osborne-Mendel rats and B6C3F$_1$ mice (gavage study). Research Triangle Park NC: NTP Tech. Rep. Ser. No. 209.

National Toxicology Program (1983) Carcinogenesis studies of polybrominated biphenyl mixture (Firemaster FF–1) (CAS no. 67774–32–7) in F344/N rats and B6C3F$_1$ mice (gavage studies). Research Triangle Park NC: NTP Tech. Rep. Ser. No. 244.

National Toxicology Program (1993) Toxicology and carcinogenesis studies of polybrominated biphenyls (Firemaster FF–1) (CAS no. 67774–32–7) in F344/N rats and B6C3F$_1$ mice (feed studies). Research Triangle Park NC: NTP Tech. Rep. Ser. No. 398.

Norback, D.H.; Weltman, R.H. (1985) Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ. Health Perspect. 60:97–105.

Oakley, G.G.; Robertson, L.W.; Gupta, R.C. (1996) Analysis of polychlorinated biphenyl-DNA adducts by ^{32}P-postlabeling. Carcinogenesis 17(1):109–114.

Oliver, B.G.; Niimi, A.J. (1988) Trophodynamic analysis of polychlorinated biphenyl congeners and other chlorinated hydrocarbons in the Lake Ontario ecosystem. Environ. Sci. Technol. 22:388–397.

Patterson, D.G.; Todd, G.D.; Turner, W.E.; Maggio, V.; Alexander, L.R.; Needham, L.L. (1994) Levels of non-ortho-substituted (coplanar), mono-, and di-ortho-substituted polychlorinated biphenyls, dibenzo-p-dioxins, and dibenzofurans in human serum and adipose tissue. Environ. Health Perspect. 102(Suppl. 1):195–204.

Phillips, D.L.; Smith, A.B.; Burse, V.W.; Steele, G.K.; Needham, L.L.; Hannon, W.H. (1989) Half-life of polychlorinated biphenyls in occupationally exposed workers. Arch. Environ. Health 44(6):351–354.

Rao, C.V.; Banerji, A.S. (1988) Induction of liver tumors in male Wistar rats by feeding polychlorinated biphenyls (Aroclor 1260). Cancer Lett. 39:59–67.

Rickenbacher, U.; McKinney, J.D.; Oatley, S.J.; Blake, C.C.F. (1986) Structurally specific binding of halogenated biphenyls to thyroxine transport protein. J. Med. Chem. 29:641–648.

Rose, N.; Laib, R.J.; Brunn, H.; Bolt, M.M. (1985) Biotransformation and toxicity of polychlorinated biphenyls (PCBs): investigation of initiating and promoting activities of 2,2',4,5'-tetra- and 2,2',4,4',5,5'-hexachlorobiphenyl. Naunyn-Schmiedeberg's Arch. Pharmacol. Suppl. 330 (Abstr. 87), R21.

Safe, S. (1990) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic consideration which support the development of toxic equivalency factors (TEFs). Crit. Rev. Toxicol. 21(1):51–88.

Safe, S. (1994) Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit. Rev. Toxicol. 24(2):87–149.

Sargent, L.; Dragan, Y.P.; Erickson, C.; Laufer, C.J.; Pitot, H.C. (1991) Study of the separate and combined effects of the non-planar 2,5,2',5'- and 3,4,3',4'-tetrachlorobiphenyl in liver and lymphocytes *in vivo.* Carcinogenesis 12(5):793–800.

Schaeffer, E.; Greim, H.; Goessner, W. (1984) Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol. Appl. Pharmacol. 75:278–288.

Schecter, A.; Stanley, J.; Boggess, K.; Masuda, Y.; Mes, J.; Wolff, M.; Fürst, P.; Fürst, C.; Wilson-Yang, K.; Chisholm, B. (1994) Polychlorinated biphenyl levels in the tissues of exposed and nonexposed humans. Environ. Health Perspect. 102(Suppl. 1):149–158.

Schulz, D.E.; Petrick, G.; Duinker, J.C. (1989) Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography—electron capture detection. Environ. Sci. Technol. 23(7):852–859.

