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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 congeners that can be unequivocally identified and quantitated. Some PCB mixtures 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′,5-pentaCB, 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

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

equivalent (TEQ) of a mixture is related to the TEFs and concentrations of the individual (*i*) congeners as indicated in the equation (note: n = the number of congeners). Based on the results of quantitative structure-activity studies, the following TEF values have been estimated by making use of the data available 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, 0.01; 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 because both additive and nonadditive (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 that uses cancer as the endpoint cannot solely utilize a TEF approach and requires more quantitative information on the individual congeners contributing to the tumor-promoter activity of PCB mixtures.

KEY WORDS: PCBs, toxicology, structure-function, risk assessment, toxic equivalency factors.

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I. INTRODUCTION

Polychlorinated biphenyls (PCBs) are members of the halogenated aromatic group of environmental pollutants that have been identified worldwide in diverse environmental matrices. PCBs were produced by the chlorination of biphenyl and the resulting products were marketed according to their percentage of chlorine content (by weight).[44,143,233,457] For example, Aroclors 1221, 1232, 1242, 1248, 1254, and 1260 are commercial PCBs that 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 percentage of chlorine content. Aroclor 1016 is a redistilled version of Aroclor 1242, with a chlorine composition of 41%. 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 also were manufactured in several other countries, including the former U.S.S.R. and Czechoslovakia. Commercial PCBs exhibit a broad range of physicochemical properties that are dependent, in part, on their degree of chlorination, and these properties contributed to the diverse applications of PCBs in numerous products. For example, PCBs have been used as organic diluents, plasticizers, pesticide extenders, adhesives, dust-reducing 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 their direct introduction 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 that is present in the environment are unknown; however, it has been estimated that approximately 1.5 million metric tons have been produced worldwide.[143]

The chemical properties primarily responsible for many of the industrial applications of PCBs, that is, their inflammability, chemical stability, and miscibility with organic compounds (i.e., lipophilicity), also are the same properties that have contributed to their environmental problems. Once introduced into the environment, the stable PCBs degrade relatively slowly and undergo cycling and transport within the various components of the global ecosystem. Moreover, due to their lipophilicity, these compounds preferentially bioaccumulate and biomagnify in higher trophic levels of the food chain.[211,350,461,462] The commercial PCBs and PCBs in environmental extracts are complex mixtures of congeners; moreover, due to various physical and biological (e.g., metabolism and biodegradation) processes, the composition of the commercial and environmental PCB mixtures may differ significantly. Thus, the impacts of PCBs on the environment and biota are due to the individual components of these mixtures, their additive and/or nonadditive (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 requires 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 focuses on some of the more recent studies that add to our understanding of PCBs and also discusses problems associated with PCB toxicology and risk assessment that 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 mid-1960s, Soren Jensen first detected PCBs in environmental samples as a series of complex peaks 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 (see References 31, 37, 41–45, 77, 171, 202, 220, 236, 261, 263, 264, 308, 374, 433, 462, 524, 531–536, 575, 585). 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.[577] 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,[503] and there have been continued improvements in both the resolution capabilities of capillary columns and detection methods.[8,9,46,264,371–373,418,459,482,503] 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,[373] and subsequent studies have identified and quantitated all the PCB congeners present in several different Aroclor and Clophen mixtures.[482] 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 its chlorine composition.[482] 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.[577] 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.[254] Moreover, as noted earlier, 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.[164]

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 that 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).[82–84,103,233] 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 U.K.[151,461] The results demonstrate that the PCB composition of the commercial Aroclor differs markedly from the distribution of PCB congeners in extracts from the two 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 nondetectable for both compounds). The high-resolution analytical data also show significant differences in the composition of the PCBs obtained from North American or U.K. 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 U.K. sample was 13.7%, whereas these lower chlorinated congeners were not detected in the North American samples. There were some

TABLE 1
Quantitative and Qualitative Analysis of PCBs on Aroclor 1260 and Extracts from Human Milk Samples[151,461]

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	0.9	
PCB-149	7.4	—	1.8				

[a] Congener names adapted from Ballschmiter and Zell.[46]
[b] Human milk sample collected and extracted 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.

congeners, such as 2,2′,3,4,4′,5′-hexaCB and 2,2′,4,4′,5,5′-hexaCB, that constituted >10% of the total PCBs in both milk samples and also are major components of Aroclor 1260 (6.5 and 9.6%, respectively). Several high-resolution congener-specific analyses of numerous fish and wildlife samples from different parts of the world also have 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 (Figure 1).[82–84,121,350]

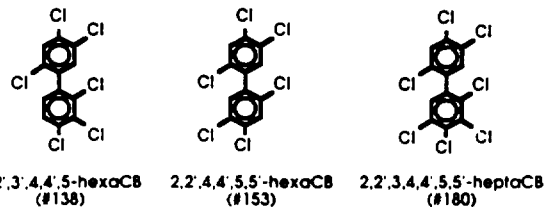


FIGURE 1. PCB congeners that persist in human tissues.

Three PCB congeners, 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.[190,194,421–423,447,453,455,456,460,599] 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.[30,149,151,218,226,269–272,354,477,511,531–537,539,581] The potential adverse impacts of these non-ortho-coplanar PCBs and their monoortho analogs are 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.[149,218,226,269,270,354,477,523,533,535,537,539,581] There was considerable variability in the range or mean concentrations of these compounds and this may be due to several factors, including differences in laboratory analytical procedures. 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. Moreover, there also are difficulties in quantitative analyses of the mixtures derived from different environmental matrices.

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, risk assessment of PCBs in food products or environmental samples should take into account the potential adverse impacts of the individual congeners and their concentrations in these samples and should not rely solely on the toxicity of a known commercial mixture such as Aroclor 1260 or Clophen A60. However, in some cases, the toxicity or carcinogenicity of the commercial mixtures may be appropriate. The toxic equivalency factor (TEF) approach, which is now being used as an interim measure for the risk assess-

TABLE 2
Relative Concentrations of Coplanar PCBs in Human Milk and Adipose Tissue Samples

Samples	Congener and concentration (ng/g) 3,3′,4,4′- (77)[a]	3,3′,4,4′5- (126)[a]	3,3′,4,4′,5,5′- (169)[a]	Ref.
Upstate New York (milk)	0.16–0.49	Nondetectable	Nondetectable	226
Ontario (adipose tissue)	Nondetectable	0.124–0.303	0.113–0.198	581
Quebec (milk)	0.008	0.081	0.032	149
Japan (adipose tissue)	0.094–0.86	0.12–0.73	0.036–0.20	269

[a] IUPAC numbering scheme for PCB congeners.

ment of PCDDs and PCDFs,[2-5,51,62,316,385,453] has been discussed as a model for congener-specific risk assessment of PCBs.[3,4,462,562] The TEF model for specific structural classes of compounds such as PCBs presupposes a common mechanism of toxic action and additivity for the toxic effects of the individual congeners in the mixture. 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 require 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 that may be etiologic agents in PCB-induced adverse effects in humans.

There have been three major scenarios in which humans have been exposed to PCB mixtures and these include (1) exposure of workers who produced PCBs or utilized PCB-containing products; (2) accidental exposure of individuals; and (3) 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.[213,283-285,309,449,450,543,584] 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 the effects that have been reported include chloracne and related dermal lesions; diverse hepatic effects, including increased serum levels of liver enzymes and lipids, induced hepatic drug-metabolizing enzymes, and 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 co-workers[160,161,166] 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 involving PCB-containing equipment, such as transformers or capacitors, also have been investigated.[172,282,396,519,520] Although some neurobehavioral dysfunction may have been associated with PCB exposure (firemen),[282] there

TABLE 3
Effects of PCBs on Occupationally Exposed Workers

Effects	Ref.
Chloracne and related dermal lesions	170, 213, 347, 401
Diverse hepatic responses, including hepatomegaly, increased liver and serum enzymes and lipids, induction of drug-metabolizing enzymes	17, 125, 160, 170, 213, 321, 401 508, 521
Decreases in pulmonary function	574
Decreased birth weight in offspring of occupationally exposed mothers	541, 542
Eye irritation	213
No increased mortality	101, 102
Variable effects on cancer formation	38, 39, 70, 139, 207, 495, 601

were no correlations between PCB levels and any sign of PCB-induced effects. Fitzgerald and coworkers[172] 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.[38,39,70,101,102,139,207,452,495,601] In the cohorts containing 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,[38,39] and the grouping of liver, gall bladder, and biliary tract cancers,[101,102] 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 also was 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 certain mixtures of PCBs in laboratory animals have been amply demonstrated[452,495] 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 that was subsequently sold to consumers.[312–314,438,439] 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 that may be associated with neurological problems. In addition, offspring of Yu-Cheng mothers were smaller, exhibited modest learning deficits, and displayed some of the same toxic symptoms observed in their mothers.[438,439] 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 2000 ppb for lower-chlorinated congeners, whereas the mean PCB blood levels of Yu-Cheng victims taken a short time after the accident varied from 39 to 101.7 ppb,[229] suggesting that chemical contaminants other than PCBs played an important role in the etiology of Yu-Cheng/Yusho poisoning. Moreover, the distribution of PCB congeners in Yusho patients was similar to that observed in other exposed populations.[315] 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.[87,88,120,361–364,368] PCDFs and polychlorinated quaterphenyls were subsequently identified in the PCB industrial fluid that contaminated the rice oil in both the Yusho and Yu-Cheng poisonings.[120,127–129,273,361,363] 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 (note: in Aroclors, this ratio is on the order of 2×10^{-6}). 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.[273,311] Laboratory studies using rodents,[47,311] different fractions of simulated "rice oil PCBs" (containing the PCDF fraction), or reconstituted PCB and PCDF mixtures that 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 that were present in relatively high concentrations in the industrial fluid that leaked into the rice oil.

