POLYCHLORINATED BIPHENYLS (PCBs): ENVIRONMENTAL IMPACT, BIOCHEMICAL AND TOXIC RESPONSES AND IMPLICATIONS FOR RISK ASSESSMENT

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ABSTRACT

Commercial polychlorinated biphenyls (PCBs) and environmental extracts contain complex mixtures of isomers and congeners which can be unequivocally identified and quantitated. PCBs elicit a spectrum of biochemical and toxic responses in humans and laboratory animals and many of these effects resemble those caused by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related halogenated aromatic hydrocarbons which act through the aryl hydrocarbon (Ah) receptor signal transduction pathway. Structure-activity relationships developed for PCB congeners and metabolites have demonstrated that several structural classes of compounds exhibit diverse biochemical and toxic responses. Structure-toxicity studies suggest that the coplanar PCBs, namely 3,3',4,4'-tetrachlorobiphenyl (tetraCB), 3,3',4,4'-pentaCB and 3,3',4,4',5,5'-hexaCB and their monoortho analogs are Ah receptor agonists and contribute significantly to the toxicity of the PCB mixtures. Previous studies with TCDD and structurally related compounds have utilized a toxic equivalency factor (TEF) approach for the hazard and risk assessment of polychlorinated dibenzo-*p*-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) congeners in which the TCDD or toxic equivalents (TEQ) of a mixture is related to the

$$TEQ = \sum ([PCDF_i \times TEF_i]_n) + \sum ([PCDD_i \times TEF_i]_n)$$

TEFs and concentrations of the individual (i) congeners (note: n = the number of congeners). Based on the results of quantitative structure-activity data, the following TEFs are recommended for the coplanar and monoortho coplanar PCBs: 3,3',4,4',5-pentaCB, 0.1; 3,3',4,4',5,5'-hexaCB, 0.05; 3,3',4,4'-tetraCB, 0.02; 2,3,3',4,4'-pentaCB, 0.001; 2,3',4,4',5-pentaCB, 0.0001; 2,3,3',4,4',5-hexaCB, 0.0003; 2,3,3',4,4',5'-hexaCB, 0.0003; 2',3,4,4',5-

pentaCB, 0.00005; and 2,3,4,4',5-pentaCB, 0.0002. Application of the TEF approach for the risk assessment of PCBs must be used with considerable caution. Analysis of the results of laboratory animal and wildlife studies suggests that the predictive value of TEQs for PCBs may be both species- and response-dependent since both additive and non-additive (antagonistic) interactions have been observed with PCB mixtures. In the latter case, the TEF approach would significantly overestimate the toxicity of a PCB mixture. Analysis of the rodent carcinogenicity data for Aroclor 1260 using the TEF approach suggests that this response is primarily Ah receptor-independent. Thus, risk assessment of PCB mixtures which uses cancer as an endpoint cannot utilize a TEF approach and requires more quantitative information on the individual congeners which contribute to the tumor promoter activity of PCB mixtures.

I. INTRODUCTION

Polychlorinated biphenyls (PCBs) are members of the halogenated aromatic group of environmental pollutants which have been identified worldwide in diverse environmental matrices. PCBs are produced by the chlorination of biphenyl and the resulting products are marketed according to their % chlorine content (by weight) [45,142,232,455]. For example, Aroclor 1221, 1232, 1242, 1248, 1254 and 1260 are commercial PCBs which were formerly produced by the Monsanto Chemical Company and contain 21, 32, 42, 48, 54 and 60% chlorine (by weight). The last two digits in the numerical designation for the different Aroclors denotes the % chlorine content. Similar commercial PCB mixtures have been produced by other manufacturers and these include the Clophens (Bayer, Germany), Phenoclors and Pyralenes (Prodelec, France), Fenclors (Caffaro, Italy) and Kanechlors (Kanegafuchi, Japan). Commercial PCBs have also been manufactured in several other countries including the former U.S.S.R. and Czechoslovakia. The commercial PCBs exhibit a broad range of physicochemical properties which are dependent, in part, on their degree of chlorination and these properties contribute to the diverse applications of PCBs in numerous products. For example, PCBs have been used as organic diluents, pesticide extenders, adhesives, dedusting agents, cutting oils, flame retardants, heat transfer fluids, dielectric fluids for transformers and capacitors, hydraulic lubricants, sealants, and in carbonless copy paper. Some of the uses of PCBs have resulted in the direct introduction of PCBs into the environment; however, a significant portion of the environmental burden of these compounds has resulted from careless disposal practices, accidents, leakage from various industrial facilities, and from chemical waste disposal sites. The total amount of PCBs produced worldwide and the proportion which is present in the environment is unknown; however, it has been estimated

that 1.5 million metric tons have been produced worldwide [142].

The chemical properties which are primarily responsible for many of the industrial applications of PCBs, namely their chemical stability and miscibility with organic compounds (*i.e.* lipophilicity), are also the same properties which have contributed to their environmental problems. Once introduced into the environment, the relatively stable PCBs resist environmental breakdown and undergo cycling and transport within the various components of the global ecosystem. Moreover, due to the lipophilicity of PCBs, these compounds preferentially bioaccumulate and biomagnify in higher trophic levels of the food chain [211, 349, 459, 460]. The environmental problems and the difficulties encountered in the hazard and risk assessment of PCBs have also arisen because of another chemical property of these compounds, namely the relatively non-specific chlorination of biphenyl [232]. This lack of chlorination site specificity means that the commercial PCB products and environmental PCB residues are complex mixtures of isomers and congeners. Thus, the impacts of PCBs on the environment and biota are due to the individual components of these mixtures, their additive and/or non-additive (synergistic or antagonist) interactions with themselves and other chemical classes of pollutants. Therefore, the development of scientifically-based regulations for the risk management of PCBs which would protect against adverse environmental and human health effects would require analytical and toxicological data on the individual PCB congeners present in any PCB mixture and information regarding their interactive effects. There are significant challenges associated with a congener-specific approach for the analysis and risk assessment of PCBs and these studies are currently ongoing in several laboratories and regulatory agencies. This review will focus on some of the more recent studies which have added to our understanding of PCBs and will also

discuss problems associated with PCB toxicology and risk assessment which are ongoing and have not yet been resolved.

II. PCBs: ENVIRONMENTAL IMPACT

The development of improved techniques for PCB analysis has played a pivotal role in understanding the environmental fate and potential adverse human health and environmental impacts of PCBs. In the late 1960s, Soren Jensen first detected PCBs in environmental samples as a series of complex peaks which were observed in a gas chromatographic screening of environmental samples for DDT and related compounds [26]. Subsequent studies in several laboratories have identified PCBs in almost every component of the global ecosystem including air, water, sediments, fish, wildlife and human tissues [31, 38, 42-45, 77, 170, 201, 219, 235, 260, 262, 263, 307, 372, 431, 460, 522, 529-534, 573, 583]. Most of the early analyses utilized low resolution packed column gas chromatographic separation of the PCB mixtures in which concentrations were determined by matching specific peak patterns and their intensities with the corresponding peaks in commercial PCBs or combinations of different commercial mixtures which were used as standards [575]. The criteria for the selection of commercial PCB standards were variable; however, in many cases, the choice was due to the similarities between the chromatographic peak patterns observed for the standard mixture and the PCBs in the analyte. High resolution analysis for PCB mixtures was first reported by Sissons and Welti [501] and there has been continued improvements in both the resolution capabilities of capillary columns and detection methods [8, 9, 47, 263, 369-371, 416, 457, 480, 501]. However, the unambiguous identification of the 209 possible PCB congeners required the synthesis of all these compounds and their subsequent use as analytical standards. This synthesis was

reported in 1984 [371] and subsequent studies have identified and quantitated all the PCB congeners present in several different Aroclor and Clophen mixtures [480]. A total of 132 different individual PCBs were identified in these mixtures at concentrations ≥ 0.05% (w/w) and the congener composition of each PCB mixture was dependent on their chlorine composition [480]. Inspection of the analytical data shows that some congeners occur in only one of the PCB mixtures whereas others are detected in all of the mixtures.

PCBs have been identified as residues from extracts of diverse environmental samples. In all cases, the PCBs are present as complex mixtures of isomers and congeners and, until recently, most routine analytical surveys reported "total PCB" levels using the peak matching technique with commercial Aroclors as standards [575]. The PCB levels in extracts are dependent on the nature of the environmental sample and the location. In localized areas with high levels of PCB contamination, there is an increased concentration of PCBs in various environmental extracts. For example, atmospheric PCB levels in an electroindustrial plant in Belakrajina (Yugoslavia) averaged 2000 $\mu g/m^3$ and the levels over a PCB-containing waste landfill were 22 to 70 $\mu g/m^3$. In contrast, PCB levels 300 m from the factory and in a nearby residential area were 4 to 7 and 2 to 5 $\mu g/m^3$, respectively [253]. Moreover, as noted above, PCBs bioconcentrate in higher trophic levels of the food chain and this has been aptly demonstrated within the North American Great Lakes ecosystem. For example, PCBs were biomagnified 12.9-fold from plankton to fish in a Lake Michigan food web [163].

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. Individual PCBs exhibit different physicochemical properties which

influence their rates of partitioning, uptake and retention in environmental matrices and their rates of breakdown by various environmental pathways (*e.g.* photolysis, microbial degradation, and metabolism) [232]. The results in Table 1 summarize the congener-specific analysis of Aroclor 1260 and PCBs in human breast milk samples collected from mothers living in the Great Lakes region and the United Kingdom [150, 459]. The results demonstrate that the PCB composition of the commercial Aroclor differs markedly from the distribution of PCB congeners in extracts from both breast milk samples. For example, some compounds such as 2,4,4′,5-tetrachlorobiphenyl are present in relatively high concentrations in human milk (3.7 to 11% of total PCBs) but are a minor component (0.03%) of Aroclor 1260. Other congeners such as 2,2′,3,3′,4,5,6′-heptaCB and 2,2′,3,4,5,5′,6-heptaCB are major components of Aroclor 1260 (5.5 and 4.1% of total PCBs, respectively) but are trace components of human milk extracts (< 0.4% to non-detectable for both compounds). The high resolution analytical data also shows significant differences in the composition of the PCBs obtained from North America or United Kingdom human milk samples and this no doubt reflects differences in composition of the PCBs present in food products from these countries. For example, the combined level of 2,2′,5-triCB, 2,2′,4-triCB and 4,4′-diCB in the United Kingdom sample was 13.7% whereas these lower chlorinated congeners were not detected in the North American samples. There were some congeners such as 2,2′,3,4,4′,5′-hexaCB and 2,2′,4,4′,5,5′-hexaCB which constituted > 10% of the total PCBs in both milk samples and are also major components of Aroclor 1260 (6.5 and 9.6%, respectively). Several high resolution congener-specific analysis of numerous fish and wildlife samples from different parts of the world have also revealed both similarities and differences in the relative concentrations of the PCB congeners. However, in most extracts from biota, the

predominant compounds are 2,2′,3,4,4′,5′-hexaCB, 2,2′,4,4′,5,5′-hexaCB and 2,2′,3,4,4′,5,5′-heptaCB [82-84, 120, 349] (Figure 1).

Three PCB congeners, namely 3,3′,4,4′-tetraCB, 3,3′,4,4′-5-pentaCB and 3,3′,4,4′,5,5′-hexaCB, elicit toxic responses similar to those reported for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and were not routinely detected or quantitated in analytic surveys for PCBs [189, 193, 419-421, 445, 450, 453, 454, 458, 597]. However, several recent studies have reported analytical methods for the detection and quantitation of these congeners and several of their monoortho-substituted analogs in commercial PCBs, environmental samples and in humans [30, 148, 150, 217, 225, 268-271, 353, 475, 509, 529-535, 537, 579]. The potential adverse impacts of these non-ortho-coplanar PCBs and their monoortho analogs will be discussed in more detail in Section V of this review. The results in Table 2 illustrate the levels of the coplanar PCBs in human milk or adipose tissue samples from different locations including upper New York State, Ontario, Quebec and Japan [148, 217, 225, 268, 269, 353, 475, 521, 531, 533, 535, 537, 579]. Again there was considerable variability in the range of or mean concentrations of these compounds. Fish and wildlife samples taken from different locations also exhibit large differences in the relative concentrations of the coplanar PCBs. These no doubt reflect the variable environmental distribution of PCBs which is dependent on several factors including the magnitude of local and regional inputs, differential rates of environmental breakdown, the importance of transport processes, and the composition of PCB residues in the food chain species.

Thus, analysis of environmental samples clearly demonstrates that their PCB composition is highly variable and does not resemble the composition of the commercial PCB mixtures. Currently, environmental standards for PCBs are derived from the results

of animal studies with commercial PCB mixtures (*e.g.* Aroclor 1260). However, a meaningful risk assessment of PCBs in food products or environmental samples must take into account the potential adverse impacts of the individual congeners and their concentrations in these samples and should not rely on the toxicity of a known commercial mixture such Aroclor 1260 or Clophen A60. The toxic equivalency factor (TEF) approach which is now being used as an interim measure for the risk assessment of PCDDs and PCDFs [2-5, 52, 62, 315, 384, 450] and has been discussed as a model for congener-specific risk assessment of PCBs [3, 5, 460, 560]. The TEF model for specific structural classes of compounds such as PCBs presupposes a common mechanism of toxic action. Before the potential utility and pitfalls of this model for risk assessment of PCBs can be discussed, the biochemical and toxic effects of PCBs (mixtures and congeners) in humans, laboratory animals and other model systems must be understood.

III. PCBs: ADVERSE HUMAN HEALTH EFFECTS

The development and validation of a more scientifically-based approach for the risk assessment of PCB congeners requires information on the adverse effects of PCB mixtures on exposed human populations and laboratory animal models. These data coupled with the results of studies on the effects of individual PCB congeners in animal and cell model systems can be utilized to identify specific structural classes of PCBs which may be etiologic agents in PCB-induced adverse effects in humans.

There have been 3 major scenarios in which humans have been exposed to PCB mixtures and these include (i) exposure of workers who produced PCBs or utilized PCB-containing products; (ii) accidental exposure of individuals, and (iii) environmental exposure

of populations through contaminated food, air and water. The adverse human health effects of PCBs on several groups of occupationally-exposed workers have been extensively documented and reviewed [220, 282-284, 308, 447, 452, 541]. PCB exposure in the workplace can result in exceedingly high body burdens of these compounds and this human population is the most highly exposed group. The reported effects of PCBs on occupationally-exposed humans are variable and dependent on the objectives and design of each study (Table 3). Some of these effects include chloracne and related dermal lesions, diverse hepatic effects including increased serum levels of liver enzymes and lipids, induced hepatic drug metabolizing enzymes, hepatomegaly, decreased birthweight in the offspring of occupationally-exposed mothers, decreased pulmonary function, and eye irritation. Worker exposure to PCBs did not affect mortality [101, 102]. Many of the responses in the exposed workers were reversible and, in some studies, no significant correlations were observed between PCB levels (serum or adipose tissue) and a response. For example, Emmett and coworkers [156, 160, 165] examined serum and adipose tissue PCB levels in transformer repair workers. It was shown that PCB levels were highest in currently exposed workers, lowest in unexposed workers and intermediate in post-exposed workers. However, there was no significant correlation between PCB levels and symptoms of putative PCB-induced toxicosis. These studies also quantitated the concentrations of several individual PCB congeners in the three different groups and the relative concentrations of the major congeners were similar. The adverse health effects of PCBs on workers exposed at toxic waste sites or during accidents or fires which involved PCB-containing equipment such as transformers or capacitors have also been investigated [171, 281, 394, 518, 519]. Although some neurobehavioral dysfunction may have been associated with PCB exposure (firemen) [281], there were no correlations between PCB levels

and any sign of PCB-induced effects. Fitzgerald and coworkers [171] reported a number of problems reported by firemen; however, these were not directly linked to PCB exposure.

Several studies have reported or reviewed the incidence of cancer in workers exposed to PCBs [39, 40, 70 101, 102, 138, 206, 449, 493, 599]. In the cohorts which contained the largest number of workers, the results indicated that no overall increases in cancer-related mortality could be correlated with occupational exposure to PCBs. However, in several of these studies, there are increased incidences of specific cancers including melanomas [39, 40] rectal and liver cancer [102], liver gall bladder and biliary tract cancer [101], gastrointestinal tract cancer in males, and hematologic neoplasms [70]. Some of the increases in cancer incidences at specific sites were not statistically significant and it was also evident that the carcinogenic effects observed in these workers were different for each study. These results suggest that in the highly exposed worker population, PCBs do not cause a consistent increase in one or more cancers and, therefore, their carcinogenicity in humans has not been established. However, the carcinogenic effects of PCBs in laboratory animals has been amply demonstrated [449, 493] and, for this reason, continued monitoring of occupationally-exposed workers is warranted.

Several thousand individuals were poisoned with PCBs in two separate accidents in Japan and Taiwan when PCB-containing industrial fluid accidentally leaked into rice oil which was subsequently sold to consumers [311-313, 436, 437]. The symptomology of victims of the Yusho (Japan) and Yu Cheng (Taiwan) accidents has been extensively investigated and includes severe and persistent chloracne, dark brown pigmentation of nails, distinctive hair follicles,skin thickening, various ocular problems, numbness in some extremities, and numerous subjective complaints which may be associated with neurological problems. In addition, offspring of Yu Cheng mothers were smaller, exhibited learning deficits, and

displayed some of the same symptoms observed in their mothers [436, 437]. The rather severe effects caused by the PCB-contaminated rice oil indicated that there were differences in the toxic potency of PCB contaminated rice oil and "normal" industrial PCBs. Many of the acute and chronic effects observed in Yusho and Yu Cheng victims were not observed in the occupationally-exposed population even though serum PCB levels in Yusho/Yu Cheng patients and industrial workers exposed to PCBs were comparable and in many cases higher in the latter group. For example, the PCB serum levels in occupationally-exposed workers can be as high as 100 ppm whereas the mean PCB blood levels of Yu Cheng victims taken a short time after the accident varied from 39 to 101.7 ppb [228], suggesting that chemical contaminants other than PCBs played an important role in the etiology of Yu Cheng/Yusho poisoning. Moreover, the distribution of PCBs in Yusho patients was similar to that observed in other exposed populations [314]. Several papers have reported that the highly toxic polychlorinated dibenzofurans (PCDFs) are present as trace (ppm) impurities in many commercial Japanese and North American PCB preparations [87, 88, 119, 360-363, 367]. PCDFs and other chlorinated aromatic hydrocarbons were subsequently identified in the PCB industrial fluid which contaminated the rice oil in both the Yusho and Yu-Cheng poisonings [119, 127, 128, 272, 360, 362]. The ratio of PCDFs/PCBs in the Yu-Cheng and Yusho oils was 2.4×10^{-3} and 9.0×10^{-3}, respectively, whereas the ratio in the commercial PCB, Kanechlor 400, was 3.3×10^{-5} indicating the relatively higher concentration of the PCDFs in the Yusho oil. Moreover, adipose tissue and serum analysis of Yusho/Yu Cheng victims, workers and normal individuals clearly showed that although their PCB levels were comparable, the corresponding PCDF concentrations were consistently higher in the Yusho and Yu Cheng patients [272, 310]. Laboratory studies using rodents [48, 310] and different fractions of simulated

"rice oil PCBs" (containing the PCDF fraction) or reconstituted PCB and PCDF mixtures which resemble the distribution of these compounds in Yusho patients have demonstrated that the PCDFs were significantly more potent than the PCB fraction. Thus, although PCBs were involved in the Yusho and Yu-Cheng poisonings, the evidence suggests that the major etiologic agents in these incidents were the PCDF contaminants which were present in relatively high concentrations in the industrial fluid which leaked into the rice oil.