Schwartz, T.R.; Stalling, D.L.; Rice, C.L. (1987) Are polychlorinated biphenyl residues adequately described by Aroclor mixture equivalents? Isomer-specific principal components analysis of such residues in fish and turtles. Environ. Sci. Technol. 21:72–76.

Shalat, S.L.; True, L.D.; Fleming, L.E.; Pace, P.E. (1989) Kidney cancer in utility workers exposed to polychlorinated biphenyls (PCBs). Br. J. Ind. Med. 46(11):823–824.

Silberhorn, E.M.; Glauert, H.P.; Robertson, L.W. (1990) Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit. Rev. Toxicol. 20(6):439–496.

Sinks, T.; Steele, G.; Smith, A.B.; Watkins, K.; Shults, R.A. (1992) Mortality among workers exposed to polychlorinated biphenyls. Am. J. Epidemiol. 136(4):389–398.

Sipes and Schnellman (1987) Biotransformation of PCBs: metabolic pathways and mechanisms. In: Safe and Hutzinger, eds., Polychlorinated biphenyls (PCBs): mammalian and environmental toxicology. Heidelberg: Springer Verlag, pp. 97–110.

Smith, A.H. (1987) Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions. Risk Analysis 7(3):347–353.

Steele, G.; Stehr-Green, P.; Welty, E. (1986) Estimates of the biologic half-life of polychlorinated biphenyls in human serum. New Engl. J. Med. 314(14):926–927.

Swierenga, S.H.H.; Yamasaki, H.; Piccoli, C.; Robertson, L.; Bourgon, L.; Marceau, N.,; Fitzgerald, D.J. (1990) Effects on intercellular communication in human keratinocytes and liver-derived cells of polychlorinated biphenyl congeners with differing *in vivo* promotion activities. Carcinogenesis 11(6):921–926.

Taylor, P. (1988) The health effects of polychlorinated biphenyls. Boston: Harvard School of Public Health, unpublished thesis.

U.S. Environmental Protection Agency (1980) Water quality criteria documents; availability. Federal Register 45(231):79318–79379.

U.S. Environmental Protection Agency (1986a) Guidelines for carcinogen risk assessment. Federal Register 51(185):33992–34003.

U.S. Environmental Protection Agency (1986b) Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014–34025.

U.S. Environmental Protection Agency (1988a) Drinking water criteria document for polychlorinated biphenyls (PCBs). Cincinnati: U.S. EPA, ECAO–CIN–414.

U.S. Environmental Protection Agency (1988b) Methodology for evaluating potential carcinogenicity in support of reportable quantity adjustments pursuant to CERCLA section 102. Washington, DC. Report No. EPA/600/8–89/053.

U.S. Environmental Protection Agency (1991) Workshop report on toxicity equivalency factors for polychlorinated biphenyl congeners. Risk Assessment Forum, Washington, DC. Report No. EPA/625/3–91/020.

U.S. Environmental Protection Agency (1992a) Guidelines for exposure assessment. Federal Register 57(104):22888–22938.

U.S. Environmental Protection Agency (1992b) Draft report: a cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg$^{3/4}$/day; notice. Federal Register 57(109):24152–24173.

U.S. Environmental Protection Agency (1994a) Technical background document to support rulemaking pursuant to the Clean Air Act—section 112(g): ranking of pollutants with respect to hazard to human health. Research Triangle Park, NC. Report No. EPA–450/3–92–010.

U.S. Environmental Protection Agency (1994b) Health assessment document for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Prepared by the Office of Health and Environmental Assessment, Office of Research and Development, Washington, DC. External Review Draft, 3 vol. Report No. EPA/600/BP–92/001c, Available from the National Technical Information Service, Springfield, VA; PB 94-205457.

U.S. Environmental Protection Agency (1996a) Proposed guidelines for carcinogen risk assessment; notice. Federal Register 61(79):17960–18011.

U.S. Environmental Protection Agency (1996b) Report on peer review workshop on *PCBs: cancer-dose response assessment and application to environmental mixtures*. Washington, DC, National Center for Environmental Assessment.