Based on the relatively mild 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[167] indicated that PCB and pesticide 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.[310]

Jacobson and co-workers 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.[169,246–252] 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 co-workers also showed a correlation between the levels of prenatal PCB exposure of North Carolina infants from the general population and tests for neurodevelopment deficits, although not the same as those observed by Jacobson and co-workers.[183,184,440–442] In a follow-up study on the Michigan children at 4 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.[250,251] 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 3, 4, or 5 years of age.[183] Moreover, in the studies by Rogan and co-workers, there was no correlation between PCB levels and lower birth weights or head circumference. The reasons for the differences in the two studies are unclear and weaken the contention that PCBs are the cause of the developmental problems in infants, and it is possible that some other compounds not determined by chemical analysis may have contributed to or been responsible for the observed responses.

Rogan, Hsu and co-workers have investigated the comparable developmental deficits in infants exposed to PCDFs/PCBs in the Yu-Cheng poisoning incident in Taiwan.[129,438,439,600] Many of the toxic responses observed in the mothers also were 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 are unknown. 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 was similar and indicates that the highly toxic PCDFs may not be the major etiologic agents responsible for the developmental problems. Thus, it has been suggested that there may be an association between *in utero* exposure to PCBs and developmental deficits observed in infants and young children. However, due to several factors, including the inconsistent results between the various studies, further research is required to determine the identity of the etiologic agents.

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 are available on the toxic effects of other PCB mixtures that 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 identified as contaminants in several commercial PCB preparations. In most studies, the PCDF content was not determined and its

contribution to PCB-induced toxic responses is unknown, but in most cases its effects may be relatively minor.[453]

Commercial PCBs elicit a broad spectrum of toxic responses that are dependent on several factors including (1) the chlorine content and purity of the commercial mixture; (2) the animal species and strain; (3) the age and sex of the animal; and (4) 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 previously; however, the data suggest 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 analyses of PCB-induced toxic responses have been previously reviewed[283,447,452,453,455,456,460,495,599] and are not further elaborated in this article; however, the effects of various factors on the toxicities mediated by PCB mixtures are briefly discussed.

1. Species/Strain-Dependent Responses

The dermal toxicity of PCBs has been noted in occupationally exposed workers[213,347,401] and also has been observed in laboratory animals, including some strains of mice, rabbits (ears), and monkeys.[10,422,424] 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.[194,422,423,448]

2. 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 incidences of hepatocellular adenocarcinomas and trabecular carcinomas were 51 and 40% in female rats and 4 and 0% in male rats, respectively.[394] In contrast, an increased incidence of gastric intestinal metaplasia and adenocarcinoma was observed in both male and female F344 rats maintained on diets containing Aroclor 1254.[573] 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.

3. 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.[169,183,184,246,252,440–442] 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 that were pre- and postnatally exposed to Clophen A30.[326,327] 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 the human and animal studies were complementary and suggest that the fetus may be more susceptible to PCB-induced neurodevelopmental deficits than are infants or older animals.

4. Structure-Dependent Toxicities

Commercial PCB mixtures differ with respect their chlorine content and their relative distribution of individual congeners. Egg production in White Leghorn pullets was decreased in animals maintained on a diet containing Aroclor 1232,

TABLE 4
Toxicity of Commercial PCBs

Response	PCB mixture	Species	Ref.
	Lethality		
LD_{50}, 1.14, 1.30 ml/kg (F, M)	Kanechlor 400	Rat	283
LD_{50}, 1.05, 1.15 g/kg (F, M)	Kanechlor 300		
LD_{50}, 4.25 g/kg (M)	Aroclor 1242	Rat	105, 283
LD_{50}, 1.3–25 g/kg (M, F/age-dependent)	Aroclor 1254	Rat	199
LD_{50}, 0.358–10 g/kg (M, F)	Aroclors 1254 and 1260	Rat	329
LD_{50}, 4.0 g/kg (F)	Aroclor 1221	Rat	387
LD_{50}, 11.3 g/k/g (F)	Aroclor 1260		
LD_{50}, 1.57–1.875 g/kg (F, M)	Kanechlor 400	Mouse	283
LD_{50}, 0.8–1.2 g/kg	Aroclor 1254	Mouse	325
LD_{50}, 2.0–3.17 g/kg	Aroclor 1221	Rabbit	387
LD_{50}, 1.26–2.0 g/kg	Aroclor 1232		
LD_{50}, 0.79–1.27 g/kg	Aroclor 1242		
LD_{50}, 0.79–1.27 g/kg	Aroclor 1248		
LD_{50}, 1.26–2.0 g/kg	Aroclor 1260		
LD_{50}, 1.26–3.16 g/kg	Aroclor 1262		
LD_{50}, 2.5 g/kg	Aroclor 1268		
LD_{50}, 0.5–4.0 g/kg	Aroclors 1221, 1242, and 1254	Mink	32, 228
	Reproductive Toxicity		
Effect on fetal viability	Aroclor 1254	Rabbit	565, 566
Fetal toxicity	Aroclor 1254	Monkey	553
Severe reproductive failure	Aroclor 1242	Mink	76
Reproductive problems	Aroclors, 1016, 1221, 1242, and 1254	Mink	32
Fetal death and resorption	Aroclor 1254	Rabbit	565
Reduced litter size	Aroclors 1254 and 1260	Rat	329
Fetal death and reduced litter weight	Aroclor 1254	Rat	515
Cleft palate	Kanechlor 500	Mouse	576
Fetal resorption	Aroclor 1254	Rat	40
Fetal resorption	Clophen A60	Mouse	400
Abortions in chronically fed animals	Aroclor 1254	Monkey	29
Reproduction failure	Clophen A50	Mink	281
Review of reproductive toxicity from animal studies			195
Effects on male fertility	Aroclor 1254	Rat	464
Delayed first vaginal opening and lower testis weights	Clophen A50	Guinea pig	341
Decrease in reproductive efficiency	Aroclor 1254	Mourning dove	307
Decreased reproductive ability and smaller reproductive organs	Aroclor 1254	Mouse	330
Decreased weight of seminal vesicles	Clophen A60	Mouse	400
Resorptions, abortions, and lower birth weights	Aroclor 1248	Monkey	53
Multiple testicular abnormalities	Aroclor 1254	Fish	467
Impaired ovulation	Clophen A30	Monkey	370
Decreased reproductive success	Aroclor 1254	Ring dove	349
Decreased egg hatchability	Aroclors 1232, 1242, 1248, and 1254	Hen	328
Repressed sex accessory glands	Aroclor 1254	Rat	201

TABLE 4 (continued)
Toxicity of Commercial PCBs

Response	PCB mixture	Species	Ref.
Inhibition of Body Weight Gain or Body Weight Loss			
Short-term feeding			
10 days	Aroclor 1254	Rat	515
14–21 days			124
14–30 days			296
2–5 weeks			178
6 weeks	Clophen A50		55
6 weeks	Aroclor 1248 > 1254 > 1260		11
4 weeks	Aroclor 1242		107
38 days	Phenoclor DP6, Clophen A60, and Aroclor 1260	Rabbit	567
2–3 months	Aroclor 1248	Monkey	14
Chronic dietary feeding			
2 years	Aroclor 1254	Rat	367
21 months	Aroclor 1260		287
1 year	Kanechlors 300, 400, and 500		238
20 weeks	Aroclor 1254		602
~40 months	Aroclor 1248	Monkey	52
Up to 245 days	Aroclor 1242		58
20 weeks	Kanechlor 400		227
20 weeks	Aroclor 1254	Mink	33, 228
Acute, subchronic, and chronic studies via various routes of exposure	Aroclor 1254	Rat	55, 124, 178, 505, 515
	Aroclor 1248		11
	Aroclor 1242		107
	Aroclor 1248	Monkey	10
Porphyria			
Elevated urinary coproporphyrins	Aroclor 1242	Rat	106, 107
Hepatic porphyrin fluorescence	Aroclor 1254	Rat	602
Increased kidney porphyrins	Aroclor 1242	Quail, rats	359
Increased liver and small intestinal porphyrins	Aroclor 1242	Quail	358
Increased liver porphyrins and increased ALAS synthesis	Aroclors 1232, 1248, 1254, and 1260	Rat	204, 478
Increased liver porphyrins	Aroclors 1242 and 1016	Rat	191
Immunotoxicity			
Increased mortality to microbial infection	Aroclors 1042 and 1016	Mouse	332, 333, 546
Decrease formation of splenic PFCs in response to SRBCs	Aroclor 1242	Mouse	332
Altered graft vs. host response	Aroclor 1016	Mouse	498
Reduction in splenic and thymic gamma globulin	Aroclor 1254	Rabbit	525
Reduction in tetanus antitoxin-producing cells	Clophen A60 and Aroclor 1260	Guinea pig	569
Reduction in gamma globulin-producing cells	Aroclor 1260	Guinea pig	568
Reduction in antibody production to SRBCs	Aroclor 1254	Monkey	553
	Kanechlor 400		227
	Aroclor 1254		554