Based on the moderate adverse human health effects of PCBs on occupationally-exposed workers, it is unlikely that adult exposure to relatively low environmental levels of PCBs would be associated with any adverse health effects. One recent study [166] reported that PCBs levels were significantly elevated in human breast lipids from breast cancer patients. The significance of this correlation and the relationship between organochlorine pollutant exposure levels and human breast cancer has not been established and requires further investigation particularly since some PCBs exhibit antiestrogenic activity [309]. Jacobson and coworkers designed a series of studies to examine the developmental effects associated with exposure to environmental contaminants including PCBs by examining the offspring of mothers who consumed Lake Michigan sports fish [168, 245-251]. Their results showed that there was a correlation between cord serum PCB levels and several parameters such as decreased birth weight and head circumference and neurodevelopmental deficits in infants which included poorer performance on the Brazelton Neonatal Behavioral Assessment Scale, on the psychomotor index of the Bayley Scales of Infant Development and on Fagan's Visual Recognition Memory Test. Rogan, Gladen and their coworkers also showed a correlation between the levels of prenatal PCB exposure of North Carolina infants from the general population and the former two tests for neurodevelopment deficits [182, 183].

[438-440]. In a follow-up study on the Michigan children at four years of age, the children with the high levels of prenatal exposure to PCBs showed deficits on the McCarthy Scales involving both verbal and numerical memory [249, 250]. In contrast, in the North Carolina children who exhibited neurodevelopmental deficits as infants, no significant correlations were observed between PCB levels and poorer grades on McCarthy scores at three, four, or five years of age [182].

In summary, it was shown that prenatal exposure to PCBs correlated with smaller birth weight and memory and learning deficits in infants and young children. In the North Carolina study, these effects were not observed in three to five year old children whereas at four years of age the children in the Michigan group still showed some developmental deficits. The reasons for the differences in the age-dependent outcomes are unclear and require further definition. The structural classes of PCBs which are responsible for the developmental problems are unknown; moreover, it is possible that some other chemicals which were not determined by chemical analysis may contribute to or be responsible for the observed responses. Rogan, Hsu and coworkers have investigated the comparable developmental deficits in infants exposed to PCDFs/PCBs in the Yu Cheng poisoning incident in Taiwan [128, 436, 437, 598]. Many of the toxic responses observed in the mothers were also seen in the infants and the exposed children exhibited some of the same developmental deficits reported in the low level PCB-exposed children in North Carolina. Although many of the toxic responses noted in the Yu Cheng incident were probably due to the highly toxic PCDFs, the toxins responsible for the developmental deficits may be the PCBs, PCDFs or their combination. The prenatal exposure of the Yu Cheng infants to PCDFs would be significantly higher than the children in the North Carolina study; however, the magnitude

of the neurodevelopmental deficits in both groups were similar. This suggests that the highly toxic PCDFs may not be the major etiologic agents associated with this developmental problem. Thus, there may be an association between *in utero* exposure to PCBs and developmental deficits observed in infants and young children. However, the duration of these adverse effects and the precise identification of the toxic agents are currently unknown and require further study.

IV. PCB MIXTURES: TOXIC AND BIOCHEMICAL EFFECTS

(a) Toxicity of Commercial Mixtures

The toxic and biochemical effects of various commercial PCB mixtures have been extensively investigated in various laboratory animals, fish and wildlife species. Unfortunately, only limited data is available on the toxic effects of other PCB mixtures which resemble environmental PCB residues or of fractionated PCB mixtures. One of the major problems associated with the toxicity of commercial PCBs is related to the relative levels of PCDFs which have been identified as contaminants in several commercial PCB preparations. In most studies, the PCDF content was not determined and their contribution to PCB-induced toxic responses are unknown but in most cases their effects may be relatively minor [450].

Commercial PCBs elicit a broad spectra of toxic responses which are dependent on several factors including (i) the chlorine content and source of the commercial mixture, (ii) the animal species and strain, (iii) the age and sex of the animal, and (iv) the route and duration of exposure to the commercial mixture. The results in Table 4 summarize many of the toxic responses observed in laboratory animals after exposure to commercial PCBs

and these effects include acute lethality, hepatomegaly, fatty liver and other indicators of hepatoxicity, porphyria, body weight loss, dermal toxicity, thymic atrophy, immunosuppressive effects, reproductive and developmental toxicity, carcinogenesis ,other genotoxic responses, modulation of diverse endocrine-derived pathways, and neurotoxicity. The development of PCB-induced toxicity is dependent on a number of factors as noted above; however, the data suggests that the liver is a common target organ and various symptoms of hepatoxicity have been observed in studies with diverse laboratory animal species. Detailed discussions and analysis of PCB-induced toxic responses have previously been reviewed [283, 445, 449, 450, 453, 454, 458, 499, 597] and will not be further elaborated in this article; however, the effects of various factors on the toxicities mediated by PCB mixtures will be briefly discussed.

(i) **Species/strain-dependent responses.** The dermal toxicity of PCBs has been noted in occupationally-exposed workers [220, 346, 398] and has also been observed in laboratory animals including some strains of mice, rabbits (ears) and monkeys. The PCB-induced dermal toxicities are most pronounced in monkeys and these effects include alopecia, edema, distinctive hair follicles, hair loss, hyperkeratosis and fingernail loss (see Table 4). In contrast, most other laboratory animals are insensitive to PCB-mediated dermal effects and this response pattern is reminiscent of TCDD and related HAHs which act through the aryl hydrocarbon (Ah) receptor [193, 420, 421, 446].

(ii) **Sex-dependent effects.** Many of the toxic effects caused by PCBs are observed in both males and females; however, some responses can be sex-specific. After chronic administration of Aroclor 1260 to male and female Sprague-Dawley rats, the incidence of hepatocellular adenocarcinomas and trabecular carcinomas were 51 and 40% in female rats

and 4 and 0% in male rats, respectively [392]. In contrast, the increased incidence of gastric intestinal metaplasia and adenocarcinoma was observed in both male and female F344 rats maintained on diets containing Aroclor 1254 [571]. Thus the carcinogenic effects of commercial PCBs can be both sex-dependent and -independent depending on the animal species used, the target organ site and possibly the composition of the PCB mixture.

(iii) **Age-dependent effects.** Several studies have shown that there was a correlation between developmental deficits in infants and young children and cord serum PCB levels [168, 182, 183, 245, 251, 438-440]. These data suggested that prenatal *in utero* exposure, and not postnatal exposure through breast milk, was important for the impaired development in humans. Comparable results were obtained in rats which were pre- and postnatally exposed to Clophen A30 [325, 326]. The PCB mixture caused alterations in active avoidance learning and retention of a visual discrimination task in prenatally-exposed offspring whereas postnatal exposure did not cause any detectable behavioral changes. These data from both human and animal studies were complementary and suggest that the fetus may be more susceptible to PCB-induced neurodevelopmental deficits than infants or older animals.

(iv) **Structure-dependent toxicities.** The commercial PCB mixtures differ with respect their chlorine content and their relative distribution of individual isomers and congeners. A few studies have compared the relative potencies of more than one PCB mixture and the results indicate that there are both structure-dependent and -independent potency differences. Egg production in White Leghorn pullets was decreased in animals maintained on a diet containing Aroclor 1232, 1242, 1248 and 1254 (20 ppm) but no effects were observed for Aroclors 1221 or 1268 [327]. Moreover, based on other parameters measured in this study, the most toxic mixtures were Aroclors 1242, 1248 and 1254. These

data showed that both the high and low chlorinated PCB mixtures exhibited the lowest toxicity. Schaeffer and coworkers [471] utilized male Wistar rats as model for determining the effects of chronic feeding of 100 ppm of Clophen A30 and Clophen A60. After 800 days, the incidence of hepatocellular carcinomas in the Clophen A60, Clophen A30 and control rats was 61, 3 and 2%, respectively. The results of this study illustrated the significant differences between the hepatocarcinogenicity of the more potent higher chlorinated Clophen A60 (60% Cl by weight) versus the lower chlorinated Clophen A30 (42% Cl by weight) PCB mixture. These data, coupled with other studies on PCB-induced carcinogenicity [493] suggest that the higher chlorinated PCB mixtures such as Aroclor 1260 and Clophen A60 were more carcinogenic than lower chlorinated mixtures. This was also observed for PCB-induced immunotoxicity in mice in which the order of potency was Aroclor 1260 > 1254 > 1248 > 1242 > 1016 > 1232 [139]. In contrast, PCB-induced lethality (Table 4) was not consistently dependent on the degree of chlorination of the commercial PCB. The toxicities of commercial PCBs are due to the individual isomers and congeners in these mixtures and it is possible that one or more structural subclasses of the PCBs contribute to the different toxic responses elicited by PCB mixtures. The identification of these structural subclasses will be discussed in Section V of this review. However, it is clear that there is not a consistent structure-dependent effect of the commercial PCB mixtures for all induced toxicities and this suggests that more than one structural subclass of PCB congeners is responsible for these responses. This conclusion is important for developing schemes for congener-specific hazard and risk assessment of PCBs (see Section VI).

(b) Carcinogenicity of Commercial Mixtures

Several studies have reported that after a single or repeated administration of

commercial PCBs to laboratory rodents they develop an increased incidence of liver lesions including neoplastic nodules and hepatocellular carcinomas. These responses were primarily observed in studies with Aroclor 1260 and Clophen A60 in rats and, in addition, Aroclor 1254 increased the incidence of intestinal metaplasia in F344 rats and this may lead to glandular adenocarcinoma in stomachs of these animals. The evidence for the mutagenicity and genotoxicity of PCBs has been extensively reviewed [449, 493]. PCB mixtures and congeners tend to be non-mutagenic in the Ames test for bacterial mutagenesis and there is only limited data which support the genotoxic action of these mixtures. A recent study [383] showed that after multiple administration of high doses of Aroclor 1254 (500 mg/kg) no PCB-DNA adducts were detected in the liver, lung or kidney DNA using the highly sensitive ^{32}P-postlabeling assay. There have been extensive studies on the activities of PCBs as cancer promoters using several different experimental protocols and both long and short term assays which measure the formation of tumors or putative preneoplastic lesions such as nodules or papillomas. The results in Table 5 summarize results of promotion studies with PCB mixtures. In all of these studies, the animals are initiated with a carcinogen followed by repeated or continuous (dietary) administration of the promoter (*i.e.* PCB mixture). The results show that after initiation with a variety of carcinogens, PCBs promote hepatocellular carcinomas and neoplastic nodules in the rat and similar effects were observed in mouse skin and lung. In addition, PCB mixtures also promote the formation of enzyme-altered foci in rats and chickens initiated with different carcinogens. The enzyme-altered foci which are typically characterized in the short term initiation/promotion bioassays for PCBs exhibit decreased ATPase or increased γ-glutamyl transpeptidase (GGT) activities. The results obtained for PCB mixtures are similar to those reported for other tumor promoters

including phenobarbital, TCDD and other halogenated aromatic compounds [197, 261, 418, 427, 451, 479].

Aroclor 1254 also inhibited aflatoxin B1-mediated carcinogenesis in rainbow trout and this was related to altered metabolism and decreased DNA binding by the carcinogen [488, 489]. The effects of PCB mixtures and selected congeners have also been investigated [221, 222] using the resistant hepatocyte model [508]. The PCBs used in these studies included Aroclor 1254 and a reconstituted mixture of PCBs, and no initiating activity was observed for these mixtures at the doses used in this study. The antitumor activity of Aroclor 1254 in rats inoculated with Walker 256 carcinosarcoma cells has also been reported [279]. Depending on the timing of the treatment with PCBs and the number of tumor cells used in the study, Aroclor 1254 inhibited tumor growth, increased the latency period for tumor development, increased the host survival time and caused tumor regression (if administered after the tumors were established). It has also been reported that Aroclor 1254 did not promote carcinogen-initiated tumors in a two-stage mouse (CD-1) skin tumorigenesis assay [68]. In a subsequent study [69], treatment of CD-1 mice with Aroclor 1254 18 hours prior to application of 7,12-dimethylbenzanthracene resulted in decreased papilloma formation (note: TPA was used as a promoter in this experiment). Thus, although the results strongly support the promoting activity of several commercial PCB mixtures, these same mixtures also inhibit carcinogen-induced tumor or preneoplastic cell formation in certain animal models.

Smith and coworkers [504] have reported a synergistic interaction between Aroclor 1254 and iron in Ah-responsive C57BL/10ScSn mice in the development of hepatocellular carcinomas whereas the toxic effects were significantly lower in Ah non-responsive DBA/2

mice. Due to limitation in the number of animals used and toxicity, the role of iron status and the Ah locus requires further investigation. Using this same model system, it was reported that Aroclor 1254 (+ iron overload)-induced carcinomas were not accompanied by H-*ras* mutations which frequently are observed in hepatomas induced by other carcinogens [441]. The mutations of protooncogenes or tumor suppressor genes and their role in PCB-induced carcinogenesis is unknown and should be further investigated.

(c) Biochemical Changes Induced by PCB Mixtures

The results in Table 6 summarize the biochemical changes which have been observed in laboratory animals after exposure to PCB mixtures. The induction of hepatic cytochrome P450 and diverse P450-dependent monooxygenases is a sensitive indicator of PCB exposure which has been observed in multiple species including rats [11-13, 15, 16, 18, 28, 74, 103-106, 153, 176, 204, 209, 218, 224, 234, 239-244, 266, 317, 334, 335, 378-381, 393, 412, 415, 505, 527, 544, 549, 595], rat hepatoma cells in culture [91, 469, 470, 546, 550], mice [20, 60, 61, 78, 231, 254, 334, 464], rabbits [21, 486], monkeys [338], ferrets [317], quail [118, 354, 355, 432], mink [111, 114], guinea pig [115], kestrel [158], herring gulls [175], cockerels [211], barn owls [429, 430], insects [24] and fish [1, 156, 157, 173, 205, 212, 223, 252, 352, 382, 568]. The PCB-induced microsomal enzymes from different species increase the oxidative metabolism of diverse substrates such as benzo[a]pyrene and related polynuclear aromatic hydrocarbons (PAHs), aflatoxin, nitrosamines and other carcinogens, various *N*- and *O*-alkyl-substituted compounds (dealkylation), direct hydroxylation and epoxidation of many other xenobiotics and drugs. Inducers of hepatic drug-metabolizing enzyme activities were traditionally divided into two main classes typified by phenobarbital (PB) and 3-methylcholanthrene (MC) [135, 136, 507]. Pretreatment of rats with PB-type inducers enhances numerous hepatic drug-metabolizing enzyme activities including several cytochrome P-450-dependent monooxygenases (such as

dimethylaminoantipyrine (DMAP), ethylmorphine and related *N*-dealkylases, biphenyl-4-hydroxylase, aldrin epoxidase and several *O*-dealkylases including pentoxyresorufin *O*-dealkylase. In contrast, MC and MC-type inducers enhance hepatic microsomal benzo[a]pyrene hydroxylase (aryl hydrocarbon hydroxylase, AHH), ethoxyresorufin *O*-deethylase (EROD) and several other cytochrome P450-dependent monooxygenases. The commercial PCBs, typified by Aroclor 1254 induces both MC and PB-inducible monoxygenase and were initially classified as "mixed-type" inducers [16]. Subsequent studies in several laboratories have demonstrated that the mixed-type induction pattern observed for PCB mixtures in rodents was due to the induction of both PB (CYP2A1, CYP2B1, CYP2B2)- and MC (CYP2A1, CYP1A1, CYP1A2)-inducible P450 isozymes [86, 411, 442-444, 541-543]. In contrast to rodents, PB does not induce P450 isozymes in fish and only CYP1A1 is induced by PCB mixtures [516]. PCBs also induce P450 isozymes which regulate steroid metabolism in some species [179, 185, 264] and inhibited various adrenal steroid hydroxylases in the guinea pig [184-186]. There are other reports which indicate that commercial PCBs repress the constitutive expression of pulmonary P450 isozymes [486, 557-559]. Borlakoglu and coworkers [79, 81] have also reported the induction of lauric acid hydroxylase activity by Aroclor 1254 in both rat and pigeon liver suggesting that PCBs induce CYP4A1.

Commercial PCBs induce other enzymes associated with drug-metabolism and these include glutathione S-transferases, epoxide hydrolase and glucuronosyl transferases. Moreover, Table 6 summarizes a host of other biochemical responses induced by various commercial PCBs and these include δ-aminolevulinic acid synthetase (ALAS), c-Ha-ras, c-raf, c-yes, c-erbA and c-erbB protooncogene mRNA levels, various serum lipids and lipoproteins, and HMG-CoA reductase, hepatic lipoperoxidation, fatty acid desaturases, lung

pepsinogen isozymes and aldehyde dehydrogenase activities. PCBs also cause a decrease in ALA dehydratase and uroporphyrinogen decarboxylase activities and these responses are associated with development of PCB-induced porphyria.

Thus commercial PCBs elicit a large number of toxic and biochemical responses in multiple species and target organs. Since these industrial compounds are complex mixtures, the induced responses must be due to the contributions of individual PCB congeners and their possible non-additive (synergistic or antagonist) responses. Extensive research on the structure-activity relationships (SARs) among various structural classes of PCBs has been carried out in order to identify the individual congeners which are responsible for PCB (mixture)-induced effects. Characterization of the effects of individual PCB congeners and their relative potencies is also important for the development of procedures for the risk and hazard assessment of this class of pollutants since the PCB composition of environmental residues does not resemble that of the commercial products.

V. PCB CONGENERS AND DERIVED METABOLITES: STRUCTURE-FUNCTION RELATIONSHIPS

(a) Characterization of Ah Receptor Agonists

(i) Coplanar PCBs. Structure-induction studies in several laboratories demonstrated that three congeners, namely 3,3′,4,4′-tetrachlorobiphenyl (tetraCB), 3,3′,4,4′,5-pentaCB and 3,3′,4,4′,5,5′-hexaCB (Figure 2) resembled TCDD or MC as inducers of CYP1A1 and CYP1A2 gene expression and several associated enzyme activities in a variety of species (Table 7). In addition, 3,4,4′,5-tetraCB also exhibited comparable activity [496]. These compounds are all substituted in both *para* and at least two *meta* positions and the removal

of any one of these substituents or the addition of one or more *ortho*-chlorine groups results in a significant loss of "MC-type" activity. The data summarized in Table 7 demonstrate that the coplanar PCBs which are present in relatively low concentrations in the commercial Aroclors must contribute to the induction of CYP1A1 by these mixtures. 3,3',4,4',5-PentaCB also suppresses the expression of the constitutive male-specific rat hepatic CYP2C11 [590, 591] and there is evidence that both 3,3',4,4',5-pentaCB and 3,3',4,4'-tetraCB induce CYP4A1-dependent activities [79, 229]. However, the induction of w- and w-1 fatty acid hydroxylase activity (*i.e.* CYP4A1) is not specific for coplanar PCBs since 2,2',4,4',5,5'-hexaCB also induced this response. Coplanar PCBs also induce epoxide hydrolase and glutathione transferase activities and these induction responses were also observed for other structural classes of PCBs (see below). A recent report [27] suggested than the induction of the glutathione S-transferase P-form (GST-P, 7-7) may be specific for coplanar PCBs.