Vater, S.T.; Velazquez, S.F.; Cogliano, V.J. (1995) A case study of cancer data set combinations for PCBs. Regul. Toxicol. Pharmacol. 22:2–10.

Ward, J.M. (1985) Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ. Health Perspect. 60:89–95.

Wester, R.C.; Bucks, D.A.W.; Maibach, H.I.; Anderson, J. (1983) Polychlorinated biphenyls (PCBs): dermal absorption, systemic elimination, and dermal wash efficiency. J. Toxicol. Environ. Health 12:511–519.

Wester, R.C.; Mobayen, M.; Maibach, H.I. (1987) In vivo and *in vitro* absorption and binding to powdered stratum corneum as methods to evaluate skin absorption of environmental chemical contaminants from ground and surface water. J. Toxicol. Environ. Health 21:367–374.

Wester, R.C.; Maibach, H.I.; Bucks, D.A.W.; McMaster, J.; Mobayen, M. (1990) Percutaneous absorption and skin decontamination of PCBs: *in vitro* studies with human skin and *in vivo* studies in the rhesus monkey. J. Toxicol. Environ. Health 31:235–246.

Wester, R.C.; Maibach, H.I.; Sedik, L.; Melendres, J.; Wade, M. (1993) Percutaneous absorption of PCBs from soil: *in vivo* rhesus monkey, *in vitro* human skin, and binding to powdered human stratum corneum. J. Toxicol. Environ. Health 39:375–382.

WHO (World Health Organization) (1993) Polychlorinated biphenyls and terphenyls. Geneva: WHO, Environmental Health Criteria 140, second ed.

Wolff, M.S. (1985) Occupational exposure to polychlorinated biphenyls (PCBs). Environ. Health Perspect. 60:133–138.

Table A–1. Empirical modeling of liver tumors in female Sprague-Dawley rats fed Aroclor 1260

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Female Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.403	0.413	0.399	0.391	kg
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.35	0.72	1.52	mg/kg-d
Tumor incidence	1/85	10/49	11/45	24/50	
Model	Risk(d) = 1 – exp(–0.013–0.44d) in experimental range				
Potency, slope estimates	ED10=0.24, LED10=0.19, ED01=0.023, LED01=0.018, q_1*=0.56				

Table A–2. Empirical modeling of liver tumors in female Sprague-Dawley rats fed Aroclor 1254

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Female Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.403	0.375	0.355	0.321	kg
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.36	0.76	1.59	mg/kg-d
Tumor incidence	1/85	19/45	28/49	28/49	
Model	Risk(d) = 1 – exp(–0.012–1.2d) in experimental range				
Potency, slope estimates	ED10=0.086, LED10=0.067, ED01=0.0082, LED01=0.0064, q_1*=1.6				

Table A–3. Empirical modeling of liver tumors in female Sprague-Dawley rats fed Aroclor 1242

Tumors	Liver hepatocellular adenomas and carcinomas			
Animal	Female Sprague-Dawley rats			
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)			
Exposure duration	24 mo			
Study duration	24 mo (assumed animal lifespan)			
Animal weight	0.403	0.398	0.372	kg
Administered dose	0	50	100	ppm diet
Equivalent human dose	0	0.75	1.53	mg/kg-d
Tumor incidence	1/85	11/49	15/45	
Model	Risk(d) = 1 – exp(–0.012–0.28d) in experimental range			
Potency, slope estimates	ED10=0.38, LED10=0.27, ED01=0.036, LED01=0.026, q_1*=0.39			

Table A–4. Empirical modeling of liver tumors in female Sprague-Dawley rats fed Aroclor 1016

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Female Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.403	0.414	0.421	0.394	kg
Administered dose	0	50	100	200	ppm diet
Equivalent human dose	0	0.72	1.43	2.99	mg/kg-d
Tumor incidence	1/85	1/48	7/45	6/50	
Model	Risk(d) = 1 – exp(–0.012–0.044d) in experimental range				
Potency, slope estimates	ED10=2.4, LED10=1.4, ED01=0.23, LED01=0.14 q_1*=0.073				