TABLE 4 (continued)
Toxicity of Commercial PCBs

Response	PCB mixture	Species	Ref.
Modulation of several nonspecific and specific immune parameters	Aroclor 1254	Monkey	555, 556
Reduction in antibody production to SRBCs	Aroclors 1232, 1016, 1242, 1248, 1254, and 1260	Mouse	140, 335
Modulation of T-cell function	Kanechlor 500	Mouse	530
Reduced NK cell activity	Aroclor 1254	Rat	165, 505
	Hepatoxicity		
Increased liver weight and/or hepatomegaly	Several Aroclors	Rat	12, 55, 124, 178, 199, 225, 266, 274, 275, 286, 287, 413, 463, 505
	Phenoclor DP6	Rat	380, 381
	Aroclor 1254	Mouse	466
	Phenoclor DP6, Clophen A60, and Aroclor 1260	Mouse	538
	Phenoclor DP6, Clophen A60, and Aroclor 1260	Rabbit	567
	Aroclors 1221, 1242, and 1254	Rabbit	305, 525
	Clophen A60, Aroclor 1260	Guinea pig	568, 569
	Kanechlors 300, 400, and 500	Rat	238
	Aroclor 1248, 1254	Monkey	10, 13, 14, 557, 558
	Kanechlors 300, 400, and 500	Mouse	237
	Aroclors 1221, 1242, and 1254	Mouse	286, 304
	Kanechlor 400	Monkey	227
	Clophen A50	Mink	281
Diverse indices of fatty liver	Clophen A50	Rat	55, 131
	Aroclors 1242, 1248, 1254, and 1260	Rat	11, 199, 266, 275, 286
	Aroclors 1248	Monkey	10, 14
	Kanechlor 400	Rat	288
	Endocrine Effects		
Increased thyroid activity	Aroclor 1254	Rat	54
Enlarged thyroid, decreased serum T_4, and altered cellular morphology	Aroclor 1254	Rat	133–135
Enlarged thyroid	Aroclor 1254	Rat	274, 275
Decreased serum progesterone	Aroclor 1248	Monkey	52
Thyroid atrophy	Aroclor 1254	Guillemot	257
Decreased T_3 synthesis	Aroclors 1254 and 1242	Rat	487
Hypothyroidism and decreased serum T and/or T_4 levels	Aroclor 1254	Rat	122, 201, 355
Increased length of estrus	Clophen A60	Mouse	399
Elevated serum corticosterone	Aroclor 1254	Mouse	466
No effects on serum hydrocortisone levels	Aroclor 1254	Monkey	331
Suppression of serum adrenal cortex hormones	Aroclors 1254, 1242, and 1016	Rat	123

TABLE 4 (continued)
Toxicity of Commercial PCBs

Response	PCB mixture	Species	Ref.
Low estrogen levels	Clophen A30	Monkey	370
Multiple steroid and thyroid hormone abnormalities	Aroclor 1254	Ring dove	349
Estrogenic activity	Aroclor 1221 and other PCB mixtures	Rat	155, 179
Neurotoxicity			
Developmental neurotoxicity (review)			550
Neurobehavioral toxicity (review)		Monkey	474
Decreased brain catecholamines	Aroclors 1254 and 1260	Rat	483, 484
Increased locomotor activity and retarded learning activity	Aroclor 1248	Monkey	89, 90
Delayed spatial alternation deficits	Aroclor 1248	Monkey	324
Decreased brain catecholamine levels	Aroclors 1016 and 1260	Macaque	485
Central nervous system toxicity	Aroclors 1254	Mouse	7
Increased behavioral toxicity due to prenatal exposure	Clophen A30	Rat	326, 327
	Fenclor 42	Rat	406
Impaired discrimination reversal learning	Aroclor 1248	Monkey	475
Altered serotonin levels in the brain	Aroclors 1254 and 1260	Rat	483
Impaired neurobehavioral activity after perinatal exposure	Aroclor 1254	Rat	402
Increased hyperactivity	Aroclor 1248	Monkey	89, 90
Thymic Atrophy and Thymus Toxicity			
Thymic atrophy and thymus toxicity	Clophen A60 and Aroclor 1260	Guinea pig	569
	Aroclor 1254	Yorkshire pig	356
	Aroclor 1254	Rat	505
Dermal Toxicity			
Alopecia, edema, distinctive hair follicles, and hair loss	Aroclor 1248	Monkey	10, 14, 52, 53
Hyperkeratosis and other lesions on the ear	Aroclor 1254	Rat	602
Hair loss and other skin lesions	Aroclor 1254	Monkey	58
Lost fingernails	Aroclor 1254	Monkey	553
Meibomian cysts, skin hyperkeratosis	Kanechlor 400	Monkey	227
Fingernail loss and exuberant nail beds	Aroclor 1254	Monkey	557, 558
Carcinogenicity			
Neoplastic nodules, hepatocellular carcinoma	Aroclor 1260	Rat	287, 394
Neoplastic nodules, hepatocellular carcinoma, gastric adenocarcinoma, and intestinal metaplasia	Aroclor 1254	Rat	367, 386, 572
Adenofibrosis, neoplastic nodules	Aroclor 1260	Rat	428
Neoplastic nodules	Clophen A30	Rat	473
	Kanechlor 400		288
Neoplastic nodules, hepatocellular carcinoma, and/or adenofibrosis	Clophen A60	Rat	473
	Kanechlor 400		238
Neoplastic nodules, hepatocellular carcinoma	Kanechlor 500	Mouse	237

1242, 1248, and 1254 (20 ppm), but no effects were observed for Aroclors 1221 or 1268.[328] 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. Shaeffer and coworkers[473] used male Wistar rats as a model for determining the effects of chronic feeding of 100 ppm of Clophens A30 and 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 most potent higher chlorinated Clophen A60 (60% Cl by weight) vs. the lower chlorinated Clophen A30 (42% Cl by weight) PCB mixture. These data, coupled with other studies on PCB-induced carcinogenicity, suggest that the higher chlorinated PCB mixtures such as Aroclor 1260 and Clophen A60 are more carcinogenic than lower chlorinated mixtures.[237,238,287,367,394,428,473] This also was observed for PCB-induced immunotoxicity in mice in which the order of potency was Aroclor 1260 > 1254 > 1248 > 1242 > 1016 > 1232.[140] 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 congeners in these mixtures, and it is possible that one or more structural subclasses of PCBs contribute to the different toxic responses elicited by PCB mixtures. The identification of these structural subclasses is discussed in Section V of this review. However, it is clear that there is no 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.[287,394,473] In addition, Aroclor 1254 increased the incidence of intestinal metaplasia in F344 rats and this may have led to glandular adenocarcinoma in the stomachs of these animals. The evidence for the mutagenicity and genotoxicity of PCBs has been extensively reviewed.[452,495] In most studies, PCB mixtures and congeners are nonmutagenic using the Ames test for bacterial mutagenesis, and there are only limited data supporting the genotoxic action of these mixtures. A recent study[384] showed that after multiple administrations of high doses of Aroclor 1254 (500 mg/kg) no PCB-DNA adducts were reported in the liver, lung, or kidney DNA using the highly sensitive ^{32}P-postlabeling assay for detecting DNA adducts. There have been extensive studies on activities of PCBs as cancer promoters using several different experimental protocols and both long- and short-term assays that measure the formation of tumors or putative preneoplastic lesions such as nodules or papillomas. The results in Table 5 summarize the results of promotion studies with PCB mixtures. In all of these studies, the animals were 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 promoted hepatocellular carcinomas and neoplastic nodules in the rat, and similar effects were observed in mouse skin and lung. In addition, PCB mixtures also promoted the formation of enzyme-altered foci in rats and chickens initiated with different carcinogens. The enzyme-altered foci that are typically characterized in short-term initiation/promotion bioassays for PCBs exhibited 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.[198,262,420,429,481]

Aroclor 1254 also inhibited aflatoxin B1-mediated carcinogenesis in rainbow trout, and it was hypothesized that this was related to altered metabolism and decreased DNA binding by the carcinogen.[490,491] The effects of PCB mixtures and selected congeners also have been investi-

TABLE 5
PCB Mixtures as Promoters: Formation of Tumors or Preneoplastic Lesions

Response	PCB mixture	Species	Carcinogen	Ref.
Increased incidence of hepatocellular carcinoma	Aroclor 1254	S-D rats	Diethylnitrosamine	427
	Kanechlor 400	Donryu rats	3'-Methyl-4-dimethyl-aminoazo-benzene	289
	Kanechlor 500	Wistar rats	Diethylnitrosamine	392, 393
	Kanechlor 500	dd mice	β-Hexachlorocyclohexane isomers	237
Increased formation of neoplastic nodules (liver)	Kanechlor 500	F344 rats	2-Acetylaminofluorene	540
Increased incidence of skin tumors	Aroclor 1254	HRS/J hairless mice	*N'*-Methyl-*N*-nitrosoguanidine	424
Increased incidence of putative hepatic preneoplastic lesions	Aroclor 1254	S-D rats	Diethylnitrosamine	419
	Phenoclor DP6	S-D rats	Aflatoxin B1	416
	Clophen A30 + A50	S-D rats	Diethylnitrosamine	397, 398
				144
	Clophen A50	S-D rats	Benzo[a]pyrene	145
	Clophen C	Chicken	Diethylnitrosamine	108
Increased incidence of lung tumors	Aroclor 1254	Swiss mice	*N*-Nitrosodiethylamine	22, 23, 60

gated[221,222] using the resistant hepatocyte model.[510] 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 also has been reported.[280] 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 also has 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 h 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 inhibited carcinogen-induced tumor or preneoplastic cell formation in certain animal models.