The induction of CYP1A1 gene expression by TCDD, MC and related compounds has been extensively investigated [195, 576-578] and the results are consistent with the role of the Ah receptor in mediating this response. The chemical inducer initially binds to the cytosolic Ah receptor; the resulting receptor complex undergoes transformation, nuclear translocation, and binding to specific genomic sequences (dioxin responsive elements, DREs) prior to the induction of gene transcription. Thus, the liganded Ah receptor complex acts as a nuclear transcriptional enhancer for the induction of CYP1A1 gene expression. The coplanar PCBs competitively bind with relatively high affinity to the cytosolic Ah receptor [49] and this interaction is consistent with the subsequent induction of CYP1A1 gene expression by these congeners. Extensive genetic studies and structure-toxicity relationships with TCDD and related polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) support a

role for the Ah receptor in mediating many of the toxic and carcinogenic responses elicited by these compounds [193, 420, 421, 446, 576-578]. Moreover, many of these responses, including the wasting syndrome, thymic atrophy, neurotoxicity, hepatotoxicity and porphyria, reproductive and developmental toxicity, dermal toxicity, immunotoxicity, endocrine effects, decreased vitamin A levels, antiestrogenicity, altered lipid metabolism and carcinogenicity are also observed in animals treated with many of the commercial PCB mixtures (Tables 4 through 6). The results summarized in Table 7 show that the coplanar PCBs also elicit the same pattern of Ah receptor-mediated responses in diverse species suggesting that this structural class of PCB congeners contributes to the toxicities induced by commercial PCB mixtures. Moreover, the relative potencies of the coplanar PCBs for several responses in genetically inbred mice segregated with their Ah-responsiveness [433, 494, 495]. For example, 3,3′,4,4′-tetraCB (100 mg/kg) inhibited the splenic plaque-forming cell (PFC) response to sheep red blood cells (SRBCs) and induced hepatic P450 levels in Ah-responsive C57BL/6 mice whereas at the same dose no effects were observed in the less-responsive DBA/2 mice [495]. The differential induction activity of coplanar PCBs was also observed for AHH induction in the genetically inbred C57BL/6 and DBA/2 mice [433].

(ii) **Monoortho coplanar PCBs.** The results of extensive structure-function studies showed that the monoortho coplanar derivatives of the 4 coplanar PCBs (Figure 3) constituted a second major structural class of compounds which exhibited Ah receptor agonist activities. This group of PCBs includes several congeners which have been identified in commercial PCB mixtures and environmental extracts, namely 2,3,3′,4,4′-pentaCB, 2,3′,4,4′,5-pentaCB and 2,3,3′,4,4′,5-hexaCB. The monoortho coplanar PCBs resemble Aroclor 1254 as inducers of hepatic drug-metabolizing enzyme activities and induce

CYP1A1, CYP1A2, CYP2B1, CYP2B2 and CYP2A1 gene expression. Similar results have been obtained for some of the analagous brominated biphenyls [411, 433, 434]. Thus the introduction of a single ortho chloro substituent to the coplanar PCBs did not eliminate the "MC-type" induction pattern but resulted in a series of compounds which exhibited "mixed-type" activity. The monoortho coplanar PCBs also competitively bound to the rat cytosolic Ah receptor [49] and the major difference between the coplanar and monoortho coplanar PCBs as Ah receptor ligands and CYP1A1 inducers was their potency (Table 9).

Since monoortho coplanar PCBs competitively bind to the Ah receptor, these compounds should also elicit the biochemical and toxic responses comparable to other Ah receptor agonists. The results in Table 8 summarize the biochemical and toxic responses which have been observed for the monoortho coplanar PCBs and these include induction of CYP1A1 and CYP1A2 gene expression, induction of epoxide hydrolase, inhibition of body weight gain, immunosuppressive effects, thymic atrophy, hepatotoxicity, tumor promoter activity, antiestrogenicity, and reproductive and developmental toxicity. All of these responses were observed for the coplanar PCBs, TCDD and related toxic halogenated aromatics and appear to be mediated through the Ah receptor. Moreover, studies with genetically inbred C57BL/6 and DBA/2 mice also support a role for the Ah receptor in the induction and immunosuppressive responses elicited by monoortho coplanar PCBs [410, 433, 494, 495]. These data suggest that these same responses which are also caused by commercial PCB mixtures (Tables 4 through 6) are due, in part, to the individual coplanar and monoortho coplanar PCBs present in these mixtures. Moreover, since some of the monortho coplanar PCBs are present in relatively high concentrations in commercial mixtures and environmental extracts, this class of PCBs may contribute significantly to the TCDD-like

activity of PCB mixtures.

(iii) **Other structural classes of PCBs.** The activity of other structural classes of PCBs as Ah receptor agonists were also investigated by determining their activity as inducers of CYP1A1 and CYP1A2 [407-409, 411]. The 13 possible diortho substituted coplanar PCBs were synthesized and evaluated as inducers in rodents and most of these compounds, including 2,3,4,4',5,6-hexaCB, 2,2',3,3',4,4'-hexaCB, 2,2',3',4,4',6-hexaCB, 2,3,3',4,4',6-hexaCB, 2,2',3,3',4,4',5-heptaCB, 2,2',3,4,4',5,5'-heptaCB, 2,3,3',4,4',5,6-heptaCB, 2,3,3',4,4',5',6-heptaCB and 2,3,3',4,4',5,5',6-octaCB, induced AHH activity and/or the CYP1A1 isozyme [407-409, 411]. The activities of the diortho coplanar PCBs as CYP1A1 inducers have been reported in other studies [18, 188, 520] and the results confirm that with the possible exception of 2,2',4,4',5,5'-hexaCB, the diortho coplanar PCBs exhibit weak Ah receptor agonist activity. Moreover, limited studies have shown that some of these congeners cause porphyria in rats (2,2',3,4,4',5'-hexaCB and 2,2',3,3',4,4'-hexaCB) [520] and inhibit the splenic PFC response to SRBCs in C57BL/6 mice (2,3',4,4',5',6-hexaCB) [140]. It has also been reported that coplanar and monoortho coplanar PCB congeners in which one *para* substituent has been removed (*e.g.* 3,3',4,5,5'-pentaCB, 2,3,3',4,5'-pentaCB and 2,3,3',4,5,5'-hexaCB) also exhibited some weak Ah receptor agonist activity [140, 403]. Since the potencies of these compounds and the diortho coplanar PCBs are weak compared to the coplanar and monoortho coplanar PCBs, it is unlikely that they play a major role in the "TCDD-like" activity of the commercial PCBs and environmental PCB residues [450].

(b) "PB-Like" PCBs and Their Role in PCB-Induced Toxicity

The "mixed-type" monooxygenase induction activity exhibited by commercial PCBs indicates that some of the observed responses must be due to congeners which exhibit "PB-

like" activity. The monoortho and diortho coplanar PCBs constitute two structural classes of PCBs which exhibit "PB-like" induction activity and 2,2′,4,4′,5,5′-hexaCB is a congener which has been utilized as a prototypical "PB-type" inducer [189, 199, 411, 419]. 2,2′,4,4′,5,5′-HexaCB and the structurally-related 2,2′,4,4′-tetraCB are both substituted in at least two *ortho* and two *para* positions and induce CYP2B1 and CYP2B2 in rat liver [411]. In addition, many of the PB-type PCBs induce CYP3A isozymes which are prototypically induced by glucocorticoids such as dexamethasone [474]. Many of the most active "PB-type" inducers contain at least two ortho and two para chlorine substituents [145]; however, no comprehensive structure-activity rules have been developed for "PB-type" inducers since congeners with a variety of chlorine substitution patterns in the *ortho*-, *para*- and *meta*-position exhibit "PB-type" induction activities. Rodman and coworkers [434] have also reported that several tri- and tetraortho-substituted PCB congeners which induced benzphetamine *N*-demethylase activity and P450 levels in cultured chick embryo hepatocytes also induce EROD activity and cause the accumulation of uroporphyrin. The latter two effects occur at relatively high dose levels and may represent examples of Ah receptor-independent responses which are also elicited by Ah receptor agonists at much lower concentrations [435]. The only unambiguous structure-induction relationship for PCBs as "PB-type" inducers is that the coplanar 3,3′,4,4′-tetraCB, 3,3′,4,4′,5-pentaCB and 3,3′,4,4′,5,5′-hexaCB congeners do not induce the "PB-like" drug-metabolizing enzyme activity.

Inspection of the data for the structurally diverse PCBs which resemble PB as inducers indicates that with the exception of hepatomegaly and some hepatotoxic effects [72, 192, 299], these compounds do not cause most of the putative Ah receptor-mediated responses observed in experimental animals after exposure to the coplanar and monoortho coplanar

PCBs and the commercial mixtures although the reproductive toxicity of other congeners has been reported [445]. One major exception to this observation is associated with PCB-induced tumor promoter activity. Several compounds including 2,2′,5,5′-tetraCB [466], 2,2′,4,5′-tetraCB and 2,2′,4,4′,5,5′-hexaCB which induce PB-like activity also promote the formation of enzyme-altered preneoplastic focal lesions in rodents [116, 117, 316]. These results suggest that "PB-type" PCBs and possibly other structural classes of PCBs may be important contributors to the activity of the commercial mixtures as tumor promoters and this is an area of PCB structure-function relationships which requires further investigation.

(c) PCBs Which Induce Neurotoxicity

Several studies have reported the 3,3′,4,4′-tetraCB causes neurotoxic and neurobehavioral changes in rodents and these include a permanent motor disturbance or "spinning syndrome" and other changes in neuromuscular activity [129, 547, 548] and alteration in cholinergic muscarinic receptors [161, 162]. Exposure of the nonhuman primate, *Macaca nemestrina*, to Aroclor 1016 resulted in decreased dopamine levels in specific regions of the brain including the caudate, hypothalamus, substantia nigra and putamen [483]. Gas chromatographic analysis of brain samples identified only three congeners, namely, 2,4,4′-triCB (Figure 5), 2,2′,4,4′-tetraCB and 2,2′,5,5′-tetraCB. Subsequent studies have demonstrated that these compounds and other *ortho*-substituted PCBs (but not the coplanar PCB congeners) caused a concentration-dependent decrease in dopamine levels in PC-12 pheochromocytoma cells [484, 487]. Thus, these results define a new structural class of PCBs other than Ah receptor agonists which elicit neurotoxic responses. It has been hypothesized that these compounds may play a role in the neurobehavioral deficits in infants associated with *in utero* exposure to PCBs; however, this in an area of research which requires further

study to validate or invalidate this hypothesis.

(d) Toxic and Biochemical Responses Associated with PCB Metabolites

The metabolism of PCBs has been extensively reviewed [448, 478, 500, 525] and a summary of the major metabolic pathways is shown in Figure 4. PCBs are metabolized either directly or via arene oxide intermediates into phenolic metabolites which can be further hydroxylated or conjugated to form catechols and phenolic conjugates, respectively. The highly unstable arene oxides also react to form dihydrodiols, glutathione conjugates and covalently-bound protein, RNA and DNA adducts. Since oxidative metabolism of xenobiotics is a major route for the detoxication and ultimate elimination of the more hydrophilic metabolites, initial studies on PCBs focused primarily on the toxicity and genotoxicity associated with the formation and subsequent reactions of arene oxide intermediates. Several reports have shown that *in vivo* and *in vitro* metabolic activation of PCBs resulted in the formation of protein, RNA and DNA adducts and increased DNA repair in mammalian cells [365, 478, 479, 490, 491, 584, 586]. However, the PCBs which are readily metabolized and form arene oxide intermediates are the lower chlorinated congeners or those compounds which contain two adjacent unsubstituted carbon atoms. With the exception of 3,3′,4,4′-tetraCB, most of the toxic coplanar and monoortho coplanar PCB are not readily metabolized. Moreover, treatment of Wistar rats with Aroclor 1254, one of the more toxic commercial PCBs, did not result in formation of DNA adducts as determined by ^{32}P-postlabeling [383]. Thus, it is unlikely that metabolic activation plays a major role in PCB-induced toxicity and genotoxicity.

PCBs undergo metabolism to form hydroxy metabolites or their conjugates which are readily conjugated and excreted by laboratory animals. The toxicities of several hydroxy-

PCB metabolites have been evaluated and compared to the effects of their parent hydrocarbons [293, 297, 514, 515, 588, 597]. 3,3′,4,4′-Tetrachloro-5-biphenylol and 3,3′,4′,5-tetrachloro-4-biphenylol, the two major rat urinary metabolites of 3,3′,4,4′-tetraCB, were considerably less toxic than the parent hydrocarbon and did not induce Ah receptor-mediated responses [596]. Similar results were observed for the rat urinary metabolites of 3,3′,4,4′,5-pentaCB. In a parallel study, the chick embryotoxicity of the hydroxylated metabolites of 3,3′,4,4′-tetraCB were at least two orders of magnitude less toxic than the parent hydrocarbon [293]. Thus, it is unlikely that the Ah receptor-mediated biochemical and toxic responses caused by the commercial PCB mixtures (Tables 4 through 6) and individual congeners are caused by the hydroxylated metabolites.

However, hydroxylated PCBs are not devoid of biological activity. For example, hydroxylated PCB congeners can act as uncouplers and inhibitors of mitochondrial oxidative phosphorylation [152, 376, 389, 390]; hydroxylated PCBs competitively bind to the estrogen receptor and increase mouse uterine wet weight *in vivo* [305]; hydroxylated PCBs inhibit various P450-dependent enzyme activities [476]; and hydroxylated PCBs bind prealbumin, a major serum thyroxine binding protein [428]. It has also been reported that hydroxylated PCB metabolites are selectively retained in the serum of rats and this was due to high affinity binding to a thyroxine transport protein, transthyretin (TTR) [96-100, 292]. For example, 3,3′,4′,5-tetrachloro-4-biphenylol (Figure 5), a major metabolite of 3,3′,4,4′-tetraCB, exhibited higher TTR binding affinity than thyroxine, the endogenous hormone. Preliminary results indicate that hydroxylated PCBs are present in serum of wildlife and human samples [292]. It has been hypothesized that some PCB-induced toxic responses may be due to the interaction of hydroxylated PCBs with TTR and other endogenous receptors; however, this suggestion

requires further validation.

The metabolism of PCBs also results in the formation of glutathione conjugates which are excreted in the bile and undergo microbial C-S lyase cleavage in the intestine. Methylation of the resulting thiols followed by reabsorption and S-oxidation yields methylsulfonyl PCB metabolites which have been identified in human and animal serum and several organs/tissues [42, 63-66, 193, 213, 214, 262, 420, 421, 424, 446, 576-578]. Using 4,4′-bis(methylsulfonyl)-2,2′,5,5′-tetrachlorobiphenyl (Figure 5) as a model it has been shown that this metabolite preferentially accumulates in the lung and kidney and binds with high affinity ($K_d \sim 10^{-9}$ M) to a constitutive protein which resembles uteroglobin [95, 338, 339]. This compound also binds with high affinity to rabbit uteroglobin [181] and fatty acid binding proteins in chicken liver and intestinal mucosa [319]. Methylsulfonyl PCB metabolites and related binding proteins have been identified in humans [213, 338]. Methylsulfonyl PCB metabolites also inhibit induced AHH activity in both *in vivo* and *in vitro* models [289-291, 337]. Thus, both hydroxylated and methylsulfonyl PCB metabolites are biologically active and bind to endogenous proteins; however, the toxicological significance of these interactions has not been delineated.

(e) PCB Interactions

Since PCBs in commercial products and environmental samples are complex mixtures of isomers and congeners, their toxic interactions may be important determinants in the resulting toxicity of the mixtures. Several studies have investigated the interactions between individual PCB congeners and mixtures with other Ah receptor agonists such as TCDD and these studies serve as models for assessing the environmental interactions of PCBs with other halogenated aromatic hydrocarbons (HAHs) such as PCDDs and PCDFs. Denomme and coworkers reported that Aroclor 1254 and several PCB congeners significantly increased

rat hepatic cytosolic Ah receptor levels in rats [146]. For example, eight days after administration of Aroclor 1254 or 2,2′,4,4′,5,5′-hexaCB, there was approximately a 2- or 3-fold increase in cytosolic Ah receptor levels which remained elevated for the 14-day duration of this study. Comparable results were noted in C57BL/6 mice [51]. It was suggested that the 2,2′,4,4′,5,5′-hexaCB-induced receptor levels may synergistically enhance the biochemical and toxic responses elicited by Ah receptor agonists such as TCDD or coplanar PCB congeners. Cotreatment of C57BL/6 or DBA/2 mice with different concentrations of TCDD and 2,2′,4,4′,5,5′-hexaCB (500 μmol/kg) resulted in a marked enhancement of TCDD-induced hepatic microsomal AHH and EROD activity at low doses of TCDD (1 nmol/kg) but not at higher doses (100 and 500 nmol/kg) [51]. The synergistic induction response was also noted in DBA/2 mice for several doses of TCDD (10, 25, 80, 200, 500 and 5000 μmol/kg); however, the increased monooxygenase activity was less than 100% at all doses. 2,2′,4,4′,5,5′-HexaCB did not enhance TCDD-induced thymic atrophy or body weight loss in mice and the only significant interactive effect was protection of DBA/2 mice from TCDD-induced body weight loss. The interaction of 2,2′,4,4′,5,5′-hexaCB with 3,3′,4,4′,5-pentaCB and 2,3,3′,4,4′,5-hexaCB was also investigated in the male Wistar rat [322]. The interactive effects between the PCB congeners on toxicity and EROD induction were minimal and similar results were reported for the interaction of 2,2′,4,4′,5,5′-hexaCB and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin [141]. Non-additive (synergistic) interactions of 2,2′,5,5′- and 3,3′,4,4′-tetraCB as promoters of hepatic preneoplastic lesions in rats have also been reported [466]; however, the nature and significance of these interactions requires further confirmation by dose-response studies.

It has also been reported that individual PCB congeners and commercial mixtures

exhibit Ah receptor antagonist activity [50, 71, 139, 140, 208]. Davis and Safe [139] showed that Aroclors 1260, 1254, 1248, 1242, 1016 and 1232 caused a dose-response inhibition of the splenic PFC response to SRBCs in C57BL/6 mice and the ED_{50} values for this immunosuppressive effect varied from 104 to 464 mg/kg. These data indicate that the commercial PCBs were relatively weak Ah receptor agonists for this response since the corresponding ED_{50} value for TCDD was 0.77 μg/kg. The interaction of the commercial PCBs with TCDD (1.2 μg/kg) showed that Aroclors 1232, 1252, 1248, 1254 and 1260 significantly inhibited TCDD-induced immunotoxicity in C57BL/6 mice (Table 10). Table 11 summarizes the results obtained for the interactions of Aroclor 1254 and TCDD for several effects in C57BL/6 mice; it is evident that the % maximum antagonism is response-dependent and ratios of Aroclor 1254/TCDD, <20,000/1 and >1670/1, are required to observe partial antagonism. Analytical studies of extracts from human tissues and environmental extracts have shown that the ratios of PCBs/PCDDs plus PCDFs is in the range which is required for PCB-mediated antagonism of TCDD-induced responses in laboratory animal studies; however, the significance of PCB/PCDD plus PCDF interactions in wildlife species and humans is unknown.