Table A–5. Empirical modeling of liver tumors in male Sprague-Dawley rats fed Aroclor 1260

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Male Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.697	0.690	0.703	0.695	kg
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.31	0.62	1.25	mg/kg-d
Tumor incidence	7/98	3/50	6/49	10/49	
Model	Risk(d) = 1 – exp(–0.071–0.11d^2) in experimental range				
Potency, slope estimates	ED10=1.0, LED10=0.55, ED01=0.31, LED01=0.053 q_1*=0.19				

Table A–6. Empirical modeling of liver tumors in male Sprague-Dawley rats fed Aroclor 1254

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Male Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.697	0.694	0.659	0.601	kg
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.31	0.62	1.29	mg/kg-d
Tumor incidence	7/98	4/48	4/49	6/47	
Model	Risk(d) = 1 – exp(–0.075–0.0052d–0.032d^2) in experimental range				
Potency, slope estimates	ED10=1.7, LED10=0.87, ED01=0.49, LED01=0.083 q_1*=0.12				

Table A–7. Empirical modeling of liver tumors in male Sprague-Dawley rats fed Aroclor 1242

Tumors	Liver hepatocellular adenomas and carcinomas			
Animal	Male Sprague-Dawley rats			
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)			
Exposure duration	24 mo			
Study duration	24 mo (assumed animal lifespan)			
Animal weight	0.697	0.711	0.681	kg
Administered dose	0	50	100	ppm diet
Equivalent human dose	0	0.60	1.25	mg/kg-d
Tumor incidence	7/98	1/50	5/46	
Model	Risk(d) = 1 – exp(–0.058–0.012d^2) in experimental range			
Potency, slope estimates	ED10=2.9, LED10=1.2, ED01=0.91, LED01=0.16 q_1*=0.061			

Table A–8. Empirical modeling of liver tumors in male Sprague-Dawley rats fed Aroclor 1016

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Male Sprague-Dawley rats				
Reference	Brunner et al. (1996), doses from Keenan and Stickney (1996)				
Exposure duration	24 mo				
Study duration	24 mo (assumed animal lifespan)				
Animal weight	0.697	0.723	0.699	0.712	kg
Administered dose	0	50	100	200	ppm diet
Equivalent human dose	0	0.61	1.23	2.44	mg/kg-d
Tumor incidence	7/98	2/48	2/50	4/49	
Model	Risk(d) = 1 – exp(–0.058–0.0031d^2) in experimental range				
Potency, slope estimates	ED10=5.9, LED10=2.5, ED01=1.8, LED01=0.32 q_1*=0.032				

Table A–9. Empirical modeling of liver tumors in female Sherman rats fed Aroclor 1260

Tumors	Liver hepatocellular adenomas and carcinomas		
Animal	Female Sherman rats		
Reference	Kimbrough et al. (1975), reevaluated by Moore et al. (1994)		
Exposure duration	21 mo		
Study duration	23 mo (assumed animal lifespan)		
Animal weight	0.35 kg (assumed)		
Administered dose	0	100	ppm diet
Equivalent human dose	0	1.3	mg/kg-d
Tumor incidence	1/187	138/189	
Model	Risk(d) = 1 – exp(–0.0054–1.0d) in experimental range		
Potency, slope estimates	ED10=0.10, LED10=0.091, ED01=0.010, LED01=0.0086 q_1*=1.2		

Table A–10. Empirical modeling of liver tumors in male Fischer 344 rats fed Aroclor 1254

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Male Fischer 344 rats				
Reference	NCI (1978), reevaluated by Moore et al. (1994)				
Exposure duration	104–105 wk				
Study duration	104–105 wk (assumed animal lifespan)				
Animal weight	0.3 kg				
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.32	0.64	1.28	mg/kg-d
Tumor incidence	0/24	1/24	1/24	3/23	
Model	Risk(d) = 1 – exp(–0.091d–0.0099d^2) in experimental range				
Potency, slope estimates	ED10=1.0, LED10=0.55, ED01=0.11, LED01=0.052, q_1*=0.19				