Smith and co-workers[506] 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 the less Ah-responsive DBA/2 mice. Due to limitation in the number of animals and toxicity to the animals used in this study, 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 are frequently observed in hepatomas induced by other carcinogens.[443] The mutations of protooncogenes or tumor-suppressor genes and their role in PCB-induced carcinogenesis are unknown and should be investigated further.

C. Biochemical Changes Induced by PCB Mixtures

The results in Table 6 summarize the biochemical changes 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 that has been observed in multiple species, including rats (see References 11–13, 15, 16, 18, 28, 74, 104–107, 154, 177, 205, 210, 219, 225, 235, 240–245, 267, 318, 334, 336, 344, 379–382, 395, 414, 417, 507, 529, 546, 551, 587, 597), rat hepatoma cells in cul-

TABLE 6
PCB Mixture-Induced Biochemical Effects

Responses	PCB mixture	Species	Ref.
Induction of P450-Dependent Enzymes or Isozymes			
Induction of O- and N-dealkylase activity	Aroclors 1248, 1254, and 1260	Rat	11
	Aroclors 1016, 1221, 1232, 1242, 1248, 1254, and 1260		154
	Aroclor 1242		107
	Clophen A50		414
	Aroclors 1248, 1254, and 1262		12
	Aroclor 1254		60
Induced P450 levels	Aroclor 1254	Rat	19, 225
	Clophen A50		414
		Guinea pig	116
Decreased barbituate sleeping times	Aroclor 1254	Mouse	465, 466
Induction of diverse hydroxylases	Aroclors 1016, 1221, 1232, 1242, 1248, 1254, and 1260	Rat	154
	Aroclor 1242		107
Induction of AHH activity	Clophen A50	Rat	414
		Mink	115
	Aroclor 1242	Quail	359
	Aroclors 1016, 1232, 1242, 1248, 1254, and 1260	Rat	219
	Aroclor 1254		334
Other Biochemical Responses			
Increased ALA synthetase	Aroclor 1254	Rat	20
	Aroclor 1242	Quail	359
Decreased ALA dehydratase	Aroclor 1254	Rat	20
Increased epoxide hydrolase	Clophen A50	Rat	414
	Aroclor 1254		334
Increased glucuronosyl transferase	Clophen A50	Rat	414
Induction of c-Ha-*ras*, c-*raf*, c-*yes*, c-*erbA*, and c-*erbB* protooncogene mRNA levels	Clophen A50	Rat	260
Increased serum lipids and HMG CoA reductase	Clophen A50	Rat	258, 259
Increased indices of hepatic lipoperoxidation		Rat	150, 268, 416
Hypocholesterolemia	Aroclor 1248	Rat	375
Increased fatty acid desaturation	Aroclor 1254	Rat, pigeon	80
Modulation of plasma lipoproteins	Aroclor 1254	Chick	203
Induction of lung pepsinogen isozymes	Kanechlor 400	Hamster	234
Decreased uroporphyrinogen decarboxylase	Aroclor 1242	Quail	359
	Aroclor 1254	Rat	507
Increased aldehyde hydrogenase	Aroclor 1254	Rat	334
Inhibition of citrate cleavage enzyme	Aroclor 1254	Rat	295
Binding to the cytosolic Ah-receptor	Aroclor 1254	Rat	48
Others			
Increased serum cholesterol and lipids	Clophen A50	Rat	55
	Aroclors 1248, 1254, and 1262		13
Increased serum SGPT, SGOT	Clophen A50	Rat	55
Decreased hepatic vitamin A	Clophen A50	Mink	112, 115

ture,[91,471,472,548,552] mice,[20,60,61,78,232,255,336,466] rabbits,[21,488] monkeys,[239] ferrets,[318] quail,[119,355,356,434] mink,[111,115] guinea pig,[116] kestrel,[159] herring gulls,[174] cockerels,[211] barn owls,[431,432] insects,[24] and fish.[1,157,158,175,206,212,224,253,353,383,570] 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, and various *N*- and *O*-alkyl-substituted compounds (dealkylation). Direct hydroxylation and epoxidation of many other xenobiotics and drugs also have been observed. Inducers of hepatic drug-metabolizing enzyme activities were traditionally divided into two main classes typified by phenobarbital (PB) and 3-methylcholanthrene (MC).[136,137,509] 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, induce both MC and PB-inducible monooxygenase 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.[86,413,444-446,543-545] In contrast to rodents, PB does not induce P450 isozymes in fish and only CYP1A1 is induced by PCB mixtures.[518] PCBs also induce P450 isozymes that regulate steroid metabolism in some species[180,186,265] and inhibit various adrenal steroid hydroxylases in the guinea pig.[185-187] There are other reports indicating that commercial PCBs repress the constitutive expression of pulmonary P450 isozymes.[488,559-561] Borlakoglu and co-workers[79,81] also have reported the induction of lauric acid hydroxylase activity by Aroclor 1254 in both rat and pigeon liver, suggesting that PCBs induce CYP4A1.

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 reportedly induced by various commercial PCBs, including 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; 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. Because these industrial compounds are complex mixtures, the induced responses must be due to contributions of individual PCB congeners and their possible nonadditive (synergistic or antagonist) responses. Extensive research on the structure-activity relationship (SARs) among various structural classes of PCBs has been carried out in order to identify the individual compounds responsible for PCB (mixture)-induced effects. Characterization of the effects of individual PCB congeners and their relative potencies also is important for development of procedures for the risk and hazard assessment of this class of pollutants because 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

1. 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.[471] 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 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,[592,593] and there is evidence that both 3,3′,4,4′,5-pentaCB and 3,3′,4,4′-tetraCB induce CYP4A1-dependent activities.[79,230] However, the induction of w- and w-1 fatty acid hydroxylase activity (i.e., CYP4A1) is not specific for coplanar PCBs because 2,2′,4,4′,5,5′-hexaCB also induced this response.[79] Coplanar PCBs also induce epoxide hydrolase and glutathione transferase activities and these induction responses also were observed for other structural classes of PCBs. A recent report[27] suggested that the induction of the glutathione S-transferase P-form (GST-P, 7–7) may be specific for coplanar PCBs.

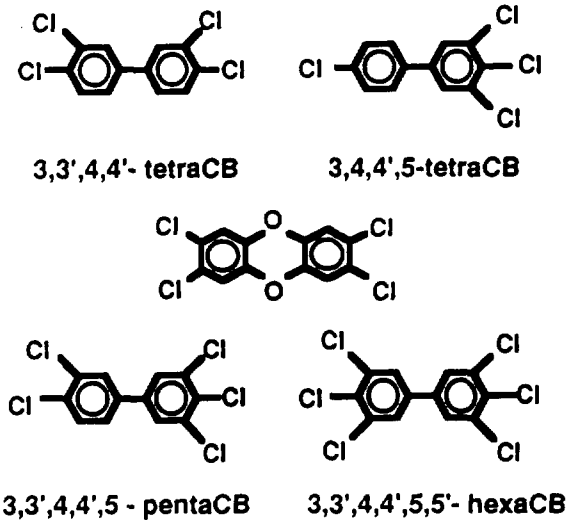


FIGURE 2. *Structures of coplanar PCB congeners and 2,3,7,8-TCDD.*

The induction of CYP1A1 gene expression by TCDD, MC, and related compounds has been extensively investigated[196,578–580] 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[48] 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 PCDDs and PCDFs support a role for the Ah-receptor in mediating many of the toxic and carcinogenic responses elicited by these compounds.[194,422,423,448,578–580] 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, also are 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.[435,496,497] 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.[497] The differential induction activity of coplanar PCBs also was observed for AHH induction in the genetically inbred C57BL/6 and DBA/2 mice.[435]

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 espression and associated monooxygenase enzyme activities	109, 115, 148, 181, 190, 197, 256, 323, 365, 388, 389, 407, 413, 421, 437, 471, 501, 518, 548, 597, 598	115, 148, 159, 323, 376, 403, 404, 407, 413, 437, 471, 501, 548, 563, 594–597, 599	110, 115, 148, 188, 190 192, 216, 253, 301, 303, 323, 342, 360, 407, 413, 421, 437, 471, 501, 526, 548, 597, 599
Suppression of constitutive *CYP2C11* gene expression			592, 593
Induction of CYP4A1-dependent activities	79	230	
Induction of glutathione S-transferases		27	27, 302
Induction of epoxide hydrolase	6		
Binding to the rat cytosolic Ah-receptor	48	48	48
Inhibition of uroporphyrinogen decarboxylase activity	276, 277, 319, 499, 500, 528		276, 277
Induction of ALAS activity	277		277
Hypothyroidism and decreased serum thyroid hormone levels	513, 564		277
Decreased hepatic or plasma vitamin A levels	35, 36, 97, 98, 100, 129, 378, 425, 514	129	
Thymic atrophy and toxicity to thymic cells	25, 323, 388, 389, 599	25, 323, 599	25, 72, 299, 300, 323, 351, 599
Hepatotoxicity, including hepatomegaly, fatty liver	599	599	72, 299, 300, 599
Reproductive and/or developmental toxicity	114, 115, 512	110, 113, 115, 346, 348	115, 345
Neurobehavioral and neurotoxic responses	130, 162, 163, 549		
Dermal toxicity	352		
Body weight loss	323	323	72, 323
Porphyria (accumulation of octa- and heptacarboxyporphyrins)	276, 358, 470, 499, 501	501	72, 193, 276, 470, 499, 501
Immunosuppressive activities	132, 348, 496, 497	348	278, 279, 348
Tumor promoter activity	117, 118, 337, 468, 469	173	
Embryolethality (fish)	571	571	

Note: Numbers in columns are References.