Individual PCB congeners which exhibit partial Ah receptor antagonist activity have also been identified [71, 140, 368]. 2,2′,4,4′,5,5′-HexaCB at high doses (400 to 1000 μmol/kg) partially antagonized TCDD-induced EROD activity, immunotoxicity and teratogenicity in C57BL/6 mice. For example, the results summarized in Table 12 [71] demonstrate that 2,2′,4,4′,5,5′-hexaCB completely protected C57BL/6 mice from TCDD-induced inhibition of the PFC response to SRBCs and comparable protection was observed for TCDD-induced teratogenicity. The mechanism of these interactions was unclear since no binding was

observed between [$^{125}I_2$]4,4′-diiodo-2,2′,5,5′-tetrachlorobiphenyl (an analog of 2,2′,4,4′,5,5′-hexaCB) and the cytosolic Ah receptor or any other cytosolic protein. Davis [140] also identified other PCB congeners which inhibited TCDD-induced immunotoxicity; however, these congeners were considerably less active than Aroclor 1254 or 2,2′,4,4′,5,5′-hexaCB as partial antagonists. The non-additive (antagonistic) PCB/TCDD interactions in mice suggests that in complex mixtures of PCBs, PCDDs and PCDFs the former compounds may suppress the activity of other Ah receptor agonists in the mixture.

The non-additive interactions of other complex mixtures of PCBs have not been extensively investigated. Reconstituted PCB mixtures of individual PCB congeners which have been identified in human milk samples have been investigated and these mixtures exhibit many of the same partial Ah receptor agonist and antagonist activities reported for the PCB mixtures [139, 207]. The potential interactions within these mixtures using a TEF approach will be discussed in Section VI of this review.

The toxicity of Clophen A50, Aroclor 1254 and fractions of the commercial PCBs containing nonortho-, monoortho-, di-tetraortho-substituted PCBs and tricyclic impurities (*e.g.* PCDFs) were investigated in mink [280]. The commercial products, monoortho and nonortho PCB fractions, caused reproductive impairment; the results showed that both fractions exhibited comparable toxic potencies and indicated that the monoortho PCBs which are less toxic than the coplanar PCBs are important contributors to the toxicity of the mixture due to their relatively high concentrations. The authors also report that in cotreatment studies the diortho- to tetraortho-substituted PCB fraction enhanced the reproductive toxicity of both the nonortho- and monoortho-substituted PCB fractions. The effects of commercial PCBs and the different fractions on several other responses in mink

were also investigated and these included effects on blood parameters [155], steroid hormone excretion [342], P450 induction [111], vitamin A levels [210], liver histology [67], and morphology of the reproductive organs [37]. The relative potencies of the individual fractions and the commercial mixtures were highly variable and response-specific. For example, elevation of serum enzymes indicative of liver damage appeared to be associated with the non-ortho PCB fraction but this activity was enhanced by cotreatment with the di- to tetraortho PCB fraction. Decreased vitamin A levels were primarily due to the non-ortho and monoortho PCB fractions [210]. These data are at variance with the reported antagonism of TCDD-induced responses by Aroclors and 2,2′,4,4′,5,5′-hexaCB in mice; therefore the interactive effects of nonortho- and monoortho-substituted with di- to tetraortho-substituted PCB fractions should be further investigated in other laboratory animals to determine the species- and response-specificity of these interactions.

VI. DEVELOPMENT AND VALIDATION OF THE TOXIC EQUIVALENCY FACTOR (TEF) APPROACH FOR THE RISK ASSESSMENT OF PCBs

(a) Background - Derivation of TEFs for PCDDs and PCDFs

PCBs, PCDDs and PCDFs are routinely detected as complex mixtures of isomers and congeners in almost every component of the global ecosystem [148, 260, 451, 453, 537]. These compounds are not intentionally produced but are formed as by-products of numerous industrial activities including the synthesis of diverse chlorinated aromatics, particularly the chlorinated phenols and their derived products, production and smelting of metallic ores, pulp and paper production, and in the combustion of municipal and industrial wastes [451]. Despite the complex composition of many PCDD/PCDF-containing wastes, the congeners

which persist in the environment and bioconcentrate in the food chain are the lateral 2,3,7,8-substituted congeners namely 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or 2,3,7,8-tetraCDD), 1,2,3,7,8-pentaCDD, 1,2,3,6,7,8-hexaCDD, 1,2,3,7,8,9-hexaCDD, 1,2,3,4,7,8-hexaCDD, 1,2,3,4,6,7,8-heptaCDD, octaCDD, 2,3,7,8-tetrachlorodibenzofuran (tetraCDF), 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF,1,2,3,7,8,9-hexaCDF,2,3,4,6,7,8-hexaCDF,1,2,3,4,6,7,8-heptaCDF,1,2,3,4,7,8,9-heptaCDFandoctaCDF. The relative and absolute concentrations of these congeners in both pollution sources and environmental matrices are highly variable. For example, octaCDD is the dominant congener which persists in all human serum and adipose tissue samples whereas this congener is a minor component in PCDD/PCDF extracts from fish [451].

Risk assessment of PCDDs/PCDFs initially focused on one congener, namely TCDD which is the most toxic member of this class of compounds. However, with the improvement of analytical methodologies it was demonstrated that in many industrial and environmental samples that TCDD was present in relatively low concentrations. Moreover, based on structure-toxicity relationships [193, 420, 421, 446, 450, 576-578] which were developed for the PCDDs and PCDFs, it was recognized that in addition to TCDD many of the 2,3,7,8-substituted PCDDs and PCDFs were also highly toxic and were major contributors to the overall toxicity of these mixtures.

Based on structure-activity, genetic and molecular biology studies, it is generally accepted that most of the toxic responses elicited by the PCDDs, PCDFs, coplanar and monoortho coplanar PCBs are mediated through the Ah receptor. One of the hallmarks of receptor-mediated responses is the stereoselective interaction between the receptor and diverse ligands and the rank order correlation between structure-binding and structure-

toxicity relationships for most of these ligands. Thus, based on these mechanistic considerations, a TEF approach has been adopted by most regulatory agencies for the risk assessment of PCDDs and PCDFs [2-5, 52, 62, 315, 384, 450]. All the relevant individual congeners have been assigned a TEF value which is the fractional toxicity of the congener relative to a standard toxin, namely TCDD. Thus, if the ED_{50} values for the immunosuppressive activity of TCDD and 1,2,3,7,8-pentaCDD were 1.0 and 2.0 μg/kg, respectively, then the TEF for the latter compound would be the ratio ED_{50} (TCDD)/ ED_{50} (1,2,3,7,8-pentaCDD) or 0.5. The relative potencies or TEF values have been determined for several different Ah receptor-mediated responses and, for every congener, the TEF values are highly response- and species-dependent [450]. For example, the TEFs for 2,3,7,8-TCDF obtained from *in vivo* and *in vitro* studies varied from 0.17 to 0.016 and 0.43 to 0.006, respectively. Regulatory agencies have chosen single TEF values for all the PCDD/PCDF congeners (Table 13) and the selection criteria include the relative importance of data obtained for specific responses (*e.g.* carcinogenicity, reproductive and developmental toxicity) and for chronic studies since these effects and duration of exposure are important for protecting human and environmental health. It should be noted that proposed TEFs are interim values which should be reviewed and revised as new data becomes available.

There are reports which indicate that the single value TEF approach for PCDDs and PCDFs can be successfully used to predict the toxicity of complex mixtures of PCDFs and PCDDs/PCDFs in laboratory animals [151, 450]. Thus, despite the range of experimental TEFs, the TEF values used for risk management can be utilized to predict the Ah receptor-mediated toxicity of PCDF/PCDD mixtures and suggesting that any non-additive interactive effects are minimal. The major application of the TEF approach has been the conversion

of quantitative analytical data for PCDD/PCDF mixtures into TCDD or toxic equivalence (TEQ) where $[PCDF]_i$ and $[PCDD]_i$ represent the concentrations of the individual congeners, TEF_i is their corresponding TEF and n is the number of congeners. Thus, the

$$TEQ = \sum ([PCDF_i \times TEF_i]_n) + \sum ([PCDD_i \times TEF_i]_n)$$

concentrations of a complex mixture of PCDDs and PCDFs in a sample can be reduced to a single TEQ value which represents the calculated concentration of TCDD equivalence in that sample. The TEQs for PCDDs/ PCDFs have been determined for several types of mixtures including extracts from industrial and combustion processes, fish and wildlife samples, various food products, and human serum and adipose tissue. For example, based on the analysis of food products and their consumption, the daily human dietary intake of TEQs in Germany was estimated as 41.7 (milk and milk products), 39.0 (meat, meat products and eggs), 33.9 (fish and fish products), 6.3 (vegetables and vegetable oils) and 9.4 pg/person (miscellaneous food products) [57]. The estimated total daily intake was 130 pg/person and only 15% of this total was due to TCDD alone. The daily intake of PCDDs/PCDFs was estimated as 2 pg/kg/day (TEQs). This value is within the 1 to 10 pg/kg/day range of acceptable daily intakes recommended by most regulatory agencies with the exception of the U.S. Environmental Protection Agency which has utilized a value of 0.006 pg/kg/day. The significant differences between the USEPA and other regulatory agencies are based on their calculation methods and assumptions [413, 492]. For example, the USEPA assumes that TCDD is a complete carcinogen [296] and their value of 0.006 is derived from the linearized dose model which assumes no threshold for the response and protects the exposed population from one additional cancer per 10^6 individuals. In contrast, most

other regulatory agencies use the same carcinogenicity data [296] but utilize a safety factor approach in which it is assumed that TCDD is a promoter and there is a threshold for this response. The disparity between the USEPA value of 0.006 pg/kg data and the current intake of 2 pg/kg/day of TEQs is of concern and is currently being reevaluated by the agency [73, 167].

(b) Development of TEFs for Coplanar and Monoortho Coplanar PCBs

The results summarized in Tables 7 through 9 demonstrate that the coplanar and monoortho coplanar PCBs are Ah receptor agonists. Thus, any calculation of TEQs for industrial, environmental, food or human samples is incomplete unless the estimated "TCDD-like" activities of other Ah receptor agonists such as PCBs are included. Safe [450] has previously reviewed the QSAR studies for the coplanar PCBs and an updated summary of these data are given in Table 14. In some of these studies, the comparison of the toxic and biochemical potencies of the coplanar PCBs with TCDD are not given. In other reports [85] only the TEFs or a comparison of the maximal effects doses [435] were provided and not the ED_{50}/EC_{50} values. The results show that with few exceptions 3,3',4,4',5-pentaCB is the most active PCB congener in every assay system; however, the response-specific TEF values are highly variable (Table 15). In short term (14 day studies), the TEFs for body weight loss, thymic atrophy, and AHH and EROD induction in the rat varied from 0.093 to 0.015. These data were determined from the ratios of the ED_{50} (TCDD)/ED_{50} (3,3',4,4',5-pentaCB) for the different responses. Van Birgelen and coworkers [561] calculated TEF values by comparing the ratios of the no observed effect levels (NOELs) and lowest observed effects levels (LOELs) for TCDD and 3,3',4,4',5-pentaCB based on their modulation of

thyroid hormone levels, liver and thymus weights, body weight gain and induction of EROD activity. In this study, the compounds were administered in the diet for 3 months and preliminary results indicate that the TEFs varied from 0.6 to 0.06 and were higher than observed in the 14 day study. The inhibition of the splenic PFC response to SRBCs [347] and trinitrophenyl-lipopolysaccharide (TNP-LPS) [216] antigens by 3,3′,4,4′,5-pentaCB has been determined in C57BL/6 and DBA/2 mice and the TEF values for immunotoxicity varied between 0.08 and 0.77. In contrast, the TEF for 3,3′,4,4′,5-pentaCB-induced teratogenicity was approximately 0.07 to 0.04. Several studies have reported the induction effects of 3,3′,4,4′,5-pentaCB in chick embryos and chick embryo hepatocytes [85, 99, 589]; the TEFs varied from 0.1 to 0.017 and this range was lower than the corresponding induction-derived TEFs (0.32 to 0.40) in rat hepatoma H4II-E cells. Flodstrom and coworkers [172] estimated that the TEF for tumor promoter activity using the rat liver model was 0.1. With the exception of the low TEF observed for early life stage mortality in rainbow trout (*i.e.* 0.003), the TEFs for 3,3′,4,4′,5-pentaCB varied between 0.77 to 0.015 and the mean value for the TEFs summarized in Table 15 was 0.19 $\pm$ 0.22. However, based on the tumor promotion- and teratogenicity-derived TEFs, the value of 0.1 proposed by Safe [450] represents a reasonable TEF for 3,3′,4,4′,5-pentaCB.

The biochemical and toxic potencies and the derived TEF values for 3,3′,4,4′-tetraCB and 3,3′,4,4′,5,5′-hexaCB are summarized in Tables 14 and 15 and the range of experimentally-derived TEF values varied from 7.0×10^{-6} to 0.13 and 5.9×10^{-4} to 1.1, respectively. These variations were not totally unexpected for 3,3′,4,4′-tetraCB since this congener is rapidly metabolized in rats and many of the lowest TEFs were observed in this species [321]. In contrast, the TEF values for inhibition of the splenic PFC response to SRBCs

in C57BL/6 mice [347] were considerably higher (0.13 to 0.03) than TEFs derived from 14-day studies in the rat. Sargent and coworkers [467] also compared the tumor promoting potencies of 3,3′,4,4′-tetraCB and TCDD in the rat liver model and the TEF for this response was 0.029. The mean of the 14 TEFs in Table 15 and the 0.29 value for tumor promotion is 0.018 ± 0.034. Several of the 3,3′,4,4′-tetraCB-induced responses summarized in Table 14 were not used in these calculations due to the lack of data for TCDD. However, TEFs can be estimated for both 3,3′,4,4′-tetraCB and 3,3′,4,4′,5,5′-hexaCB by calculating the ED_{50} (3,3′,4,4′,5-pentaCB)/ED_{50} (3,3′,4,4′-tetraCB) ratios and multiplying this ratio by 0.1 (*i.e.* the TEF for 3,3′,4,4′,5-pentaCB). This calculation gives the following estimated TEFs for 3,3′,4,4′-tetraCB: 0.036 (LD_{50} - chick embryos); 0.0055 (EROD induction - chick embryos); 0.009 (inhibition of lymphoid development - chick embryos); 0.008 (inhibition of bursal lymphoid development - chick embryos). The mean of these four TEFs was 0.014; the combined mean for all the responses was 0.017 ± 0.030. Thus, based on the experimental data, a reasonable TEF value for 3,3′,4,4′-tetraCB would be 0.02 and this is higher than the 0.01 value proposed by Safe [450].

A similar approach can be taken for calculating the mean TEF for 3,3′,4,4′,5,5′-hexaCB based on the data summarized in Table 14. A TEF of 0.13 is a mean of 14 responses and this value decreases to 0.053 ± 0.089 if the unusually high immunotoxic TEF (1.1) is deleted from this calculation. In addition, estimation of TEFs for 3,3′,4,4′,5,5′-hexaCB relative to 3,3′,4,4′,5-pentaCB as noted above gave values of 0.0018 (LD_{50} - chick embryos), 0.0067 (EROD induction - chick embryos), 0.0012 (inhibition of lymphoid development - chick embryos), 0.0013 (inhibition of bursal lymphoid development - chick embryos). The mean TEF for these responses was 0.0012. Thus, the TEFs for 3,3′,4,4′,5,5′-

hexaCB range from 0.00059 to 1.1; Safe [450] assigned a TEF of 0.05 which is lower than the average of the responses noted in Tables 14 and 15 but higher than the 0.0012 values obtained for the effects in chick embryos. The assignment of a final TEF value for 3,3′,4,4′,5,5′-hexaCB should await the results of further studies; however, the proposed TEF [450] of 0.05 may be useful on an interim basis.

The relative potencies and TEFs for several monoortho coplanar PCBs are summarized in Table 16. For risk management of this structural class of PCBs, TEFs should be determined for the major congeners present in the commercial mixtures and environmental samples, namely, 2,3,3′,4,4′-pentaCB, 2,3′,4,4′,5-pentaCB and 2,3,3′,4,4′,5-hexaCB. Safe [450] proposed a TEF of 0.001 for all the monoortho coplanar PCBs; however, this value may be too high based on the results given in Table 16. Mean TEFs of 0.00098 $\pm$ 0.002, 0.000088 $\pm$ 0.000096 and 0.00040 $\pm$ 0.00043 were observed for 2,3,3′,4,4′-pentaCB (10 responses), 2,3′,4,4′,5-pentaCB (11 responses) and 2,3,3′,4,4′,5,-hexaCB (14 responses), respectively. Based on these data, the following interim TEFs are proposed for the monoortho coplanar PCBs: 0.001, 0.0001 and 0.0004 for the 2,3,3′,4,4′-pentaCB, 2,3′,4,4′,5-pentaCB and 2,3,3′,4,4′,5-hexaCB congeners, respectively (Table 17). In addition, the mean TEFs for 2,3,3′,4,4′,5′-hexaCB, 2′,3,4,4′,5-pentaCB and 2,3,4,4′,5-pentaCB were 0.00029, 0.00005 and 0.00019, respectively, and the suggested TEFs for these compounds are 0.0003, 0.00005 and 0.0002, respectively.

Recent studies have reported the relative induction potencies of the coplanar PCBs, 2,3,3′,4,4′-pentaCB, 2,3,3′,4,4′,5-hexaCB and 2,3,3′,4,4′,5′-hexaCB, administered 5 days per week by gavage to female B6C3F1 mice for 4 weeks. The relative induction potencies of these congeners were estimated by comparing their induced EROD (P4501A1) and

acetanilide-4-hydroxylase (P4501A2) activities to that observed for TCDD. The estimated TEFs were < 0.1 (3,3',4,4',5-pentaCB), < 0.00001 (3,3',4,4'-tetraCB), < 0.05 (3,3',4,4',5,5'-hexaCB), < 0.00005 (2,3,3',4,4'-pentaCB), < 0.001 (2,3,3',4,4',5'-hexaCB), and < 0.0005 (2,3,3',4,4',5-hexaCB). Some of these estimated TEFs are higher and others lower than the values proposed in Table 17. However, the induction-derived TEFs in the female B6C3F1 mice were consistent with the induction-derived TEFs obtained from single dose experiments in male Wistar rats [321].

(c) Application of TEFs Derived for PCBs

TEFs for PCDDs/PCDFs have been extensively used to determine TEQs in industrial, commercial and environmental mixtures of these compounds. Tanabe and coworkers [268-271, 529-535] were the first to develop analytical techniques to quantitate coplanar PCBs in various mixtures and they initially determined PCB-derived TEQs utilizing TEFs derived from the relative potencies of PCB congener-induced AHH and EROD activities in rat hepatoma H4II-E cells [469]. Their results showed that the TEQs for PCBs in most extracts from environmental samples or human tissues exceeded the TEQs calculated for the PCDDs/PCDFs in these same extracts. The results in Table 18 summarize the calculation of TEQ values in human adipose tissue samples based on the TEF values and the concentrations of individual PCDDs, PCDFs and PCBs present in this sample. The data indicate that the TEQs for the PCB fraction are higher than those for the combined PCDDs/PCDFs and comparable results have been observed in other studies [30, 148, 349, 537].

