# POLYCHLORINATED BIPHENYLS - TOXICOLOGY AND RISK ASSESSMENT

S. Safe
Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX 77843-4466

## Abstract

Commercial polychlorinated biphenyls (PCBs) and environmental extracts are complex mixtures of congeners which can be unequivocally identified and quantitated. Many of the biochemical and toxic responses associated with PCB exposure resemble those caused by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds which act through the aryl hydrocarbon (Ah) receptor. Structure-toxicity studies indicate that the coplanar PCBs, namely 3,3′,4,4′-tetrachlorobiphenyl (tetraCB), 3,3′,4,4′,5-pentaCB and 3,3′,4,4′,5,5′-hexaCB and their monoortho analogs are Ah receptor agonists and contribute 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

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

toxic equivalents (TEQ) for 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). The following TEF values are proposed 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 since there is evidence from both laboratory and environmental studies that both additive and non-additive interactions are observed.

# PCB

## Introduction and Background

Commercial PCBs are complex mixtures of congeners which have been identified as residues in almost every component of the global ecosystem. The PCB composition of environmental extracts can be highly variable and extracts from the same analyte (*e.g.* human adipose tissue or milk) from different locations can exhibit significant differences with respect to both PCB congener composition and their relative concentrations. This variability is primarily due to the PCB congener distribution and relative concentrations present in the major intake sources (*e.g.* food) for human populations in different geographical locations. Despite these differences, in most extracts from biota, the predominant compounds are 2,2′,3,4,4′,5′-hexachlorobiphenyl (hexaCB), 2,2′,4,4′,5,5′-hexaCB and 2,2′,3,4,4′,5,5′-heptaCB.

Currently, PCB regulatory standards are derived from results of animal studies with commercial PCB mixtures (*e.g.* Aroclor 1260). However, it has been recognized that PCBs in food products or environmental samples do not necessary resemble the commercial mixtures and risk assessment should take into account the contributions of individual PCBs in these mixtures. The toxic equivalency factor (TEF) approach which is now being used as an interim measure for the risk assessment of PCDDs and PCDFs (1) and has been discussed as a model for congener-specific risk assessment of PCBs (2). The TEF model for specific structural classes of compounds such as PCBs presupposes a common Ah receptor-mediated mechanism of toxic action and additivity for the toxic effects of the individual congeners in the mixture. The TEF for an individual congener relative to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is defined by the following equation. The half-maximal effect values have been frequently

$$TEF = \frac{EC_{50}/ED_{50}\ (TCDD\ reference\ standard)}{EC_{50}/ED_{50}\ (PCB\ congener)}$$

used for these calculations; however, other common reference points of comparison are also appropriate. The TEF approach can be utilized for the conversion of complex analytical data into a single value which represents the TCDD equivalent or toxic equivalents (TEQ) for this mixture where $PCB_i$ and $TEF_i$ are the concentration and TEF, respectively, for an individual congener for the n congeners in a mixture which exhibit TCDD-like activity.

$$TEQ = \sum \left( [PCB_i \times TEF_i] \right)_n$$

**Development of TEFs for PCBs**

The toxic and biochemical effects of various commercial PCB mixtures have been extensively investigated in various laboratory animals, fish and wildlife species (3). Commercial PCBs elicit a broad spectrum of toxic responses which are dependent on several factors including (i) the chlorine content and purity of the commercial mixture, (ii) the animal species and strain, (iii) the age and sex of the animal, and (iv) the route and duration of exposure to the commercial mixture. For example, some of the responses observed in laboratory animals after exposure to commercial PCBs 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, neurotoxicity, and the induction of phase I and II drug-metabolizing enzyme activity.

Many of the toxic responses elicited by the commercial PCBs resemble those caused by TCDD and related Ah receptor agonists and extensive research on the structure-activity relationships (SARs) among various structural classes of PCBs has been carried out in order to identify the individual TCDD-like congeners. 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 1) resembled TCDD as inducers of *CYP1A1* and *CYP1A2* gene expression and their toxic responses were also similar to those observed for TCDD (1,3). In addition,

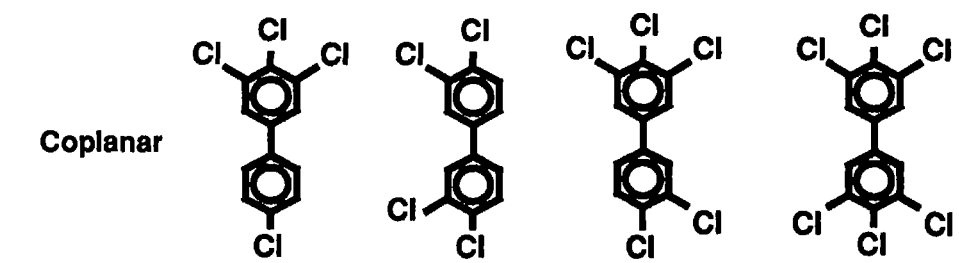


**Figure 1. Structures of the coplanar PCB congeners (top) and their monoortho analogs (bottom).**

Table 1. Proposed TEFs for coplanar and selected monoortho coplanar PCBs (6).