2. Monoortho Coplanar PCBs

The results of extensive structure-function studies showed that the monoortho coplanar derivatives of the 4 coplanar PCBs (Figure 3) constitute a second major structural class of compounds that exhibit Ah-receptor agonist activities. This group of PCBs includes several congeners that have been identified in commercial PCB mixtures and environmental extracts: 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 CYP1A1, CYP1A2, CYP2B1, CYP2B2, and CYP2A1 gene expression. Similar results have been obtained for some of the analogous brominated biphenyls.[413,435,436] Thus, the introduction of a single ortho chloro-substituent to the coplanar PCBs did

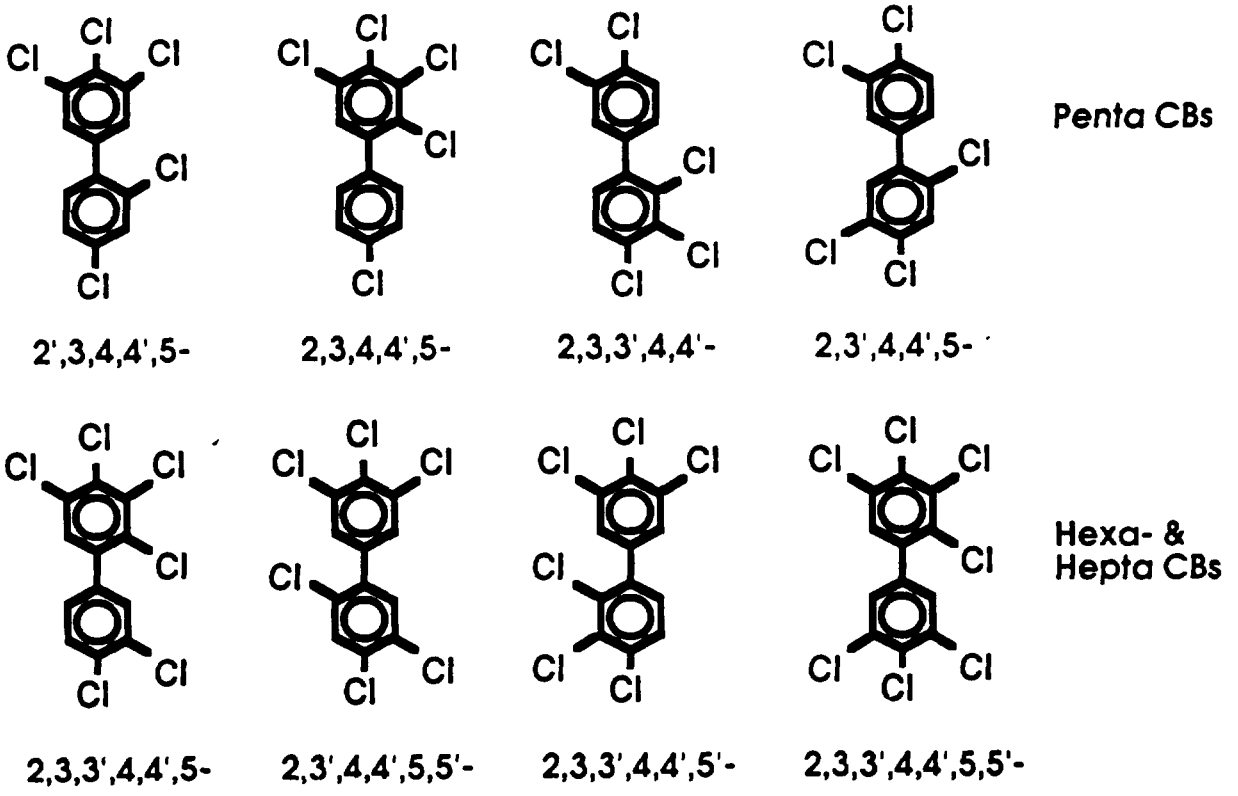


FIGURE 3. Structures of monoortho coplanar PCBs.

not eliminate the "MC-type" induction pattern, but resulted in a series of compounds exhibiting "mixed-type" activity. The monoortho coplanar PCBs also competitively bound to the rat cytosolic Ah-receptor,[48] and the major difference between the coplanar and monoortho coplanar PCBs as Ah-receptor ligands and CYP1A1 inducers was their potency (Table 8).

Because monoortho coplanar PCBs competitively bind to the Ah-receptor, these compounds also should elicit the biochemical and toxic responses comparable to other Ah-receptor agonists. The results in Table 9 summarize the biochemical and toxic responses observed for the monoortho coplanar PCBs, including 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.[412,435,496,497] These data suggest that these same responses 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, because some of the monoortho 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.

3. Other Structural Classes of PCBs

The activity of other structural classes of PCBs as Ah-receptor agonists also was investigated by determining their activity as inducers of CYP1A1 and CYP1A2.[409-411,413] 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, 2,3',4,4',5',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

TABLE 8
PCBs: Summary of Structure-Induction/Binding Relationships[456]

PCB structures	Cytochrome P450 induction (% of control)[a] P450c + P450d	P450b + P450e	Relative activity AHH Induction (%) *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′-Hexachlorobiphenyl	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 H4II-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 to the Ah-receptor, although this congener binds to other proteins.[59]

isozyme.[409–411,413] The activities of the diortho coplanar PCBs as CYP1A1 inducers have been reported in other studies[18,189,522] 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)[522] and inhibit the splenic PFC response to SRBCs in C57BL/6 mice (2,3′,4,4′,5′,6-hexaCB).[141] It also has 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) exhibited some weak Ah-receptor agonist activity.[141,405,589] Because 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.[453]

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 that exhibit "PB-like" activity. The monoortho and diortho coplanar PCBs constitute two structural classes of PCBs that exhibit "PB-like" induction activity, and 2,2′,4,4′,5,5′-hexaCB is a congener that has been utilized as a prototypical "PB-type" inducer.[190,200,413,421] 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 the two *para* positions and induce CYP2B1 and CYP2B2 in rat liver.[413] In addition, many of the PB-type PCBs induce CYP3A isozymes, which are prototypically induced by glucocorticoids such as dexamethasone.[476] Many of the most active "PB-type" inducers contain at least two *ortho* and two *para* chlorine substituents;[146] however, no comprehensive structure-activity rules have been developed for "PB-type" inducers inasmuch as congeners with a variety of chlorine substitution patterns in the *ortho*-, *para*-, and *meta*-position exhibit "PB-type" induction activities. Rodman and co-workers[436] also have 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 that also are elicited by Ah-receptor agonists at much lower concentrations.[436] The only unambiguous structure-induction relationship for PCBs as

TABLE 9
Biochemical and Toxic Responses Elicited by the Monoortho Coplanar PCBs

Response	Congener	Ref.
Induction of *CYP1A1* and *CYP1A2* gene expression and associated monooxygenase activities	2',3,4,4',5-pentaCB	323, 407, 413, 435, 471
	2,3,4,4',5-pentaCB	407, 412, 413, 437, 471
	2,3,3',4,4'-pentaCB	148, 173, 323, 407, 413, 435, 471, 599
	2,3',4,4',5-pentaCB	323, 407, 413, 435, 471, 504
	2,3,3',4,4',5-hexaCB	148, 323, 407, 413, 435, 471, 563
	2,3',4,4',5,5'-hexaCB	148, 407, 413, 471
	2,3,3',4,4',5'-hexaCB	323, 407, 413, 435, 437, 471
	2,3,3',4,4',5,5'-heptaCB	138, 407, 408, 413, 435, 471
Induction of epoxide hydrolase	All eight congeners noted above	413
Inhibition of body weight gain	2,3,3',4,4'-pentaCB	323, 590
	2,3',4,4',5-pentaCB	323
	2',3,4,4',5-pentaCB	323
	2,3,3',4,4',5-hexaCB	323
	2,3,3',4,4',5'-hexaCB	323
Immunosuppressive effects	2,3,3',4,4',5-hexaCB	141, 496
Thymic atrophy	2,3,3',4,4'-pentaCB	25, 323, 413, 435
	2,3,3',4,4',5-hexaCB	25, 323, 413, 435
	2,3,3',4,4',5'-hexaCB	323, 413
	2,3,4,4',5-pentaCB	323
Hepatoxicity including hepatomegaly, fatty liver	2,3,3',4,4'-pentaCB	590, 599
Tumor promoter activity	2,3,3',4,4'-pentaCB	173
	2,3,4,4',5-pentaCB	118
Reproductive and developmental toxicity including embryolethality (fish)	2,3',4,4',5-pentaCB	34, 571
	2,3,3',4,4'-pentaCB	571
	2,3,3',4,4',5-hexaCB	75, 110, 113
	2,3,3',4,4',5'-hexaCB	110, 113
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	310