(d) Validation and Limitations of the TEF Approach

The potential interactions of different structural classes of PCB congeners may have important implications for the risk assessment of PCBs, PCDDs and PCDFs. Previous studies have demonstrated that Aroclor 1254 and other PCB congeners inhibit TCDD-induced enzyme induction, teratogenicity and immunotoxicity in C57BL/6 mice [50, 71, 139, 140, 208] and it is conceivable that for PCB mixtures the interactions would also decrease coplanar PCB-induced toxicity. These potential inhibitory interactions between different structural classes of PCBs would result in overestimation of the toxicity of PCB mixtures using the TEF approach. Davis and Safe [139] reported the effects of various Aroclors on the inhibition of the splenic PFC response to SRBC in C57BL/6 mice. This effect is one of the most sensitive indicators of exposure to Ah receptor agonists. The concentrations of coplanar and monoortho coplanar PCBs in these mixtures have been reported and are summarized in Table 19. Unfortunately, the immunotoxicity-derived TEFs are available only for 3,3',4,4',5-pentaCB (0.45), 3,3',4,4'-tetraCB (0.13), 3,3',4,4',5,5'-hexaCB (1.1) and 2,3,3',4,4',5-hexaCB (0.0011) (see Tables 15 and 16); however, these values can be used to estimate the TEQs for these four congeners in Aroclors 1016, 1242, 1254 and 1260 (note: the analysis of the coplanar and monoortho coplanar PCBs has been determined [270, 480]. The TEQs for these Aroclors can be calculated from the immunotoxicity-derived TEFs and the concentrations of the individual PCBs in these mixtures (*i.e.* $TEQ = \Sigma [PCB_i \times TEF_i]_a$). The results in Table 20 summarize the calculated TEQs and ED_{50} values for the immunotoxicity of the commercial PCBs using TEQs only derived from only four of the coplanar and monoortho coplanar PCBs. The calculated ED_{50}s are maximum values since the contributions from Ah receptor agonists other than the compounds noted above have not been included in the calculation. In all cases, the calculated ED_{50} values are significantly lower than the observed

ED_{50} values and the ratios of ED_{50} (observed)/ED_{50} (calculated) were 7.1, 22.5, 364 and ∞ for Aroclors 1260, 1254, 1242 and 1016. These values represent the fold-overestimation of PCB-induced immunotoxicity in C57BL/6 mice if the TEF approach is used. The data suggest that there are non-additive (antagonistic) interactions between the PCB congeners in these mixtures and this is consistent with the results of comparable antagonistic interactions between PCBs and TCDD [139, 140].

Recent studies in this laboratory have investigated the dose-response induction of hepatic microsomal AHH and EROD activities by Aroclor 1232, 1242, 1248, 1254 and 1260 in male Wistar rats and the ED_{50} values were 137, 84, 51, 92 and 343 mg/kg (for AHH induction) and 678, 346, 251, 137, 442 mg/kg (for EROD induction), respectively [218]. Since the induction-derived TEF values for the coplanar and monoortho coplanar PCB congeners in rats have been determined (Tables 15 and 16) and their concentrations in Aroclors 1242, 1254, 1260 are also known (Table 19) then the TEQ values can be readily calculated (Table 21). The results show that with one exception there was less than a 2-fold difference between the observed versus calculated ED_{50} values; these data suggest that for AHH and EROD induction in the rat by the commercial PCBs, the interactive effects were minimal. Using a similar approach, it has been shown that for the induction of AHH and EROD activity by PCB mixtures in rat hepatoma H4II-E there were also minimal interactive effects [270, 470]. It has previously been reported that there was a linear correlation between the -logEC_{50} (*in vitro* induction) versus the -logED_{50} (*in vivo* responses) in rat hepatoma cells and rats, respectively [450,456]; this would indicate that there are minimal non-additive interactions of PCBs for Ah receptor-mediated responses in rats such as thymic atrophy and body weight loss. Thus, the TEF approach is useful for estimating "TCDD-like" activity in rats and this

contrasts with the results obtained for immunotoxicity in mice in which the TEF approach significantly overestimate the immunotoxicity of PCB mixtures. The value of TEFs for risk management is dependent on minimal non-additive interactions among the PCBs, PCDDs and PCDFs. The results obtained in mice and rats for PCB mixtures illustrate that there are significant species and possibly response-specific differences in the non-additive antagonist interactions between PCBs and other Ah receptor agonists. Analysis of the data in rats supports the TEF approach for several responses (AHH and EROD induction, body weight loss and thymic atrophy); however, it is possible that there may be response-specific differences within the same animal species.

Geisy, Tillitt and coworkers have utilized both *in vitro* and *in vivo* studies to investigate the role of "TCDD-like" PCBs, PCDDs and PCDFs as possible etiologic agents in wildlife toxicity [545, 546, 580, 581]. Tillitt and coworkers [545] extracted double-breasted cormorant eggs and determined their TEQ values for PCBs in these extracts using the rat hepatoma H4II-E cells as a bioassay. This assay provides TEQ values for mixtures and the results showed that there were minimal (non-additive) interactive effects as noted above [470]. In this study, their was a linear correlation between the PCB-TEQs in specific colonies and their reproductive success. These results suggest that this response may be Ah receptor mediated and that the "TCDD-like" PCB congeners may be responsible for the observed reproductive toxicity. However, in a second study [581] the PCB-TEQs in extracts from Lake Michigan chinook salmon were determined by high resolution chemical analysis and there was not a correlation between the calculated PCB-TEQs and the mortality of eggs and fry from the different clutches. Most of the calculated TEQs were significantly higher than the observed total rearing mortality and this may be analogous to the immunotoxicity in mice in which

the calculated TEQs overestimate toxicity due to non-additive (antagonistic) interactions. It is also possible that the rearing mortality response is not Ah receptor-mediated and is due to other classes of toxic chemicals.

Thus, the TEF approach can be used to calculate the TEQs of PCBs, PCDDs and PCDFs in extracts of environmental samples and in commercial mixtures. However, the results of laboratory animal and wildlife studies suggests that the predictive value of TEQs for PCBs, PCDDs and PCDFs may be both species- and response-dependent since both additive and non-additive (antagonistic) interactions have been observed. Therefore these data would suggest that TEFs for PCBs and other halogenated aromatics such as PCDDs and PCDFs should be used in risk management of these contaminants with considerable care.

(e) Application of TEFs for Carcinogenic Potencies

The development of regulations for PCBs and many other environmental toxins often utilizes data from long term rodent carcinogenesis bioassays. Many of the current regulations for PCBs are derived from the carcinogenicity of Aroclor 1260 [392] in which it is assumed to be a complete carcinogen. However, since most studies indicate that the higher chlorinated PCBs are non-genotoxic [449, 493] and do not form persistent DNA adducts *in vivo* [383], it is more likely that these mixtures act as cancer promoters as summarized in Table 5. The relative potencies of PCB mixtures as carcinogens or promoters have not been extensively investigated; however, the results suggest that the most active PCBs are the higher chlorinated mixtures such as Aroclor 1260 or Clophen A60 [471]. However, based on the concentrations of the coplanar and monoortho coplanar PCBs in the commercial

Aroclors and Clophens, the TEQs for Aroclor 1260 and Clophen A60 are lower than observed for low chlorinated mixtures such as Aroclors 1242, 1248 and 1254 [270, 560]. The carcinogenicity of Aroclor 1260 and TCDD has previously been determined in female Sprague Dawley rats and the results in Table 22 compare the effects of dietary concentrations of TCDD and Aroclor 1260 on the development of hepatocellular carcinomas. The data illustrate a lack of correspondence between the calculated TEQ values and cancer potency for Aroclor 1260 and TCDD. The low TEQ value for Aroclor 1260 suggests that only a fraction of the carcinogenicity of this mixture is due to the "TCDD-like" congeners and that other structural classes of PCBs are major contributors to this response. As noted in section V(b), PB-type PCBs are also tumor promoters; these congeners predominate in higher chlorinated PCB mixtures and may play an important role in the carcinogenicity of Aroclor 1260. This is supported by the results of recent studies [218] which showed that Aroclor 1260 was considerably more active than Aroclors 1232, 1242, 1248 and 1254 as inducers of CYP2B1-dependent activity in rats and this also corresponded to the potencies of these mixtures as rodent carcinogens. The use of TEFs and TEQs for risk management is limited only to Ah receptor-mediated responses. Therefore, since the data summarized in Table 22 suggest that development of PCB-induced hepatocellular carcinomas in female Sprague-Dawley rats may primarily be an Ah receptor-independent response, the TEF/TEQ approach may not be appropriate for risk management based on this endpoint. The higher chlorinated PCBs such as Aroclor 1254 and Aroclor 1260 are poorly metabolized and it is likely that the carcinogenicity of these mixtures is associated with their activity as tumor promoters. Thus, cancer-based risk assessment of PCB mixtures requires additional data on the tumor-promoting potencies of the major congeners present

in these mixtures and environmental samples.

VII. SUMMARY

1. Commercial PCBs and environmental extracts contain complex mixtures of isomers and congeners which can be identified and quantitated by chromatographic procedures. The environmental PCB residues do not resemble the commercial PCBs and congener-specific risk assessment of these mixtures is warranted.

2. The effects of occupational exposure to relatively high levels of PCBs resulted in a number of adverse responses which appear to be reversible. Epidemiological surveys of several occupationally-exposed groups did not reveal any increased incidence of specific cancers in all studies. Some reports showed increased incidence of cancer at different sites whereas in other studies no increases were observed. The major adverse human health effects associated with environmental exposure to PCBs may be neurodevelopmental deficits associated with *in utero* exposures. The role of PCBs or other as yet unidentified chemicals as etiologic agents for this response requires further investigation.

3. Commercial PCB mixtures elicit a broad spectrum of biochemical and toxic responses and most of these effects are similar to those caused by TCDD and other Ah receptor agonists. Two major structural classes of PCBs, namely the coplanar and monoortho coplanar PCBs exhibit Ah receptor agonist activity and appear to responsible for many of the PCB mixture-induced responses.

4. Other structural classes of PCB also elicit biochemical and toxic responses. PCBs which exhibit "PB-like" activity are also tumor promoters and these compounds

comprise a high percentage of higher chlorinated PCB mixtures. The results of most studies suggest that PCBs are not genotoxic but act as tumor promoters in several bioassays. Thus congener-specific regulation of PCBs based on their tumor-promoting activity must take into account the contributions of the "PB-like" congeners. This is an area of PCB risk assessment which requires further study.

5. Other structural classes of PCBs and PCB metabolites also exhibit diverse activities including neurotoxicity, estrogenicity, endogenous protein binding activities and inhibition of oxidative phosphorylation. The toxicologic role of these compounds in PCB-induced toxicity has not been determined.

6. Several studies have demonstrated that PCB mixtures and individual congeners inhibited TCDD-induced responses and these studies suggests that in some animal models and for some responses non-additive (antagonistic) interactions may be important.

7. TEFs for the coplanar and monoortho coplanar PCBs have been estimated: 3,3′,4,4′,5-pentaCB, 0.1; 3,3′,4,4′,5,5′-hexaCB, 0.05; 3,3′,4,4′-tetraCB, 0.02; 2,3,3′,4,4′-pentaCB, 0.001; 2,3′,4,4′,5-pentaCB, 0.0001; 2,3,3′,4,4′,5-hexaCB, 0.0003. These values can be used to calculate TEQs only for Ah receptor-mediated responses.

8. The calculated TEQs for various environmentally-derived extracts tended to be higher for the PCBs than the calculated TEQs for the PCDDs plus PCDFs.

9. The TEF approach for the risk assessment of PCBs must be used with considerable caution. The results of laboratory animal and wildlife studies suggests that the predictive value of TEQs for PCBs, PCDDs and PCDFs may be both species- and

response-dependent since both additive and non-additive (antagonistic) interactions have been observed with PCB mixtures. Moreover, analysis of the rodent carcinogenicity data for Aroclor 1260 using the TEF approach suggests that this response is primarily Ah receptor-independent. Thus, risk assessment of PCB mixtures which uses cancer as an endpoint requires more quantitative information on the PCBs congeners which contribute to the tumor promoter activity of these mixtures.

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Table 1. Quantitative and qualitative analysis of PCBs on Aroclor 1260 and extracts from human milk samples (Safe, 1985b; Duarte-Davidson, 1991).

Congener Name[a]	% in Aroclor 1260	% of Total PCBs in Human Milk[b]		Congener Name[a]	% in Aroclor 1260	% of Total PCBs in Human Milk[b]	
PCB-015	- - -	- - -	9.4	PCB-118	0.49	6.5	4.2
PCB-018	0.12	- - -	4.3	PCB-134	0.35	- - -	
PCB-017	0.05	- - -		PCB-114	- - -	0.33	
PCB-024	0.01	- - -		PCB-131	0.07	- - -	
PCB-016	0.04	- - -		PCB-122	0.12	0.53	
PCB-029	0.02	- - -		PCB-146	1.3	1.9	
PCB-026	0.02	- - -		PCB-153	9.6	12.0	12.7
PCB-028	0.04	8.8	4.7	PCB-141	2.5	0.29	
PCB-021	0.01	- - -		PCB-176	0.33	- - -	
PCB-033	0.09	2.2		PCB-137	0.22	0.87	
PCB-053	0.04	- - -		PCB-130	- - -	0.59	
PCB-022	0.01	0.65		PCB-138	6.5	10.0	10.1
PCB-045	0.07	- - -		PCB-158	0.70	0.55	
PCB-046	0.02	0.25		PCB-129	0.20	- - -	
PCB-052	0.25	1.9	3.9	PCB-178	1.2	- - -	
PCB-043	0.02	- - -		PCB-175	0.49	- - -	
PCB-049	0.06	0.66		PCB-187	4.5	1.5	6.3
PCB-048	0.29	0.37		PCB-183	2.3	1.4	1.2
PCB-044	0.11	0.78	1.8	PCB-128	0.47	0.33	0.8
PCB-037	0.04	2.9		PCB-167	0.16	0.85	
PCB-042	0.04	- - -		PCB-185	4.1	0.11	
PCB-041	0.25	1.3		PCB-174	5.5	0.39	
PCB-040	0.03	- - -		PCB-177	1.9	0.61	
PCB-100	0.02	- - -		PCB-171+202	1.2	0.37	
PCB-074	0.03	11.0	3.7[c]	PCB-156	0.45	4.87	2.5[f]
PCB-070+076	0.15	0.61		PCB-173	0.06	- - -	
PCB-095	2.7	- - -		PCB-200	0.78	- - -	
PCB-091	0.07	- - -		PCB-157	- - -	0.47	
PCB-056+060	0.14	0.71		PCB-172	0.78	0.31	
PCB-084	0.65	- - -		PCB-180	9.1	5.3	11.1
PCB-101	2.5	0.97	2.2	PCB-193	0.47	0.19	
PCB-099	0.13	4.8	4.0	PCB-191	0.10	0.90	
PCB-119	- - -	0.08	1.9	PCB-199	0.33	- - -	
PCB-083	0.04	- - -		PCB-170	6.8	5.3	3.5
PCB-097	0.45	- - -		PCB-201	2.9	0.85	1.8
PCB-087	0.45	0.82		PCB-203	3.1	0.79	
PCB-085	0.13	- - -		PCB-196	2.5	0.18	
PCB-136	1.4	- - -		PCB-189	0.15	2.4	
PCB-110	1.7	1.0	1.3[d]	PCB-195	3.1	0.31	
PCB-154	0.02	- - -		PCB-207	0.080	- - -	
PCB-082	0.11	- - -		PCB-194	1.7	0.48	
PCB-151	2.5	0.59	0.9[e]	PCB-205	0.11	0.06	0.7[g]
PCB-144+135	1.5	0.51		PCB-206	0.85	0.24	
PCB-107	0.03	0.31		PCB-209	0.06	0.09	
PCB-149	7.4	- - -	1.8				

[a] Congener names adapted from Ballschmiter (1980).

[b] Human milk sample collected and extraced by Michigan Department of Public Health under Cooperative Agreement CR807192 with the Large Lakes Research Station, U.S. Environmental Protection Agency.

[c] 61/74 combined; [d] 77/110 combined; [e] 82/151 combined; [f] 156/202 combined; [g] 194/205 combined.

Table 2. Relative concentrations of coplanar PCBs in human milk and adipose tissue samples.

Samples	Congener and Concentration (ng/g)			Reference(s)
	3,3',4,4'-(77)[a]	3,3',4,4'5-(126)[a]	3,3',4,4',5,5'-(169)[a]	
Upstate New York (milk)	0.16 - 0.49	non-detectable	non-detectable	Hong, 1992
Ontario (adipose tissue)	non-detectable	0.124 - 0.303	0.113 - 0.198	Williams, 1991
Quebec (milk)	0.008	0.081	0.032	Dewailly, 1991
Japan (adipose tissue)	0.094 - 0.86	0.12 - 0.73	0.036 - 0.20	Kannan, 1989

Table 3. Effects of PCBs on occupationally-exposed workers.

Effects	References
Chloracne and related dermal lesions	Hara, 1985 Ouw, 1976 Fischbein, 1979 Maroni, 1981
Diverse hepatic responses including hepatomegaly, increased liver and serum enzymes and lipid, induction of drug-metabolizing enzymes	Hara, 1985 Ouw, 1976 Fischbein, 1979, 1983 Chase, 1982 Lawton, 1985 Steinberg, 1980 Alvares, 1977b Smith, 1982 Emmett, 1985
Decreases in pulmonary function	Warshaw, 1979
Decrease birth weight in offspring of occupationally-exposed mothers	Taylor, 1984, 1989
Eye irritation	Hara, 1985
No increased mortality	Brown, 1981, 1987
Variable effects on cancer formation	Gustavsson, 1986 Silberhorn, 1990 Bertazzi, 1987 Bahn, 1976, 1977 Davidorf, 1979 Zack, 1979

Table 4. Toxicity of commercial PCBs.

Response	PCB Mixture	Species	Reference
	Lethality		
LD_{50}, 1.14, 1.30 ml/kg (F, M) LD_{50}, 1.05, 1.15 g/kg (F, M)	Kanechlor 400 Kanechlor 300	Rat	Kimbrough, 1978
LD_{50}, 4.25 g/kg (M)	Aroclor 1242	Rat	Bruckner, 1973; Kimbrough, 1978
LD_{50}, 1.3-25 g/kg (M, F / age-dependent)	Aroclor 1254	Rat	Grant, 1974
LD_{50}, 0.358-10 g/kg (M, F)	Aroclors 1254 and 1260	Rat	Linder, 1974
LD_{50}, 4.0 g/kg (F) LD_{50}, 11.3 g/k/g (F)	Aroclor 1221 Aroclor 1260	Rat	Nelson, 1972
LD_{50}, 1.57-1.875 g/kg (F, M)	Kanechlor 400	Mouse	Kimbrough, 1978
LD_{50}, 0.8-1.2 g/kg	Aroclor 1254	Mouse	Lewin, 1972
LD_{50}, 2.0-3.17 g/kg LD_{50}, 1.26-2.0 g/kg LD_{50}, 0.79-1.27 g/kg LD_{50}, 0.79-1.27 g/kg LD_{50}, 1.26-2.0 g/kg LD_{50}, 1.26-3.16 g/kg LD_{50}, 2.5 g/kg	Aroclor 1221 Aroclor 1232 Aroclor 1242 Aroclor 1248 Aroclor 1260 Aroclor 1262 Aroclor 1268	Rabbit	Nelson, 1972
LD_{50}, 0.5-4.0 g/kg	Aroclors 1221, 1242 and 1254	Mink	Auerlich, 1977; Hornshaw, 1986
	Reproductive Toxicity		
Effect on fetal viability	Aroclor 1254	Rabbit	Villeneuve, 1971a,b
Fetal toxicity	Aroclor 1254	Monkey	Truelove, 1982
Severe reproductive failure	Aroclor 1242	Mink	Bleavins, 1980

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
Reproductive problems	Aroclors, 1016, 1221, 1242 and 1254	Mink	Auerlich, 1977
Fetal death and resorption	Aroclor 1254	Rabbit	Villeneuve, 1971a
Reduced litter size	Aroclors 1254 and 1260	Rat	Linder, 1974
Fetal death and reduced litter weight	Aroclor 1254	Rat	Spencer, 1982
Cleft palate	Kanechlor 500	Mouse	Watanabe, 1981
Fetal resorption	Aroclor 1254	Rat	Baker, 1977
Fetal resorption	Clophen A60	Mouse	Orberg, 1973
Abortions in chronically fed animals	Aroclor 1254	Monkey	Arnold, 1990
Reproduction failure	Clophen A50	Mink	Kihlstrom, 1992
Review of reproductive toxicity from animal studies			Golub, 1991
Effects on male fertility	Aroclor 1254	Rat	Sager, 1991
Delayed first vaginal opening and lower testis weights	Clophen A50	Guinea pig	Lundkvist, 1990
Decrease in reproductive efficiency	Aroclor 1254	Mourning dove	Koval, 1987
Decreased reproductive ability and smaller reproductive organs	Aroclor 1254	Mouse	Linzey, 1988
Decreased weight of seminal vesicles	Clophen A60	Mouse	Orberg, 1973
Resorptions, abortions and lower birth weights	Aroclor 1248	Monkey	Barsotti, 1976
Multiple testicular abnormalities	Aroclor 1254	Fish	Sangalang, 1981
Impaired ovaulation	Clophen A30	Monkey	Müller, 1978
Decreased reproductive success	Aroclor 1254	Ring dove	McArthur, 1983
Decreased egg hatchability	Aroclors 1232, 1242, 1248 and 1254	Hen	Lillie, 1974

Table 4. cont'd.