Table A–11. Empirical modeling of liver tumors in female Fischer 344 rats fed Aroclor 1254

Tumors	Liver hepatocellular adenomas and carcinomas				
Animal	Female Fischer 344 rats				
Reference	NCI (1978), reevaluated by Moore et al. (1994)				
Exposure duration	104–105 wk				
Study duration	104–105 wk (assumed animal lifespan)				
Animal weight	0.2 kg				
Administered dose	0	25	50	100	ppm diet
Equivalent human dose	0	0.29	0.58	1.16	mg/kg-d
Tumor incidence	0/23	1/24	2/24	1/24	
Model	Risk(d) = 1 – exp(–0.084d) in experimental range				
Potency, slope estimates	ED10=1.2, LED10=0.61, ED01=0.12, LED01=0.058, q_1*=0.17				

Table A–12. Empirical modeling of liver tumors in male Wistar rats fed Clophen A 30

Tumors	Liver hepatocellular adenomas and carcinomas		
Animal	Male Wistar rats		
Reference	Schaeffer et al. (1984), reevaluated by Moore et al. (1994)		
Exposure duration	24 mo		
Study duration	24 mo (assumed animal lifespan)		
Animal weight	0.35 kg (assumed)		
Administered dose	0	100	ppm diet
Equivalent human dose	0	1.3	mg/kg-d
Tumor incidence	8/120	16/128	
Model	Risk(d) = 1 – exp(–0.069–0.050d) in experimental range		
Potency, slope estimates	ED10=2.1, LED10=1.0, ED01=0.20, LED01=0.096, q_1*=0.10		

Table A–13. Empirical modeling of liver tumors in male Wistar rats fed Clophen A 60

Tumors	Liver hepatocellular adenomas and carcinomas		
Animal	Male Wistar rats		
Reference	Schaeffer et al. (1984), reevaluated by Moore et al. (1994)		
Exposure duration	24 mo		
Study duration	24 mo (assumed animal lifespan)		
Animal weight	0.35 kg (assumed)		
Administered dose	0	100	ppm diet
Equivalent human dose	0	1.3	mg/kg-d
Tumor incidence	8/120	114/125	
Model	Risk(d) = 1 – exp(–0.069–1.8d) in experimental range		
Potency, slope estimates	ED10=0.058, LED10=0.047, ED01=0.0055, LED01=0.0045, q_1*=2.2		

Table A–14. Empirical modeling of liver tumors in male Sprague-Dawley rats fed Aroclor 1260

Tumors	Liver hepatocellular adenomas and carcinomas		
Animal	Male Sprague-Dawley rats		
Reference	Norback and Weltman (1985), reevaluated by Moore et al. (1994)		
Exposure duration	24 mo		
Study duration	29 mo (assumed animal lifespan)		
Animal weight	0.35 kg (assumed)		
Administered dose	0	100	ppm diet
Equivalent human dose	0	1.3	mg/kg-d
Tumor incidence	0/31	5/40	
Model	Risk(d) = 1 – exp(–0.10d) in experimental range		
Potency, slope estimates	ED10=1.0, LED10=0.53, ED01=0.098, LED01=0.051, q_1*=0.20		

Table A–15. Empirical modeling of liver tumors in female Sprague-Dawley rats fed Aroclor 1260

Tumors	Liver hepatocellular adenomas and carcinomas		
Animal	Female Sprague-Dawley rats		
Reference	Norback and Weltman (1985), reevaluated by Moore et al. (1994)		
Exposure duration	24 mo		
Study duration	29 mo (assumed animal lifespan)		
Animal weight	0.35 kg (assumed)		
Administered dose	0	100	ppm diet
Equivalent human dose	0	1.3	mg/kg-d
Tumor incidence	1/45	41/46	
Model	Risk(d) = 1 – exp(–0.022–1.7d) in experimental range		
Potency, slope estimates	ED10=0.062, LED10=0.046, ED01=0.0059, LED01=0.0044, q_1*=2.3		