"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 that resemble PB as inducers indicates that, with the exception of hepatomegaly and some hepatotoxic effects,[72,193,300] 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 reproductive toxicity of other congeners has been reported.[447] One major exception to this observation is associated with PCB-induced tumor-promoter activity. Several compounds, including 2,2',5,5'-tetraCB,[468] 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.[117,118,317] These results suggest that "PB-type" PCBs and possibly other structural classes of PCBs

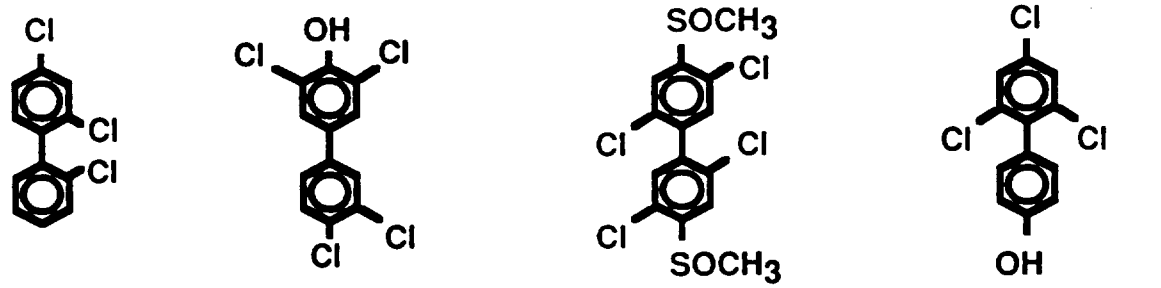
may be important contributors to the activity of the commercial mixtures as tumor promoters and this is an area of PCB structure-function relationships that requires further investigation.

C. PCBs That Induce Neurotoxicity

Several studies have reported that 3,3′,4,4′-tetraCB causes neurotoxic and neurobehavioral changes in rodents, including a permanent motor disturbance or "spinning syndrome" and other changes in neuromuscular activity[130,549,550] and alteration in cholinergic muscarinic receptors.[162,163] Exposure of the non-human 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.[485] Gas chromatographic analysis of brain samples identified only three congeners, 2,4,4′-triCB (Figure 4), 2,2′,4,4′-tetraCB, and 2,2′,5,5′-tetraCB, and these congeners also persist in other organs/tissues. 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.[486,489] Thus, these results define a new structural class of PCBs, other than Ah-receptor agonists, that 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 requiring 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[451,480,502,527] and a summary of the major metabolic pathways is shown in Figure 5. PCBs are metabolized either directly or via arene oxide intermediates into phenolic metabolites, which can be hydroxylated further 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. Because 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.[366,480,492,493,586,588] However, the PCBs that are readily metabolized and form arene oxide intermediates are the lower chlorinated congeners, or those compounds that 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.[384] Thus, it is unlikely



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

FIGURE 4. Examples of PCBs and metabolites that elicit Ah-receptor-independent responses.

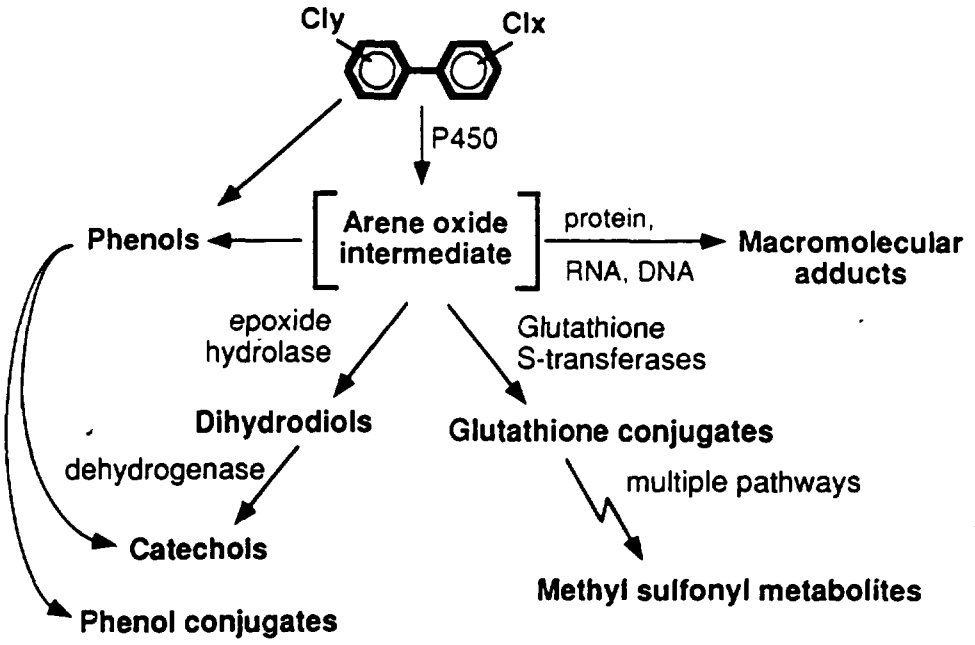


FIGURE 5. Scheme for the metabolism of PCBs.

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.[294,298,516,517,590,599] 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.[598] 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.[294] 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;[153,377,390,391] hydroxylated PCBs competitively bind to the estrogen receptor and increase mouse uterine wet weight *in vivo*;[306] hydroxylated PCBs inhibit various P450-dependent enzyme activities;[479] and hydroxylated PCBs bind prealbumin, a major serum thyroxine-binding protein.[430] It also has 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).[96–100,293] For example, 3,3′,4′,5-tetrachloro-4-biphenylol (Figure 4), 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.[293] 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 (see References 41, 63, 65–67, 92–94, 194, 214, 215, 263, 357, 426, 448). Using 4,4′-bis(methylsulfonyl)-

2,2′,5,5′-tetrachlorobiphenyl (Figure 4) 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 that resembles uteroglobin.[95,339,340] This compound also binds with high affinity to rabbit uteroglobin[182] and fatty acid-binding proteins in chicken liver and intestinal mucosa.[320] Methylsulfonyl PCB metabolites and related binding proteins have been identified in humans.[215,339] Methylsulfonyl PCB metabolites also inhibit induced AHH activity both *in vivo* and *in vitro*.[290-292,338] Thus, 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

Because 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 co-workers reported that Aroclor 1254 and several PCB congeners significantly increased hepatic cytosolic Ah-receptor levels in rats.[147] For example, 8 days after administration of Aroclor 1254 or 2,2′,4,4′,5,5′-hexaCB, there was an approximately two- or threefold 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.[50] 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).[50] The synergistic induction response also was 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 <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 also was 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.[142] Nonadditive (synergistic) interactions of 2,2′,5,5′- and 3,3′,4,4′-tetraCB as promoters of hepatic preneoplastic lesions in rats also have been reported;[468] however, the nature and significance of these interactions require further confirmation by dose-response studies.

It also has been reported that individual PCB congeners and commercial mixtures exhibit Ah-receptor antagonist activity.[49,71,140,141,209] Davis and Safe[140] showed that Aroclors 1260, 1254, 1248, 1242, 1016, and 1232 caused a dose-dependent 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 inasmuch as 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 percentage of maximum antagonism is response-dependent and ratios of Aroclor 1254 to 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 to PCDDs plus PCDFs is in the range required for

TABLE 10
Effects of Commercial Aroclors, TCDD, and Commercial Aroclors plus TCDD on the PFC Response to SRBCs in C57BL/6 Mice[140]

Treatment (dose)	Plaque-forming cells/ spleen ($\times 10^5$)	Plaque-forming cells/ 10^6 viable cells
Control (corn oil)[a]	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[c]	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]

[a] Control group contained nine animals; all other groups contained four animals; the treatments did not affect the spleen cell viability.
[b] Significantly different ($p < 0.01$) from animals treated with TCDD alone.
[c] Significantly different ($p < 0.05$) from animals treated with TCDD alone.

TABLE 11
Aroclor 1254 as a 2,3,7,8-TCDD Antagonist in C57BL/6 Mice — Summary[49,140,209]

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
Immunotoxicity	100	1,340-20,160/1
Teratogenicity	80	±12,100/1

PCB-mediated antagonism of TCDD-induced responses in laboratory animal studies; however, the significance of PCB to PCDD plus PCDF interactions in wildlife species and humans is unknown.