Response		PCB Mixture	Species	Reference
Repressed sex accessory glands		Aroclor 1254	Rat	Gray, 1992
		Inhibition of Body Weight Gain or Body Weight Loss		
Short term feeding	(10 d)	Aroclor 1254	Rat	Spencer, 1982
	(14-21 d)			Carter, 1983
	(14-30 d)			Kling, 1978
	(2-5 wk)			Garthoff, 1977
	(6 wk)	Clophen A50		Baumann, 1983
	(6 wk)	Aroclor 1248 > 1254 > 1260		Allen, 1973
	(4 wk)	Aroclor 1242		Bruckner, 1974b
	(38 d)	Phenoclor DP6, Clophen A60, and Aroclor 1260	Rabbit	Vos, 1971
	(2-3 mo)	Aroclor 1248	Monkey	Allen, 1974
Chronic dietary feeding	(2 y)	Aroclor 1254	Rat	Morgan, 1981
	(21 mo)	Aroclor 1260		Kimbrough, 1975
	(1 y)	Kanechlors 300, 400 and 500		Ito, 1974
	(20 wk)	Aroclor 1254		Zinkl, 1977
	(~ 40 mo)	Aroclor 1248	Monkey	Barsotti, 1975
	(up to 245 d)	Aroclor 1242		Becker, 1979
	(20 wk)	Kanechlor 400		Hori, 1982
	(20 wk)	Aroclor 1254	Mink	Hornshaw, 1986; Auerlich, 1986
Acute, subchronic and chronic studies via various routes of exposure		Aroclor 1254	Rat	Spencer, 1982; Carter, 1983; Garthoff, 1977; Baumann, 1983; Smialowicz, 1989
		Aroclor 1248		Allen, 1973
		Aroclor 1242		Bruckner, 1974b
		Aroclor 1248	Monkey	Allen, 1975

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
	Porphyria		
Elevated urinary coproporphyrins	Aroclor 1242	Rat	Bruckner, 1974a,b
Hepatic porphyrin fluorescence	Aroclor 1254	Rat	Zinkl, 1977
Increased kidney porphyrins	Aroclor 1242	Quail, rats	Miranda, 1992
Increased liver and small intestinal porphyrins	Aroclor 1242	Quail	Miranda, 1987
Increased liver porphyrins and increased ALAS synthesis	Aroclors 1232, 1248, 1254 and 1260	Rat	Grote, 1975a; Schmoldt, 1977
Increased liver porphyrins	Aroclors 1242 and 1016	Rat	Goldstein, 1975
	Immunotoxicity		
Increased mortality to microbial infection	Aroclors 1042 and 1016	Mouse	Loose, 1978a,b; Thomas, 1978
Decrease formation of splenic PFCs in response to SRBCs	Aroclor 1242	Mouse	Loose, 1978a
Altered graft versus host response	Aroclor 1016	Mouse	Silkworth, 1978
Reduction in splenic and thymic gamma globulin	Aroclor 1254	Rabbit	Street, 1975
Reduction in tetanus antitoxin-producing cells	Clophen A60 and Aroclor 1260	Guinea pig	Vos, 1973
Reduction in gamma globulin producing cells	Aroclor 1260	Guinea pig	Vos, 1972
Reduction in antibody production to SRBCs	Aroclor 1254 Kanechlor 400 Aroclor 1254	Monkey	Truelove, 1982 Hori, 1982 Tryphonas, 1989
Modulation of several non-sepcific and specific immune parameters	Aroclor 1254	Monkey	Tryphonas, 1991a,b
Reduction in antibody production to SRBCs	Aroclors 1232, 1016, 1242, 1248, 1254 and 1260	Mouse	Davis, 1989; Lubet, 1986

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
Modulation of T-cell function	Kanechlor 500	Mouse	Takagi, 1987
Reduced NK cell activity	Aroclor 1254	Rat	Smialowicz, 1989; Exon, 1985
	<u>Hepatoxicity</u>		
Increased liver weight and/or hepatomegaly	Several Aroclors	Rat	Sager, 1983; Carter, 1983; Grant, 1974; Allen, 1979; Garthoff, 1977; Baumann, 1983; Kasza, 1978a,b; Parkinson, 1983; Hinton, 1978; Kimbrough, 1972, 1975; Jonsson, 1981; Smialowicz, 1989
	Phenoclor DP6	Rat	Narbonne, 1979
	Aroclor 1254	Mouse	Sanders, 1974
	Phenoclor DP6, Clophen A60 and Aroclor 1260	Mouse	Tanimura, 1980
	Phenoclor DP6, Clophen A60 and Aroclor 1260	Rabbit	Vos, 1971
	Aroclors 1221, 1242 and 1254	Rabbit	Koller, 1973; Street, 1975
	Clophen A60, Aroclor 1260	Guinea pig	Vos, 1972, 1973
	Kanechlors 300, 400 and 500	Rat	Ito, 1974
	Aroclor 1248, 1254	Monkey	Tryphonas, 1986a,b; Allen, 1974, 1975, 1976
	Kanechlors 300, 400 and 500	Mouse	Ito, 1973
	Aroclors 1221, 1242 and 1254	Mouse	Koller, 1977; Kimbrough, 1974
	Kanechlor 400	Monkey	Hori, 1982

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
	Clophen A50	Mink	Kihlstrom, 1992
Diverse indices of fatty liver	Clophen A50	Rat	Chu, 1977; Baumann, 1983
	Aroclors 1242, 1248, 1254, and 1260	Rat	Allen, 1973; Jonsson, 1981; Kasza, 1978b; Grant, 1974; Kimbrough, 1972
	Aroclor 1248	Monkey	Allen, 1974, 1975
	Kanechlor 400	Rat	Kimura, 1973
	Endocrine Effects		
Increased thyroid activity	Aroclor 1254	Rat	Bastomsky, 1974
Enlarged thyroid, decreased serum T_4 and altered cellular morphology	Aroclor 1254	Rat	Collins, 1977, 1980a,b
Enlarged thyroid	Aroclor 1254	Rat	Kasza, 1978a,b
Decreased serum progesterone	Aroclor 1248	Monkey	Barsotti, 1975
Thyroid atrophy	Aroclor 1254	Guillemot	Jeffries, 1976
Decreased T_3 synthesis	Aroclors 1254 and 1242	Rat	Sepkovic, 1984
Hypothyroidism and decreased serum T_3 and/or T_4 levels	Aroclor 1254	Rat	Byrne, 1987; Meserve, 1992; Gray, 1992
Increased length of estrus	Clophen A60	Mouse	Orberg, 1973
Elevated serum corticosterone	Aroclor 1254	Mouse	Sanders, 1974
No effects on serum hydrocortisone levels	Aroclor 1254	Monkey	Loo, 1989
Suppression of serum adrenal cortex hormones	Aroclors 1254, 1242 and 1016	Rat	Byrne, 1988
Low estrogen levels	Clophen A30	Monkey	Muller, 1978

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
Multiple steroid and thyroid hormone abnormalities	Aroclor 1254	Ring dove	McArthur, 1983
Estrogenic activity	Aroclor 1221 and other PCB mixtures	Rat	Gellert, 1978; Ecobichon, 1974
	Neurotoxicity		
Developmental neurotoxicity (review)			Tilson, 1990
Neurobehavioral toxicity (review)		Monkey	Schantz, 1991
Decreased brain catecholamines	Aroclors 1254 and 1260	Rat	Seegal, 1986a,b
Increased locomoter activity and retarded learning activity	Aroclor 1248	Monkey	Bowman, 1978, 1981
Delayed spatial alternation deficits	Aroclor 1248	Monkey	Levin, 1988
Decreased brain catecholamine levels	Aroclors 1016 and 1260	Macaque	Seegal, 1991
Central nervous system toxicity	Aroclor 1254	Mouse	Albrecht, 1987
Increased behavioral toxicity due to prenatal exposure	Clophen A30	Rat	Lilienthal, 1990, 1991
	Fenclor 42	Rat	Pantaleoni, 1988
Imparied discrimination reversal learning	Aroclor 1248	Monkey	Schantz, 1989
Altered serotonin levels in the brain	Aroclors 1254 and 1260	Rat	Seegal, 1986a
Impaired neurobehavioral activity after perinatal exposure	Aroclor 1254	Rat	Overmann, 1987
	Thymic Atrophy and Thymus Toxicity		
Thymic atrophy and thymus toxicity	Clophen A60 and Aroclor 1260	Guinea pig	Vos, 1973

Table 4. cont'd.

Response	PCB Mixture	Species	Reference
	Aroclor 1254	Yorkshire pig	Miniats, 1978
	Aroclor 1254	Rat	Smialowicz, 1989
	Dermal Toxicity		
Alopecia, edema, distinctive hair follicles and hair loss	Aroclor 1248	Monkey	Allen, 1974b, 1975; Barsotti, 1975, 1976
Hyperkeratosis and other lesions on the ear	Aroclor 1254	Rat	Zinkl, 1977
Hair loss and other skin lesions	Aroclor 1254	Monkey	Becker, 1979
Lost fingernails	Aroclor 1254	Monkey	Truelove, 1982
Meibomian cysts, skin hyperkeratosis	Kanechlor 400	Monkey	Hori, 1982
Fingernail loss and exuberant nail beds	Aroclor 1254	Monkey	Tryphonas, 1986a,b
	Carcinogenicity		
Neoplastic nodules, hepatocellular carcinoma	Aroclor 1254 Aroclor 1260	Rat	Kimbrough, 1975 Norback, 1985
Neoplastic nodules, hepatocellular carcinoma, gastric adenocarcinoma and intestinal metaplasia	Aroclor 1254	Rat	Morgan, 1981; NCI, 1978; Ward, 1985
Adenofibrosis, neoplastic nodules	Aroclor 1260	Rat	Rao, 1988
Neoplastic nodules	Clophen A30 Kanechlor 400	Rat	Schaeffer, 1984 Kimura, 1973
Neoplastic nodules, hepatocellular carcinoma and/or adenofibrosis	Clophen A60 Kanechlor 400	Rat	Schaeffer, 1984 Ito, 1974
Neoplastic nodules, hepatocellular carcinoma	Kanechlor 500	Mouse	Ito, 1973

Table 5. PCB mixtures as promoters: formation of tumors or preneoplastic lesions.

Response	PCB Mixture	Species	Carcinogen	Reference
Increased incidence of hepatocellular carcinoma	Aroclor 1254	S-D rats	diethylnitrosamine	Preston, 1981
	Kanechlor 400	Donryu rats	3'-methyl-4-dimethyl- aminoazo-benzene	Kimura, 1976
	Kanechlor 500	Wistar rats	diethylnitrosamine	Nishizumi, 1976
	Kanechlor 500	dd mice	β-hexachlorocyclohexane isomers	Ito, 1973
Increased formation of neoplastic nodules (liver)	Kanechlor 500	F344 rats	2-acetylaminofluorene	Tatematsu, 1979
Increased incidence of skin tumors	Aroclor 1254	HRS/J hairless mice	*N'*-methyl-*N*-nitrosoguanidine	Poland, 1982b
Increased incidence of putative hepatic preneoplastic lesions	Aroclor 1254	S-D rats	diethylnitrosamine	Periera, 1982
	Phenoclor DP6	S-D rats	aflatoxin B1	Pelissier, 1992
	Clophen A30+A50	S-D rats	diethylnitrosamine	Oslerle, 1983, 1984 Deml, 1982
	Clophen A50	S-D rats	benzo[a]pyrene	Deml, 1983
	Clophen C	Chickens	diethylnitrosamine	Brunn, 1987
Increased incidence of lung tumors	Aroclor 1254	Swiss mice	*N*-nitrosodiethylamine	Beebe, 1991; Andersson, 1983, 1991

Table 6. PCB mixture-induced biochemical effects.

Responses	PCB Mixture	Species	Reference
	Induction of P450-Dependent Enzymes or Isozymes		
Induction of O- and N-dealkylase activity	Aroclors 1248, 1254 and 1260	Rat	Allen, 1973
	Aroclors 1016, 1221, 1232, 1242, 1248, 1254 and 1260		Ecobichon, 1975
	Aroclor 1242		Bruckner, 1974b
	Clophen A50		Parkki, 1977
	Aroclors 1248, 1254 and 1262		Allen, 1979
	Aroclor 1254		Beebe, 1991
Induced P450 levels	Aroclor 1254	Rat	Alvares, 1979; Hinton, 1978
	Clophen A50		Parkki, 1977
		Guinea pig	Brunstrom, 1982
Decreased barbituate sleeping times	Aroclor 1254	Mouse	Sanders, 1974
Induction of diverse hydroxylases	Aroclors 1016, 1221, 1232, 1242, 1248, 1254 and 1260	Rat	Ecobichon, 1975
	Aroclor 1242		Bruckner, 1974b
Induction of AHH activity	Clophen A50	Rat	Parkki, 1977
		Mink	Brunstrom, 1991
	Aroclor 1242	Quail	Miranda, 1992
	Aroclors 1016, 1232, 1242, 1248, 1254 and 1260	Rat	Harris, 1993
	Aroclor 1254		Lubet, 1991
	Other Biochemical Responses		
Increased ALA synthetase	Aroclor 1254	Rat	Alvares, 1979
	Aroclor 1242	Quail	Miranda, 1992

Table 6. cont'd.

Responses	PCB Mixture	Species	Reference
Decreased ALA dehydratase	Aroclor 1254	Rat	Alvares, 1979
Increased epoxide hydrolase	Clophen A50 Aroclor 1254	Rat	Parkki, 1977 Lubet, 1991
Increased glucuronosyl transferase	Clophen A50	Rat	Parkki, 1977
Induction of c-Ha-*ras*, c-*raf*, c-*yes*, c-*erbA* and c-*erbB* protooncogene mRNA levels	Clophen A50	Rat	Jenke, 1991
Increased serum lipids and HMG CoA reductase	Clophen A50	Rat	Jenke, 1985, 1988
Increased indices of hepatic lipoperoxidation		Rat	Dogra, 1988; Kamohara, 1984; Pelissier, 1992
Hypocholesterolemia	Aroclor 1248	Rat	Nagaoka, 1990
Increased fatty acid desaturation	Aroclor 1254	Rat, pigeon	Borlakoglu, 1990a
Modulation of plasma lipoproteins	Aroclor 1254	Chick	Griffin, 1991
Induction of lung pepsinogen isozymes	Kanechlor 400	Hamster	Imaida, 1991
Decreased uroporphyrinogen decarboxylase	Aroclor 1242 Aroclor 1254	Quail Rat	Miranda, 1992 Smith, 1990
Increased aldehyde hydrogenase	Aroclor 1254	Rat	Lubet, 1991
Inhibition of citrate cleavage enzyme	Aroclor 1254	Rat	Kling, 1981
Binding to the cytosolic Ah receptor	Aroclor 1254	Rat	Bandiera, 1982
	Others		
Increased serum cholesterol and lipids	Clophen A50 Aroclors 1248, 1254 and 1262	Rat	Baumann, 1983 Allen, 1976
Increased serum SGPT, SGOT	Clophen A50	Rat	Baumann, 1983
Decreased hepatic vitamin A	Clophen A50	Mink	Brunstrom, 1991, 1992b

Table 7. Biochemical and toxic responses elicited by the coplanar PCBs, 3,3',4,4'-tetraCB, 3,3',4,4',5-pentaCB and 3,3',4,4',5,5'-hexaCB.

Response	3,3',4,4'-TetraCB	3,3',4,4',5-PentaCB	3,3',4,4',5,5'-HexaCB
Induction of *CYP1A1* and *CYP1A2* gene expression and associated monooxygenase enzyme activities	Goldstein, 1977 Yoshimura, 1978, 1979 Poland, 1977 Parkinson, 1980, 1983 Sawyer, 1982 Brunstrom, 1986 Rodman, 1989 Gooch, 1989 Monosson, 1991 Stegeman, 1991 Tillitt, 1991 Janz, 1991 Gillette, 1987 Sinclair, 1990 Leece, 1985 Nikolaidis, 1988 Brunstrom, 1991 De Vito, 1993	Yoshimura, 1978, 1979 Ozawa, 1979a, 1979b Parkinson, 1980, 1983 Yoshihara, 1979, 1982, 1983 Sawyer, 1982 Rodman, 1989 Elliott, 1991 Nagata, 1985 Tillitt, 1991 Sinclair, 1990 Leece, 1985 Brunstrom, 1991 Van Birgelen, 1992 De Vito, 1993	Goldstein, 1977b, 1981, 1982 Yoshimura, 1978, 1979 Poland, 1977 James, 1981 Parkinson, 1980, 1983 Sawyer, 1982 Kohli, 1980, 1981b Miranda, 1990 Rodman, 1989 Hardwick, 1985 Luster, 1983 Sundheimer, 1983 Tillitt, 1991 Brunstrom, 1990 Sinclair, 1990 Leece, 1985 Brunstrom, 1991 De Vito, 1993
Suppression of constitutive *CYP2C11* gene expression			Yeowell, 1987, 1989
Induction of CYP4A1-dependent activities	Borlakoglu, 1992	Huang, 1991	
Induction of glutathione S-tranferases		Aoki, 1992	Kohli, 1979 Aoki, 1992
Induction of epoxide hydrolase	Ahotupa, 1981		
Binding to the rat cytosolic Ah receptor	Bandiera, 1982	Bandiera, 1982	Bandiera, 1982

Table 7. cont'd.