| Congener | Relative Potency Range (*in vivo* and *in vitro*) | Mean TEF (± SD) (n)[a] | Proposed TEF |
|---|---|---|---|
| 3,3',4,4',5-PentaCB | 0.003 - 0.77 | 0.19 ± 0.22 (21) | 0.1 |
| 3,3',4,4',5,5'-HexaCB | 0.00059 - 1.1 | 0.053 ± 0.089 (13) | 0.05 |
| 3,3',4,4'-TetraCB | 0.000007 - 0.13 | 0.017 ± 0.030 (19) | 0.01 |
| 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.

comparable SAR studies also showed that the monoortho coplanar derivatives of the 4 coplanar PCBs (Figure 1) constitute a second major structural class of compounds which exhibited Ah receptor agonist activities. Several monoortho coplanar PCB have been identified in commercial mixtures and environmental extracts and these include 2,3,3',4,4'-pentaCB, 2,3',4,4',5-pentaCB and 2,3,3',4,4',5-hexaCB. Although other structural classes of PCBs have been identified as Ah receptor agonists, the coplanar and monoortho coplanar PCBs constitute the most potent members of this class of compounds. A summary of the TEFs for the coplanar and monoortho coplanar PCBs is given in Table 1. These data were derived from numerous quantitative SAR studies in which the TEF was determined by comparing the toxic potency of the PCB congener to that of TCDD or another surrogate (*e.g.* 3,3',4,4',5-pentaCB). It should be noted that the TEF values can only be utilized to estimate the TCDD-like effects of PCBs; however, this does not account for the biochemical and toxic responses elicited by other structural classes of PCBs. For example, PCBs which exhibit "phenobarbital-like" activity are also tumor promoters and these compounds comprise a high percentage of higher chlorinated PCB mixtures. Other compounds exhibit neurotoxicity and PCB metabolites also elicit diverse biochemical and toxic responses.

## Applications and Validation of the TEF Approach

Several studies have utilized the TEF approach for calculating the total TEQs contributed by PCBs, PCDDs and PCDFs in various biotic extracts. Their results generally show that the coplanar and monoortho coplanar PCBs are the major contributors to the calculated TEQs (5). However, the TEF approach for the risk assessment of PCBs must be used with considerable caution. The results of laboratory animal and wildlife studies suggests that the predictive value of TEQs for PCBs, PCDDs and PCDFs may be both species- and response-dependent since both additive and non-additive (antagonistic) interactions have been observed with PCB mixtures. For example, Davis and Safe (6) reported the effects of various Aroclors on inhibition of the splenic plaque-forming cell (PFC) response to sheep red blood cells (SRBCs) in C57BL/6 mice. The concentrations of coplanar and monoortho coplanar PCBs in these mixtures have been reported and the immunotoxicity-derived TEFs were 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). 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 2 summarize the observed and calculated TEQs and $ED_{50}$ values for the immunotoxicity of the commercial PCBs. 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 $\infty$ for Aroclors 1260, 1254, 1242 and 1016. These values represent the degree of

Table 2. Application of the TEF approach for calculating the immunotoxicity of Aroclors 1016, 1242, 1254 and 1260 in C57BL/6 mice: comparison of observed versus calculated $ED_{50}$ values.

| | Aroclors | | | |
|---|---|---|---|---|
| Parameter | 1016 | 1242 | 1254 | 1260 |
| TEQs ($\mu$g/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 $\mu$g/kg) | ~ 0 | 1.1 | 5.25 | 14.6 |
| $ED_{50}$ (mg/kg) (observed) | 464 | 400 | 118 | 104 |
| $ED_{50}$ (observed) / $ED_{50}$ (calculated) | $\alpha$ | 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 and TEF values were derived from published data (reviewed in 6).

overestimation of PCB-induced immunotoxicity in C57BL/6 mice if the TEF approach is used. The data suggest that there are non-additive (antagonistic) interactions between the PCB congeners in these mixtures and this is consistent with the results of comparable antagonistic interactions between PCBs and TCDD (6).

These results and data from other studies (6) suggest that the TEF approach for risk assessment of PCBs must be used with caution. Antagonistic interactive effects by PCBs may result in overestimation of some TCDD-like responses; in contrast, the tumor promotion activity of PCBs may be underestimated using the TEF approach since a significant proportion of this response may be Ah receptor-independent (6).

**Acknowledgements**

The financial assistance of the National Institutes of Health (P42-ES04917) and the Texas Agricultural Experiment Station are gratefully acknowledged. S. Safe is a Burroughs Wellcome Toxicology Scholar.

**References**

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

2. United States Environmental Protection Agency, 1991. *Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners*. Risk Assessment Forum, EPA/625/3-91/020.

3. Safe, S. 1984. Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs): biochemistry, toxicology and mechanism of action. *CRC Crit. Rev. Toxicol.* 12:319-395.

4. Tanabe, S., N. Kannan, A. Subramanian, S. Watanabe, and R. Tatsukawa. 1987. Highly toxic coplanar PCBs: occurrence, source, persistency and toxic implications to wildlife and humans. *Environ. Pollution* 47:147-163.

5. Davis, D. and S. Safe. 1989. Dose-response immunotoxicities of commercial polychlorinated biphenyls (PCBs) and their interaction with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicol. Lett.* 48:35-43.

6. Safe, S. 1993. Polychlorinated biphenyl (PCBs): environmental impact, biochemical and toxic responses and implications for risk assessment. *C.R.C. Crit. Rev. in Toxicol.* in press.