Individual PCB congeners that inhibit TCDD-induced responses also have been identified.[71,141,369] 2,2′,4,4′,5,5′-HexaCB at high doses (400 to 1000 μmol/kg) partially inhibited 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 because 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 and Safe[141] also identified other PCB congeners that 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 nonadditive (antagonistic) PCB/

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[71]

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

TCDD interactions in mice suggest 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 nonadditive interactions of other complex mixtures of PCBs have not been extensively investigated. Reconstituted PCB mixtures of individual PCB congeners that 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.[140,208] The potential interactions within these mixtures using a TEF approach are 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) was investigated in mink.[281] 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 also were investigated and these included effects on blood parameters,[156] steroid hormone excretion,[343] P450 induction,[111] vitamin A levels,[223] liver histology,[64] and morphology of the reproductive organs.[56] 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 nonortho PCB fraction, but this activity was enhanced by cotreatment with the di- to tetraortho PCB fraction. Decreased vitamin A levels were due primarily to the nonortho and monoortho PCB fractions.[223] 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 investigated further 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

PCDDs and PCDFs are routinely detected as complex mixtures of isomers and congeners in almost every component of the global ecosys-

tem.[149,261,454,455,539] These compounds are not intentionally produced but are formed as byproducts of numerous industrial processes 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 combustion of municipal and industrial wastes.[454] Despite the complex composition of many PCDD/PCDF-containing wastes, the congeners that persist in the environment and bioconcentrate in the food chain are the lateral 2,3,7,8-substituted congeners: 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-heptaCDF, and octaCDF. The relative and absolute concentrations of these congeners in pollution sources and environmental matrices are highly variable. For example, octaCDD is the dominant congener that persists in all human serum and adipose tissue samples, whereas this compound is a minor component in PCDD/PCDF extracts from fish.[454]

Risk assessment of PCDDs/PCDFs initially focused on one congener, 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 TCDD was present in relatively low concentrations. Moreover, based on structure-toxicity relationships,[194,422,423,448,453,578-580] 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 also were 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 planar PCBs are mediated through the Ah-receptor. Two of the hallmarks of receptor-mediated responses are (1) the stereoselective interaction between the receptor and the diverse ligands and (2) 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.[2-5,51,62,316,385,453] All the relevant individual congeners have been assigned a TEF value, which is the fractional toxicity of the congener relative to a standard toxin, i.e., 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.[453] 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 2,3,7,8-substituted 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 the duration of exposure are important endpoints that are used for protecting human and environmental health. It should be noted that proposed TEFs are interim values that should be reviewed and revised as new data become available.

There are reports indicating 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.[152,453] 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, suggesting that nonadditive 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 equivalents (TEQ), where $[PCDF_i]$ and $[PCDD_i]$ represent the concentrations of the individual congeners, TEF_i is their

TABLE 13
Proposed TEFs for the 2,3,7,8-Substituted PCDDs and PCDFs[453]

Congener	Relative potency ranges: *In vivo* toxicities	Relative potency ranges: *In vitro* toxicities	TEF
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
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[a]/0.05[b]
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.[453]
[b] Currently used TEFs.[385]

corresponding TEF and n is the number of congeners. Thus, the

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

concentrations of a complex mixture of PCDDs and PCDFs in a sample can be reduced to a single TEQ value that represents the calculated concentration of TCDD equivalents 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 (miscellaneous food products) pg/person.[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 (EPA), which has utilized a value of 0.006 pg/kg/day. The significant differences between the U.S. EPA and other regulatory agencies are based on their calculation methods and assumptions.[415,494] For example, the U.S. EPA assumes that TCDD is a complete carcinogen[297] and their threshold limit 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,[297] but utilize a safety factor approach in which it is assumed that TCDD is a promoter and that there is a threshold for this response. The disparity between the U.S. EPA value of 0.006

pg/kg and the current intake of 2 pg/kg/day of TEQs is of concern and is currently being reevaluated by the agency.[73,168]

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[453] 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 is not given. In other reports,[85] only the TEFs or a comparison of the maximal effects doses[437] 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.[323] These data were determined from the ratios of the ED_{50} (TCDD)/ED_{50} (3,3',4,4',5-pentaCB) for the different responses. Preliminary data reported by Van Birgelen and co-workers[563] 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[348] and trinitrophenyl-lipopolysaccharide (TNP-LPS)[217] 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.[348] Several studies have reported the induction effects of 3,3',4,4',5-pentaCB in chick embryos and chick embryo hepatocytes;[85,99,591] 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. Flodström and co-workers[173] 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 ± 0.22. However, based on the tumor promotion- and teratogenicity-derived TEFs, the value of 0.1 proposed by Safe[453] 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 because this congener is rapidly metabolized in rats and many of the lowest TEFs were observed in this species.[323] The results of a 4-week feeding study in female B6C3F1 mice using a single dose of 3,3',4,4'-tetraCB also indicated that the induction-derived TEF was <0.00001.[148] In contrast, the TEF values for inhibition of the splenic PFC response to SRBCs in C57BL/6 mice[348] were considerably higher (0.13 to 0.03) than TEFs derived from 14-day studies in the rat. Sargent and co-workers[469] 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 is 0.029, and the 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

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				
Response	**Species**	**3,3′,4,4′-TetraCB**	**3,3′,4,4′,5-PentaCB**	**3,3′,4,4′,5,5′-HexaCB**	**TCDD**	**Ref.**
Body weight loss[a]	Rat (W)	$>1.46 \times 10^5$	1.08×10^3	5.41×10^3	16.1	323
Thymic atrophy[a]	Rat (W)	$>1.46 \times 10^5$	3.10×10^2	3.21×10^3	29.0	323
Hepatic EROD induction[a]	Rat (W)	$>1.46 \times 10^5$	39.2	236	0.97	323
Hepatic AHH induction[a]	Rat (W)	$\sim 1.46 \times 10^5$	359	181	1.29	323
Cytosolic Ah-receptor binding[b]	Rat (W)	12.6×10^4	3.9×10^4	Insoluble	3.2×10^3	48
Immunotoxicity[a]						
	Mouse (C57BL/6)	5.7	1.7	0.7	0.77	348
	Mouse (C57BL/6)	28.2	1.0	2.7	0.77	348
	Mouse (C57BL/6)	—	8.0	15	1.4	217
	Mouse (C57BL/6)	—	12	20	1.5	217
	Mouse (DBA/2)	—	69	69	11.2	217
	Mouse (DBA/2)	—	72	71	9.7	217
LD_{50}[a]	Chick embryo	8.46	3.07	173		110, 113
Hepatic EROD induction[a]	Chick embryo	1.75	0.097	14.4		110, 113
Hepatic EROD induction[b]	Chick embryo hepatocytes	0.67	0.39	—	0.025	591
Hepatic AHH induction[b]	Chick embryo hepatocytes	0.35	0.41	—	0.007	591
AHH induction[b]	H4II-E cells	10.2	0.078	21.8	0.031	471
EROD induction[b]	H4II-E cells	25.8	0.081	8.70	0.026	471
Inhibition of lymphoid development[a]	Chick embryo	14.6	1.31	108.3		110, 113
Early life stage mortality LD_{50} values	Rainbow trout (ER)	1348×10^3	74×10^3	—	240	571
Inhibition of bursal lymphoid development	Chick embryo	50	4	300		25
Inhibition of lymphoid development in mouse-thymi	Fetal mouse (C57BL/6)	58.4–87.6	0.65	72.1–108	0.064	25
Teratogenicity			261–522		<20	209, 348

[a] In micrograms per kilogram.
[b] In micrograms per liter.

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	Ref.
Rat: 14-day study				323
Body weight loss, thymic atrophy, and 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				563
Several responses in which LOELs and NOELs were compared	0.06–0.6	Not available	Not available	
Mouse: immunotoxicity and teratogenicity				217, 348
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	0.07–0.04 (est.)	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				85, 110, 113, 591
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				471
AHH induction	0.40	3.0×10^{-3}	1.4×10^{-3}	
EROD induction	0.32	1.0×10^{-3}	3.0×10^{-3}	
Rainbow trout				571
Early life-stage mortality	0.003	1.8×10^{-4}	Not available	
Tumor-promoting activity	0.1 (est.)	Not available	Not available	173

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 data derived from dose-response studies was 0.017 ± 0.030. The selection of a single TEF for 3,3′,4,4′-tetraCB is problematic due to the unusually wide species- and response-specific variations in the TEFs, and therefore the 0.01 value proposed by Safe may be useful as an interim TEF.[453]

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) in C57BL/6 mice 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[453] 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 value obtained for the effects in chick embryos. The induction-derived TEF from 4-week feeding studies with female B6C3F1 mice was <0.05.[148] The assignment of a final TEF value for 3,3′,4,4′,5,5′-hexaCB must await results of additional studies; however, the proposed TEF of 0.05 may be useful on an interim basis.[453]

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[453] proposed a TEF of 0.001 for all the monoortho coplanar PCBs; however, this value may be too high based on the results summarized in Table 16. Mean TEFs of 0.00098 ± 0.002, 0.000088 ± 0.000096, and 0.00040 ± 0.00043 were observed, respectively, 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). The induction-derived TEFs for 2,3,3',4,4'-pentaCB, 2,3,3',4,4',5-hexaCB, and 2,3,3',4,4',5'-hexaCB administered (as a single dose) 5 days per week by gavage to female B6C3F1 mice for 4 weeks were estimated as <0.00005, <0.0005, and 0.001, respectively.[148] The results from these long-term studies were within the range of values summarized in Table 17; the induction-derived TEF for 2,3,3',4,4',5-hexaCB was similar to the 0.0004 mean value, whereas the induction-derived TEFs for 2,3,3',4,4'-pentaCB and 2,3,3',4,4',5-hexaCB were lower and higher, respectively, than the mean TEFs of 0.00098 and 0.00029 (Table 17). Based on the data summarized in Table 17, the following respective 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. In addition, the respective mean TEFs for 2,3,3',4,4',5'-hexaCB, 2',3,4,4',5-pentaCB, and 2,3,4,4',5-pentaCB are 0.00029, 0.00005, and 0.00019; the respective suggested TEFs for these compounds are 0.0003, 0.0005, and 0.0002.