Response	3,3',4,4'-TetraCB	3,3',4,4',5-PentaCB	3,3',4,4',5,5'-HexaCB
Inhibition of uroporphyrinogen decarboxylase activity	Lambrecht, 1990 Sinclair, 1984, 1986 Kawanishi, 1981, 1983 Swain, 1983		Kawanishi, 1981, 1983
Induction of ALAS activity	Kawanishi, 1983		Kawanishi, 1983
Hypothyroidism and decreased serum thyroid hormone levels	Spear, 1985 Van den Berg, 1988		
Decreased hepatic or plasma vitamin A levels	Chen, 1992a Brower, 1984, 1985, 1988 Azais, 1986, 1987 Narbonne, 1990 Spear, 1986 Powers, 1987	Chen, 1992a	
Thymic atrophy and toxicity to thymic cells	Yoshimura, 1979 Leece, 1985 Nikolaidis, 1988a,b Andersson, 1991	Yoshimura, 1979 Leece, 1985 Andersson, 1991	Biocca, 1981 Yoshimura, 1979 Leece, 1985 McKinney, 1976 Andersson, 1991 Kohli, 1979, 1981
Hepatotoxicity, including hepatomegaly, fatty liver	Yoshimura, 1979	Yoshimura, 1979	Biocca, 1981 Kohli, 1979a, 1981a Yoshimura, 1979
Reproductive and/or developmental toxicity	Spear, 1989 Brunstrom, 1983, 1991	Mayura, 1993 Brunstrom, 1990a,b, 1991 Marks, 1989	Marks, 1981 Brunstrom, 1991
Neurobehavioural and neurotoxic responses	Tilson, 1979 Eriksson, 1988, 1991 Chou, 1979		
Dermal toxicity	McNulty, 1980		

Table 7. cont'd.

Response	3,3',4,4'-TetraCB	3,3',4,4',5-PentaCB	3,3',4,4',5,5'-HexaCB
Body weight loss	Leece, 1985	Leece, 1985	Leece, 1985 Biocca, 1981
Porphyria (accumulation of octa- and heptacarboxyporphyrins)	Miranda, 1987 Sinclair, 1986, 1990 Sassa, 1986 Kawanishi, 1981	Sinclair, 1990	Goldstein, 1976 Biocca, 1981 Sinclair, 1986, 1990 Sassa, 1986 Kawanishi, 1981
Immunosuppressive activities	Silkworth, 1982, 1984 Mayura, 1993 Clark 1983	Mayura, 1993	Kerkvliet, 1988a, 1988b Mayura, 1993
Tumor promoter activity	Buchmann, 1986, 1991 Sargent, 1991, 1992 Luebeck, 1991	Flodstrom, 1992	
Embryolethality (fish)	Walker, 1991	Walker, 1991	

Table 8. Biochemical and toxic responses elicited by the monoortho coplanar PCBs.

Response	Congener (Reference)
Induction of *CYP1A1* and *CYP1A2* gene expression and associated monooxygenase activities	2',3,4,4',5-pentaCB (Parkinson, 1980b, 1983; Sawyer, 1982; Leece, 1985; Robertson, 1984) 2,3,4,4',5-pentaCB (Parkinson, 1980b, 1982, 1983; Rodman, 1989; Sawyer, 1982) 2,3,3',4,4'-pentaCB (Parkinson, 1980b, 1983; Sawyer, 1982; Yoshimura, 1979; Robertson, 1984; Flodstrom, 1992; Leece, 1985; De Vito, 1993) 2,3',4,4',5-pentaCB (Parkinson, 1980b, 1983; Sawyer, 1982; Skaare, 1991; Robertson, 1984; Leece, 1985) 2,3,3',4,4',5-hexaCB (Parkinson, 1980b, 1983; Sawyer, 1982, Robertson, 1984; Van Bergelen, 1992; Leece, 1985; De Vito, 1993) 2,3',4,4',5,5'-hexaCB (Parkinson, 1980b, 1983; Sawyer, 1982; De Vito, 1993) 2,3,3',4,4',5'-hexaCB (Parkinson, 1980b, 1983; Rodman, 1989; Sawyer, 1982; Robertson, 1984; Leece, 1985) 2,3,3',4,4',5,5'-heptaCB (Parkson, 1980a,b, 1983; Sawyer, 1982; Corbett, 1982; Robertson, 1984)
Induction of epoxide hydrolase	All eight congeners noted above (Parkinson, 1983)
Inhibition of body weight gain	2,3,3',4,4'-pentaCB (Yamamoto, 1976; Leece, 1985) 2,3',4,4',5-pentaCB (Leece, 1985) 2',3,4,4',5-pentaCB (Leece, 1985) 2,3,3',4,4',5-hexaCB (Leece, 1985) 2,3,3',4,4',5'-hexaCB (Leece, 1985)

Table 8. cont'd.

Response	Congener (Reference)
Immunosuppressive effects	2,3,3',4,4',5-hexaCB (Silkworth, 1984; Davis, 1990)
Thymic atrophy	2,3,3',4,4'-pentaCB (Parkinson, 1983; Robertson, 1984; Andersson, 1991; Leece, 1985) 2,3,3',4,4',5-hexaCB (Leece, 1985; Robertson, 1984; Andersson, 1991; Parkinson, 1985) 2,3,3',4,4',5'-hexaCB (Parkinson, 1983; Leece, 1985) 2,3,4,4',5-pentaCB (Leece, 1985)
Hepatoxicity including hepatomegaly, fatty liver	2,3,3',4,4'-pentaCB (Yamamoto, 1976; Yoshimura, 1979)
Tumor promoter activity	2,3,3',4,4'-pentaCB (Flodstrom, 1992) 2,3,4,4',5-pentaCB (Buchman, 1991)
Reproductive and developmental toxicity including embryolethality (fish)	2,3',4,4',5-pentaCB (Ax, 1975; Walker, 1991) 2,3,3',4,4'-pentaCB (Walker, 1991; Brunstrom, 1990) 2,3,3',4,4',5-hexaCB (Brunstrom, 1990; Birnbaum, 1987) 2,3,3',4,4',5'-hexaCB (Brunstrom, 1990)
Antiestrogenicity in MCF-7 human breast cancer cells	2,3,3',4,4',5-hexaCB, 2,3,3',4,4'-pentaCB, 2,3,4,4',5-pentaCB (Krishnan, 1993)

Table 9. PCBs: summary of structure-induction/binding relationships (from Safe, 1985a).

PCB Structures	Cytochromes P450 Induction (% of control)[a]		Relative Activity		
			AHH Induction (%)		
	P450c + P450d	P450b + P450e	*In Vivo*[b]	*In Vitro*[c]	Receptor Binding[d] (%)
Coplanar PCBs[e] (3)	4100 - 1800	No induction	+ + +	100 - 1	100 - 35
Mono-*ortho* coplanars (8)	2400 - 750	4700 - 2600	+ +	$0.3 - 2.4 \times 10^{-5}$	6 - 1.5
Di-*ortho* coplanars (12)	900 - 250	6300 - 1000	+	Inactive	< 0.3[f]
2,2',4,4',5,5'-Hexa-chlorobiphenyl	No induction	7300	Inactive	Inactive	< 0.3[f]
2,3,7,8-TCDD	3500	No induction	+ + + + +	400	2500

[a] Male Long-Evans rats (dose: 500 μmol/kg).
[b] Male Wistar rats (dose: 300 μmol/kg).
[c] Rat hepatoma H-4-II E cells.
[d] Determined by the competitive displacement of [^{3}H]TCDD bound to male Wistar rat hepatic cytosol.
[e] 3,3',4,4'-Tetra, 3,3',4,4',5-penta- and 3,3',4,',5,5'-hexachlorobiphenyl.
[f] Represents nonspecific binding.

Table 10. Effects of commercial Aroclors, TCDD and commercial Aroclors plus TCDD on the PFC response to SRBCs in C57BL/6 mice (Davis, 1989).

Treatment (dose)	Plaque-forming Cells/ Spleen (x 10^5)	Plaque-forming Cells/ 10^6 Viable Cells
Control (corn oil)*	1.12 ± 0.17	912 ± 221
TCDD (1.2 μg)	0.30 ± 0.08	180 ± 35
Aroclor 1232 (25 mg/kg)	1.09 ± 0.10	960 ± 126
Aroclor 1232 (25 mg/kg) + TCDD (1.2 μg)	0.34 ± 0.10	244 ± 63
Aroclor 1242 (25 mg/kg)	0.94 ± 0.15	725 ± 75
Aroclor 1242 (25 mg/kg + TCDD (1.2 μg)	0.49 ± 0.04[b]	440 ± 96[b]
Aroclor 1248 (25 mg/kg)	1.04 ± 0.01	741 ± 191
Aroclor 1248 (25 mg/kg) + TCDD (1.2 μg)	0.54 ± 0.14[a]	427 ± 110[b]
Aroclor 1254 (25 mg/kg)	1.02 ± 0.07	802 ± 84
Aroclor 1254 (25 mg/kg) + TCDD (1.2 μg)	0.63 ± 0.05[b]	459 ± 86[b]
Aroclor 1260 (25 mg/kg)	0.95 ± 0.14	756 ± 112
Aroclor 1260 (25 mg/kg) + TCDD (1.2 μg)	0.71 ± 0.28[b]	459 ± 93[b]

* Control group contained 9 animals; all other groups contained 4 animals; the treatments did not affect the spleen cell viability.

[a] Significantly different ($p < 0.05$) from animals treated with TCDD alone.

[b] Significantly different ($p < 0.01$) from animals treated with TCDD alone.

Table 11. Aroclor 1254 as a 2,3,7,8-TCDD antagonist in C57BL/6 mice - summary (Davis. 1989; Haake, 1987; Bannister, 1987).

Response	% Maximum Antagonism	Antagonist/Agonist Window
AHH induction	20	1,667 - 10,000/1
EROD induction	23	1,667 - 10,000/1
Thymic atrophy	0	No antagonism observed
Immunotoxocity	100	1,340 - 20,160/1
Teratogenicity	80	± 12,100/1

Table 12. Effects of TCDD, 2,2',4,4',5,5'-hexaCB and TCDD + 2,2',4,4',5,5'-hexaCB on the splenic PFC response in C57BL/6J mice treated with SRBCs (Biegel, 1989).

Treatment (dose, μmol/kg)	Spleen Cellularity ($\times 10^7$)	PFCs/spleen ($\times 10^5$)	PFCs/10^6 Viable Spleen Cells	% of Control
Corn oil	12.6 ± 3.4	1.36 ± 0.14	1127 ± 213	100
TCDD (0.0037)	13.3 ± 2.4	0.37 ± 0.06	284 ± 48	25
HexaCB (100)	15.1 ± 3.7	1.46 ± 0.17	995 ± 88	
HexaCB (400)	17.6 ± 1.9	1.56 ± 0.08	979 ± 192	87
HexaCB (1000)	13.1 ± 2.7	1.42 ± 0.07	1117 ± 277	99
HexaCB (100) + TCDD (0.0037)	15.4 ± 3.7	0.37 ± 0.08	244 ± 60	22
HexaCB (400) + TCDD (0.0037)	12.3 ± 2.7	1.14 ± 0.04	936 ± 144	83
HexaCB (1000) + TCDD (0.0037)	13.8 ± 1.7	1.36 ± 0.08	995 ± 93	88

Table 13. Proposed TEFs for the 2,3,7,8-substituted PCDDs and PCDFs (Safe, 1990).

Congener	Relative Potency Ranges		TEF
	In Vivo Toxicities	*In Vitro* Toxicities	
A. PCDDs			
2,3,7,8-TCDD	- - -	- - -	1.0
1,2,3,7,8-PentaCDD	0.59 - 0.053	0.64 - 0.07	0.5
1,2,3,4,7,8-HexaCDD	0.24 - 0.013	0.13 - 0.05	0.1
1,2,3,6,7,8-HexaCDD	0.16 - 0.0152	0.5 - 0.005	0.1
1,2,3,7,8,9-HexaCDD	0.14 - 0.016	0.009	0.1
1,2,3,4,6,7,8-HeptaCDD	0.0076	0.003	0.01
OCDD	> 0.0013	0.0006	0.001
B. PCDFs			
2,3,7,8-TCDF	0.17 - 0.016	0.43 - 0.006	0.1
2,3,4,7,8-PentaCDF	0.8 - 0.12	0.67 - 0.11	0.5
1,2,3,7,8-PentaCDF	0.9 - 0.018	0.13 - 0.003	0.1/0.05
1,2,3,4,7,8-HexaCDF	0.18 - 0.038	0.2 - 0.013	0.1
2,3,4,6,7,8-HexaCDF	0.097 - 0.017	0.1 - 0.015	0.1
1,2,3,6,7,8-HexaCDF	- - -	0.048 - 0.037	0.1
1,2,3,7,8,9-HexaCDF	- - -	- - -	0.1
1,2,3,4,6,7,8-HeptaCDF	0.22	- - -	0.1[a]/0.01[b]
1,2,3,4,7,8,9-HeptaCDF	0.20	- - -	0.1[a]/0.01[b]
OCDF	- - -	- - -	0.001

[a] Recommended by Safe, 1990.
[b] Currently used TEFs (NATO/CCMS, 1988).

Table 14. Comparative toxic and biochemical potencies of 3,3',4,4'-tetraCB, 3,3',4,4',5-pentaCB and 3,3',4,4',5,5'-hexaCB.

		ED_{50} or EC_{50} Values ($\mu g/kg^a$ or $\mu g/L^b$)			
Response (ref.)	Species	3,3',4,4'-TetraCB	3,3',4,4',5-PentaCB	3,3',4,4',5,5'-HexaCB	TCDD
Body weight loss[a] (Leece, 1985)	Rat (W)	> 1.46×10^5	1.08×10^3	5.41×10^3	16.1
Thymic atrophy[a] (Leece, 1985)	Rat (W)	> 1.46×10^5	3.10×10^2	3.21×10^3	29.0
Hepatic EROD induction[a] (Leece, 1985)	Rat (W)	> 1.46×10^5	39.2	236	0.97
Hepatic AHH induction[a] (Leece, 1985)	Rat (W)	~ 1.46×10^5	359	181	1.29
Cytosolic Ah receptor binding[b] (Bandiera, 1982)	Rat (W)	12.6×10^4	3.9×10^4	insoluble	3.2×10^3
Immunotoxicity[a]					
(Mayura, 1993)	Mouse (C57BL/6)	5.7	1.7	0.7	0.77
(Mayura, 1993)	Mouse (C57BL/6)	28.2	1.0	2.7	0.77
(Harper, 1993)	Mouse (C57BL/6)	- - -	8.0	15	1.4
(Harper, 1993)	Mouse (C57BL/6)	- - -	12	20	1.5
(Harper, 1993)	Mouse (DBA/2)	- - -	69	69	11.2
(Harper, 1993)	Mouse (DBA/2)	- - -	72	71	9.7
LD_{50}[a] (Brunstrom, 1990a,b)	Chick embryo	8.46	3.07	173	
Hepatic EROD induction[a] (Brunstrom, 1990a,b)	Chick embryo	1.75	0.097	14.4	
Hepatic EROD induction[b] (Yao, 1990)	Chick embryo hepatocytes	0.67	0.39	- - -	0.025
Hepatic AHH induction[b] (Yao, 1990)	Chick embryo hepatocytes	0.35	0.41	- - -	0.007
AHH induction[a] (Sawyer, 1982)	H4II-E cells	10.2	0.078	21.8	0.031
EROD induction[b] (Sawyer, 1982)	H4II-E cells	25.8	0.081	8.70	0.026

Table 14. cont'd.

Response (ref.)	Species	ED_{50} or EC_{50} Values ($\mu g/kg^a$ or $\mu g/L^b$)			
		3,3',4,4'-TetraCB	3,3',4,4',5-PentaCB	3,3',4,4',5,5'-HexaCB	TCDD
Inhibition of lymphoid development[a] (Brunstrom, 1990a,b)	Chick embryo	14.6	1.31	108.3	
Early life stage mortality LD_{50} values (Walker, 1991)	Rainbow trout (ER)	1348×10^3	74×10^3	- - -	240
Inhibition of bursal lymphoid development (Andersson, 1991)	Chick embryo	50	4	300	
Inhibition of lymphoid development in mouse-thymi (Andersson, 1991)	Fetal mouse (C57BL/6)	58.4 - 87.6	0.65	72.1 - 108	0.064
Teratogenicity (Mayura, 1993; Haake, 1987)			261 - 522		< 20

Table 15. Response-specific TEF values for 3,3′,4,4′,5-pentaCB, 3,3′,4,4′-tetraCB and 3,3′,4,4′,5,5′-hexaCB.

Response	3,3′,4,4′,5-PentaCB	3,3′,4,4′-TetraCB	3,3′,4,4′,5,5′-HexaCB
Rat: 14-day study (Leece, 1985)			
body weight loss, thymic atrophy, AHH and EROD induction	0.015, 0.093, 0.07, 0.025	1×10^{-4}, 2×10^{-4}, 9×10^{-6}, 7×10^{-6}	3×10^{-3}, 9×10^{-3}, 7×10^{-3}, 4×10^{-3}
Rat: 3-month study (Van Birgelen, 1992)			
several responses in which LOELs and NOELs were compared	0.06 - 0.6	not available	not available
Mouse: immunotoxicity and teratogenicity (Mayura, 1993; Harper, 1993)			
inhibition of the SRBC-induced response	0.45, 0.77	0.13, 0.03	1.1, 0.29
inhibition of the TNP-LPS-induced response	0.09, 0.08, 0.16, 0.14	not available	0.09, 0.05, 0.16, 0.14
teratogenicity	(est.) 0.07 - 0.04	not available	not available
inhibition of thymus lymphoid development	0.098	1.1×10^{-3} - 7.3×10^{-4}	8.9×10^{-4} - 5.9×10^{-4}
Chick embryos (Brunstrom, 1990a,b; Yao, 1990; Bosveld, 1992)			
AHH induction	0.017	0.02	
EROD induction	0.06, 0.1	0.037, 0.02	$\leq 0.10 \times 10^{-3}$
Rat hepatoma H4II-E cells (Sawyer, 1992)			
AHH induction	0.40	3.0×10^{-3}	1.4×10^{-3}
EROD induction	0.32	1.0×10^{-3}	3.0×10^{-3}

Table 15. cont'd.

Response	3,3',4,4',5-PentaCB	3,3',4,4'-TetraCB	3,3',4,4',5,5'-HexaCB
Rainbow trout (Walker, 1991)			
early life-stage mortality	0.003	1.8×10^{-4}	not available
Tumor-promoting activity (Flodstrom, 1992)	(est.) 0.1	not available	not available

Table 16. Biochemical and toxic potencies for the monoortho coplanar PCBs and their derived TEF values.