C. Application of TEFs Derived for PCBs

TEFs for PCDDs/PCDFs have been used extensively to determine TEQs in industrial, commercial, and environmental mixtures of these compounds. Tanabe and co-workers[269-272,531-537] 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.[471] 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.[30,149,231,350,539]

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,[49,71,140,141,209] and it is conceivable that for PCB mixtures the interactions also would 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[140] reported the effects of various Aroclors on the inhibition of the splenic PFC response to SRBCs 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 because the coplanar and monoortho coplanar PCBs in these Aroclors have been analyzed.[271,482] 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., $TEQ = \Sigma[PCB_i \times TEF_i]_n$). The results in Table 20 summarize the

TABLE 16
Biochemical and Toxic Potencies for the Monoortho Coplanar PCBs and Their Derived TEF Values

Response	ED_{50}/EC_{50} values *(TEF)* (mg/kg)	Ref.
Induction of AHH and EROD activity in rats	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})	323
Body weight loss and thymic atrophy in rats	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})	323
Immunotoxicity in C57BL/6 mice	2,3,3',4,4',5-HexaCB, 0.72 (1.1×10^{-3})	141
Lethality (LD_{50}) in chick embryos	2,3,3',4,4'-PentaCB, 2.19 (3.8×10^{-4})[a] 2,3,3',4,4',5'-HexaCB, 2.49 (3.4×10^{-4})[a] 2,3,3',4,4',5-HexaCB, 1.52 (5.6×10^{-4})[a] 2,3',4,4',5-PentaCB, >4.01 (2.1×10^{-4})[a]	110
Hepatic EROD induction in chick embryo	2,3,3',4,4'-PentaCB, 0.15 (1.2×10^{-3})[a] 2,3',3,4,4',5-HexaCB, 0.20 (8.8×10^{-4})[a] 2,3,3',4,4',5-HexaCB, 0.14 (1.3×10^{-3})[a] 2,3',4,4',5-PentaCB, 2.19 (8.9×10^{-5})[a]	110
Hepatic AHH and EROD induction in chick embryo hepatocytes[b]	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})	591
Hepatic AHH and EROD induction in rat hepatoma H4II-E cells[b]	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})	471
Early life stage mortality LD_{50} values in rainbow trout[b]	2,3,3',4,4'-PentaCB, >6970 ($<3.4 \times 10^{-5}$) 2,3',4,4',5-PentaCB, >6970 ($<3.4 \times 10^{-5}$)	571
Inhibition of lymphoid development in the fetal mouse	2,3,3',4,4',5-HexaCB ($<9.8 \times 10^{-5}$)	25
Teratogenicity in C57BL/6N mice	2,3,3',4,4',5-HexaCB, 118.5 (3×10^{-4})	75
Tumor-promoting activity in female rats	2,3,3',4,4'-PentaCB ($\leq 1.0 \times 10^{-3}$)	173

[a] Derived from the ratio ED_{50} (3,3',4,4',5-pentaCB)/ED_{50}(congener) × 0.1.
[b] In milligrams per liter.

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	0.0059–1.1	0.053 ± 0.089 (13)	0.05
3,3',4,4'-TetraCB	0.000007–0.13	0.017 ± 0.030 (19)	0.01
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	0.0004 ± 0.00043 (14)	0.0004
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[531]

Congener	TEF (TEF)[a]	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	0.05	0.5	0.25
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	—	—
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			8.09
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)

[a] Revised TEFs as summarized in Table 17.

TABLE 19
Concentrations of Coplanar and Monoortho Coplanar PCBs in Aroclors 1016, 1242, 1254, and 1260[271,482]

Cogener 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

calculated TEQs and ED_{50} values for the immunotoxicity of the commercial PCBs using TEQs derived from only four of the coplanar and monoortho coplanar PCBs. The calculated ED_{50}s are maximum values inasmuch as 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, respectively. These values represent the degree of overestimation of PCB-induced immunotoxicity in C57BL/6 mice if the TEF approach is used. The data suggest that there are nonadditive (antagonistic) interactions between the PCB congeners in these mixtures, and this is consistent with the results of comparable antagonistic interactions between PCBs and TCDD.[140,141]

Recent studies in this laboratory have investigated the dose-response induction of hepatic microsomal AHH and EROD activities by Aroclors 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, and 442 mg/kg (for EROD induction), respectively.[219] Because 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, and 1260 also are 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 twofold difference between the observed vs. calculated ED_{50} values; these data suggest that the interactive effects were minimal for AHH and EROD induction in the rat by the commercial PCBs. Using a similar approach, it has been shown that there also were minimal interactive effects for the induction of AHH and EROD activity by PCB mixtures in rat hepatoma H4II-E cells.[241,472] For several coplanar and monoortho coplanar PCB congeners, it was reported that there was a linear correlation between the *in vitro*–logEC_{50} values for EROD/AHH induction in rat hepatoma H4II-E cells vs. the *in vivo*–logED_{50} values for AHH/EROD induction, thymic atrophy, and inhibition of body weight gain in the rat;[450,453–458] this suggests that there are minimal nonadditive interactions of PCBs for Ah-receptor-mediated responses, such as thymic atrophy and body weight loss, in rats. 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 overestimates the immunotoxicity of PCB mixtures. The value of TEFs for risk management is dependent on minimal nonadditive 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 nonadditive antagonist interactions between PCBs and other Ah-receptor agonists. Analysis of the rat data supports the TEF approach for several responses (AHH and EROD induction, body weight

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[140] vs. Calculated ED_{50} Values

Parameter	Aroclors			
	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; concentrations of individual congeners shown in Table 19 and the TEF values were derived from References 141 and 348.

TABLE 21
Application and Validation of the TEF Approach for Predicting the Induction Activities of Aroclors 1242, 1254, and 1260 in Male Wistar Rats[219]

Parameter	Aroclors		
	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

loss, and thymic atrophy); however, it is possible that there may be response-specific differences within the same animal species.

Giesy, Tillitt and co-workers have utilized *in vitro* and *in vivo* studies to investigate the role of "TCDD-like" PCBs, PCDDs, and PCDFs as possible etiologic agents in wildlife toxicity.[547,548,582,583] Tillitt and co-workers[547] 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 (nonadditive) interactive effects, as noted above.[472] In this study, there 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,[583] the PCB-TEQs in extracts from Lake Michigan chinook salmon were determined by high-resolution chemical analysis and there was no 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 overestimated the toxicity due to nonadditive (antagonis-

tic) interactions. It also is 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 suggest that the predictive value of TEQs for PCBs, PCDDs, and PCDFs may be both species- and response-dependent because both additive and nonadditive (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 with care in risk assessment of these contaminants.

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,[394] which is assumed to be a complete carcinogen. However, because most studies indicate that the higher chlorinated PCBs are nongenotoxic[452,495] and do not form persistent DNA adducts *in vivo*,[384] 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, but the results suggest that the most active PCBs are the higher chlorinated mixtures, such as Aroclor 1260 or Clophen A60.[473] 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 that observed for lower chlorinated mixtures, such as Clophen A30 and Aroclors 1242, 1248, and 1254.[271,562] 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 at most 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 also are 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 a recent study[219] showing 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-recep-

TABLE 22
Limitations of the TEF Approach for PCB-Induced Carcinogenicity in Female Sprague-Dawley Rats[297,394]

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[a]	0	24/47 (51%)

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

tor-mediated responses. Therefore, because 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 Aroclors 1254 and 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 congeners that 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. 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 incidences 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, the coplanar and monoortho coplanar PCBs, exhibit Ah-receptor agonist activity and appear to be responsible for many of the PCB mixture-induced responses.
4. Other structural classes of PCB also elicit biochemical and toxic responses. PCBs that exhibit "PB-like" activity also are 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 that 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 toxicological role of these compounds in PCB-induced toxicity has not been determined yet.
6. Several studies have demonstrated that PCB mixtures and individual congeners inhibited TCDD-induced responses, and the results of these studies suggest that in some animal models and for some responses nonadditive (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, 0.01; 2,3,3′,4,4′-pentaCB, 0.001; 2,3′,4,4′,5-pentaCB, 0.0001; 2,3,3′,4,4′,5-hexaCB, 0.0004. 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 suggest that the predictive value of TEQs for PCBs, PCDDs, and PCDFs may be both species- and response-

specific because both additive and nonadditive (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 that uses cancer as an endpoint requires more quantitative information on the PCBs congeners contributing to the tumor-promoter activity of these mixtures.

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