Response (ref.)	ED_{50}/EC_{50} Values (TEF) (mg/kg or mg/L[a])
Induction of AHH and EROD activity in rats (Leece, 1985)	2,3,4,4',5-pentaCB, 9.8 (1.3×10^{-4}); 19.6 (5.0×10^{-5}) 2,3,3',4,4',5'-hexaCB, 2.16 (6.0×10^{-4}); 2.53 (3.8×10^{-4}) 2,3,3',4,4',5-hexaCB, 2.53 (5.1×10^{-4}); 9.0 (1.1×10^{-4}) 2,3,3',4,4'-pentaCB, 21.2 (6.1×10^{-5}) 2,3',4,4',5-pentaCB, 53.8 (2.4×10^{-5}); 83.3 (1.2×10^{-5}) 2',3,4,4',5-pentaCB, 42.4 (3.0×10^{-5}); 71.1 (1.4×10^{-5})
Body weight loss and thymic atrophy in rats (Leece, 1985)	2,3,4,4',5-pentaCB, 58.7 (2.7×10^{-4}); 65.3 (4.4×10^{-4}) 2,3,3',4,4',5'-hexaCB, 79.4 (2.0×10^{-4}); 81.2 (3.6×10^{-4}) 2,3,3',4,4',5-hexaCB, 65.0 (2.5×10^{-4}); 65.0 (2.5×10^{-4}) 2,3,3',4,4'-pentaCB, 245 (6.6×10^{-5}); 336 (8.6×10^{-5}) 2,3',4,4',5-pentaCB, 366 (4.4×10^{-5}); 506 (5.7×10^{-5}) 2',3,4,4',5-pentaCB, 121 (1.3×10^{-4}); 911 (3.2×10^{-5})
Immunotoxicity in C57BL/6 mice (Davis, 1990)	2,3,3',4,4',5-hexaCB, 0.72 (1.1×10^{-3})
Lethality (LD_{50}) in chick embryos (Brunstrom, 1990)	2,3,3',4,4'-pentaCB, 2.19 (3.8×10^{-4})* 2,3,3',4,4',5'-hexaCB, 2.49 (3.4×10^{-4})* 2,3,3',4,4',5-hexaCB, 1.52 (5.6×10^{-4})* 2,3',4,4',5-pentaCB, > 4.01 (2.1×10^{-4})*
Hepatic EROD induction in chick embryo (Brunstrom, 1990)	2,3,3',4,4'-pentaCB, 0.15 (1.2×10^{-3})* 2,3',3,4,4',5-hexaCB, 0.20 (8.8×10^{-4})* 2,3,3',4,4',5-hexaCB, 0.14 (1.3×10^{-3})* 2,3',4,4',5-pentaCB, 2.19 (8.9×10^{-5})*
Hepatic AHH and EROD induction in chick embryo hepatocytes (Yao, 1990)*	2,3,3',4,4'-pentaCB, 0.13 (5.4×10^{-5}); 0.030 (8.3×10^{-4}) 2,3',4,4',5-pentaCB, 0.030 (2.3×10^{-4}); 0.098 (2.6×10^{-4}) 2,3,3',4,4',5-hexaCB, 0.54 (1.3×10^{-5}); 0.51 (4.9×10^{-5})
Hepatic AHH and EROD induction in rat hepatoma H4II-E cells (Sawyer, 1982)*	2,3,3',4,4'-pentaCB, 0.029 (1.1×10^{-3}); 0.039 (6.7×10^{-3}) 2,3',4,4',5-pentaCB, 3.75 (8×10^{-6}); 2.89 (8.9×10^{-6}) 2,3,4,4',5-pentaCB, 0.32 (9.8×10^{-5}); 0.184 (1.4×10^{-4}) 2',3,4,4',5-pentaCB, 1.28 (2.4×10^{-5}); 0.362 (7.2×10^{-5}) 2,3,3,',4,4',5-hexaCB, 0.74 (4.1×10^{-5}); 0.32 (8.1×10^{-5}) 2,3,3',4,4',5-hexaCB, 0.46 (6×10^{-5}); 0.26 (10^{-4})

Table 16. cont'd.

Response (ref.)	ED_{50}/EC_{50} Values (TEF) (mg/kg or mg/L*)
Early life stage mortality LD_{50} values in rainbow trout (Walker, 1991)*	2,3,3',4,4'-pentaCB, > 6970 ($\leq 3.4 \times 10^{-5}$) 2,3',4,4',5-pentaCB, > 6970 ($\leq 3.4 \times 10^{-5}$)
Inhibition of lymphoid development in the fetal mouse (Andersson, 1991)	2,3,3',4,4',5-hexaCB, ($\leq 9.8 \times 10^{-5}$)
Teratogenicity in C57BL/6N mice (Birnbaum, 1987)	2,3,3',4,4',5-hexaCB, 118.5 (3×10^{-4})
Tumor promoting activity in female rats (Flodstrom, 1992)	2,3,3',4,4'-pentaCB, ($\leq 1.0 \times 10^{-3}$)

* Derived from the ratio ED_{50}(3,3',4,4',5-pentaCB)/ED_{50}(congener) x 0.1.

Table 17. Proposed TEFs for coplanar and selected monoortho coplanar PCBs.

Congener	Relative Potency Range (*in vivo* and *in vitro*)	Mean TEF (± SD) (n)[a]	Proposed TEF
3,3',4,4',5-PentaCB	0.003 - 0.77	0.19 ± 0.22 (21)	0.1
3,3',4,4',5,5'-HexaCB	0.00059 - 1.1	0.053 ± 0.089 (13)	0.05
3.3',4,4'-TetraCB	0.000007 - 0.13	0.017 ± 0.030 (19)	0.02
2,3,3',4,4'-PentaCB	0.000034 - 0.0012	0.00098 ± 0.002 (10)	0.001
2,3,3',4,4',5-HexaCB	0.0011 - 0.000013	0.00048 ± 0.00043 (14)	0.0003
2,3',4,4',5-PentaCB	0.0000089 - 0.00026	0.000088 ± 0.000096 (11)	0.0001
2,3,3',4,4',5'-HexaCB	0.0006 - 0.00006	0.00029 ± 0.00019 (7)	0.0003
2',3,4,4',5-PentaCB	0.00013 - 0.000014	0.00005 ± 0.000044 (6)	0.00005
2,3,4,4',5-PentaCB	0.00044 - 0.00005	0.00019 ± 0.00014 (6)	0.0002

[a] Number of responses.

Table 18. 2,3,7,8-TCDD equivalents in human adipose tissue samples from the PCDDs, PCDFs and coplanar PCBs (Tanabe, 1989).

Congener	TEF (TEF)*	Concentration (ppt)	2,3,7,8-TCDD Equivalents (ppt)
2,3,7,8-TCDD	1.0	3.7	3.7
1,2,3,7,8-PentaCDD	0.5	6.4	3.2
1,2,3,4,7,8-HexaCDD	0.1	3.9	0.39
1,2,3,6,7,8-HexaCDD	0.1	34	3.4
1,2,3,7,8,9-HexaCDD	0.1	5.7	0.57
1,2,3,4,6,7,8-HeptaCDD	0.01	33	0.33
OCDD	0.001	510	0.51
Total			12.01
2,3,7,8-TCDF	0.1	3.1	0.31
1,2,3,7,8-PentaCDF	0.1	0.5	0.05
2,3,4,7,8-PentaCDF	0.5	11.0	6.5
1,2,3,4,7,8-HexaCDF	0.1	5.6	0.56
2,3,4,6,7,8-HexaCDF	0.1	1.4	0.14
1,2,3,6,7,8-HexaCDF	0.1	5.3	0.53
1,2,3,7,8,9-HexaCDF	0.1	- - -	0.029
1,2,3,4,6,7,8-HeptaCDF	0.01	2.9	0.029
1,2,3,4,7,8,9-HeptaCDF	0.01	- - -	- - -
OCDF	0.001	- - -	- - -
Total			8.12
3,3',4,4',5-PentaCB	0.1 (0.1)	330	33.0 (33.0)
3,3',4,4',5,5'-HexaCB	0.05 (0.05)	90	4.5 (4.5)
3,3',4,4'-TetraCB	0.10 (0.02)	350	3.5 (7.0)
Total			41.0 (44.5)

* Revised TEFs as summarized in Table 17.

Table 19. Concentrations of coplanar and monoortho coplanar PCBs in Aroclors 1016, 1242, 1254 and 1260 (Schulz, 1989[a]; Kannan, 1988b[b]).

Congener Substitution	Concentration (μg/g)			
	1016	1242	1254	1260
3,3',4,4',5-	- - -	17	46	8.3
3,3',4,4',5,5'-	- - -	0.05	0.5	0.05
3,3',4,4'-	- - -	5,200	600	260
2,3',4,4',5-	- - -	16,200	63,900	5,700
2,3,3',4,4'-	- - -	8,600	38,300	700
2,3',4,4',5,5'-	- - -	- - -	2,100	2,600
2,3,3',4,4',5-	- - -	900	16,200	8,800
2,3,3',4,4',5'-	- - -	- - -	- - -	1,400
2',3,4,4',5-	- - -	- - -	8,100	- - -
2,3,3',4,4',5,5'-	- - -	- - -	- - -	1,100
Total				

[a] Concentrations of monoorthocoplanar PCBs.
[b] Concentrations of coplanar PCBs.

Table 20. Application of the TEF approach for calculating the immunotoxicity of Aroclors 1016, 1242, 1254 and 1260 in C57BL/6 mice: comparison of observed (Davis, 1989) versus calculated ED_{50} values.

	Aroclors			
Parameter	1016	1242	1254	1260
TEQs (μg/g (calculated) (4 congeners only)[a]	~ 0	696	146.6	52.6
ED_{50} (mg/kg) (calculated from the TEQs and utilizing ED_{50} (TCDD) = 0.77 μg/kg)	~ 0	1.1	5.25	14.6
ED_{50} (mg/kg) (observed)	464	400	118	104
ED_{50} (observed) / ED_{50} (calculated)	α	364	22.5	7.1

[a] 3,3',4,4'-TetraCB,3,3',4,4',5-pentaCB,3,3',4,4',5,5'-hexaCB,2,3,3',4,4',5-hexaCB;concentrationsofindividual congeners shown in Table 19 and the TEF values were derived from Davis (1990) and Mayura (1993).

Table 21. Application and validation of the TEF approach for predicting the induction activities of Aroclors 1242, 1254 and 1260 in male Wistar rats (Harris, 1993).

	Aroclors		
Parameter	1242	1254	1260
TEQs (μg/g)			
AHH induction-derived	1.41	12.35	5.45
EROD induction-derived	2.24	9.95	2.43
ED_{50} (mg/kg) (calculated from TEQs and utilizing ED_{50}(TCDD))			
AHH induction (ED_{50}(TCDD) = 1.29 μg/kg)	915	104	422
EROD induction (ED_{50}(TCDD) = 0.97 μg/kg)	433	102	251
ED_{50} (mg/kg) observed			
AHH induction	84	92	343
EROD induction	346	137	442
ED_{50}(observed)/ED_{50}(calculated)			
AHH induction	0.09	0.88	0.812
EROD induction	0.80	1.34	1.76

Table 22. Limitations of the TEF approach for PCB-induced carcinogenicity in female Sprague-Dawley rats (Kociba, 1978; Norback, 1985).

Treatment	Concentration in feed	TEQ (ppt)	Adenocarcinomas	
			Male	Female
Control (corn oil)	- - -	- - -	0	0
TCDD	210 ppt	210	0	2/50 (4%)
TCDD	2100 ppt	2100	0	11/50 (22%)
Aroclor 1260	100 ppm	1040*	0	24/47 (51%)

* The TEQ of 10.4 ppm was calculated from the concentrations given in Table 19 and the TEFs in Table 17.

FIGURE CAPTIONS

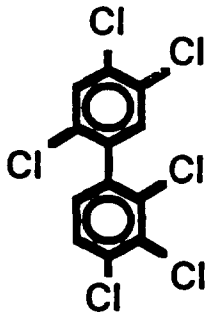
Figure 1. PCB congeners which persist in human tissues.

Figure 2. Structures of coplanar PCB congeners and 2,3,7,8-TCDD.

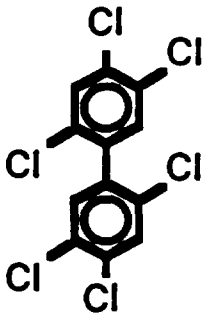
Figure 3. Structures of monoortho coplanar PCBs.

Figure 4. Scheme for the metabolism of PCBs.

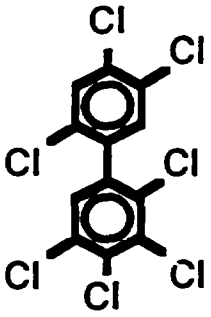
Figure 5. Examples of PCBs and metabolites which elicit Ah receptor-independent responses.



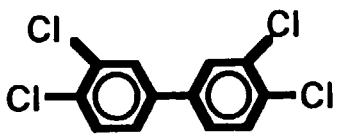
2,2',3',4,4',5-hexaCB
(#138)



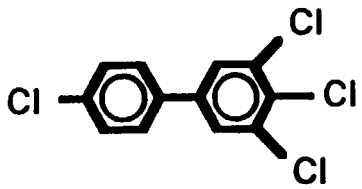
2,2',4,4',5,5'-hexaCB
(#153)



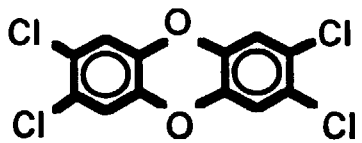
2,2',3,4,4',5,5'-heptaCB
(#180)

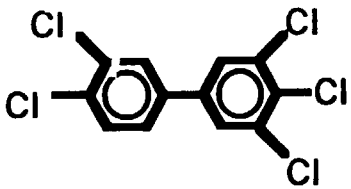


3,3',4,4'- tetraCB

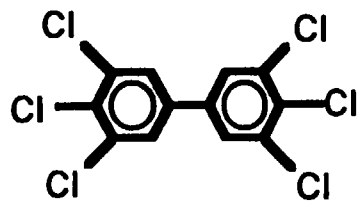


3,4,4',5-tetraCB

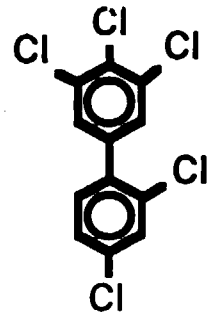




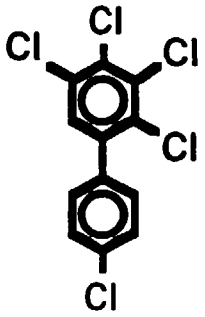
3,3',4,4',5 - pentaCB



3,3',4,4',5,5'- hexaCB



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



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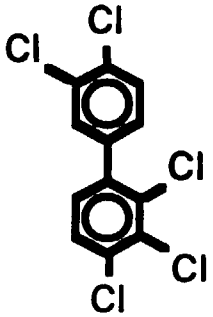
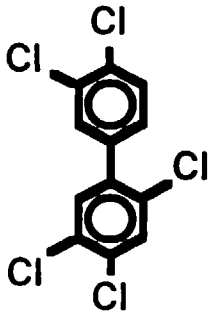
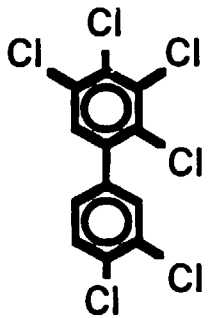


2,3,3',4,4'-

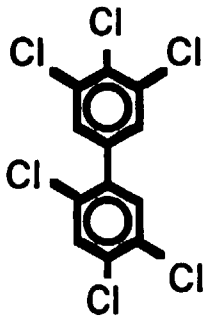


2,3',4,4',5-

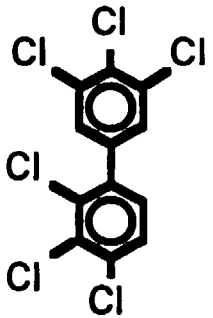
Penta CBs



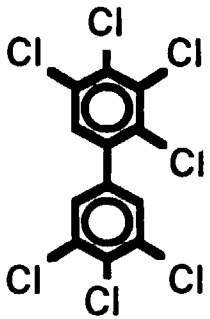
2,3,3',4,4',5-



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

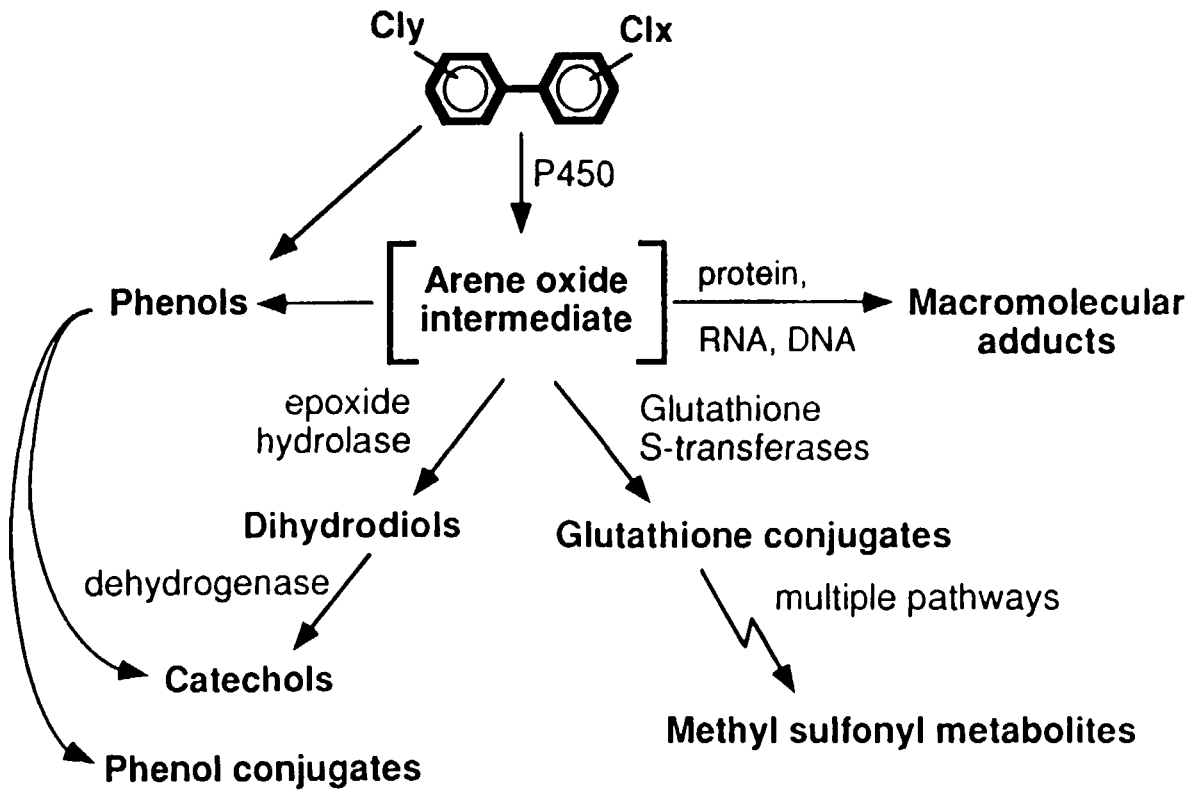


2,3,3',4,4',5'-



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

Hexa- &
Hepta CBs


Cly
Clx
P450
Phenols
Arene oxide intermediate
protein,
RNA, DNA
Macromolecular adducts
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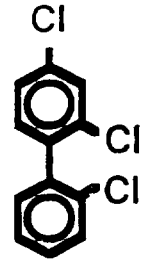
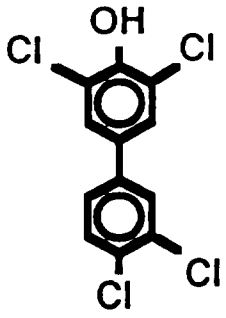
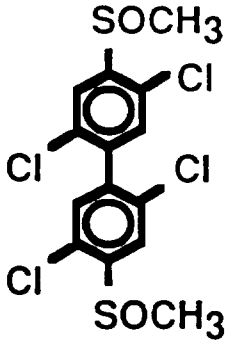
Dihydrodiols
Glutathione conjugates
dehydrogenase
multiple pathways
Catechols
Methyl sulfonyl metabolites
Phenol conjugates



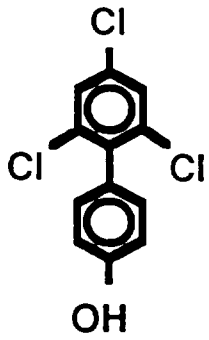
2,2',4-triCB



3,3',4',5-tetrachloro-4-biphenylol



4,4'-bis(methylsulfonyl)-2,2',5,5'-tetraCB



2,4,6-tetrachloro-4'-biphenylol