

Development and Validation of the Toxic Equivalency Factor (TEF) Approach for the Risk Assessment of PCBs

Stephen H. Safe

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

1. 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 ecosystem¹⁻⁵⁾. These compounds are not intentionally produced but are formed as by-products 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 wastes³⁾. Despite the complex composition of many PCDD/PCDF-containing wastes, the congeners which persist in the environment and bioconcentrate in the food chain are the lateral 2,3,7,8-substituted congeners namely 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or 2,3,7,8-tetraCDD), 1,2,3,7,8-pentaCDD, 1,2,3,6,7,8-hexaCDD, 1,2,3,7,8,9-hexaCDD, 1,2,3,4,7,8-hexaCDD, 1,2,3,4,6,7,8-heptaCDD, octaCDD, 2,3,7,8-tetrachlorodibenzofuran (tetraCDF), 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,7,8,9-hexaCDF, 2,3,4,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, 1,2,3,4,7,8,9-heptaCDF and octaCDF. The relative and absolute concentrations of these congeners in both pollution sources and environmental matrices are highly variable. For example, octaCDD is the dominant congener which persists in all human serum and adipose tissue samples whereas this compound is a minor component in PCDD/PCDF extracts from fish³⁾.

Risk assessment of PCDDs/PCDFs initially focused on one congener, namely TCDD which is the most toxic member of this class of compounds. However, with the improvement of analytical methodologies it was demonstrated that in many industrial and environmental samples TCDD was present in relatively low concentrations. Moreover, based on structure-toxicity relationships⁶⁻¹⁰⁾ which were developed for the PCDDs and PCDFs, it was recognized that in addition to TCDD many of the 2,3,7,8-substituted PCDDs and PCDFs were also highly toxic and were major contributors to the overall toxicity of these mixtures.

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

ligands and the rank order correlation between structure-binding and structure-toxicity relationships for most of these ligands. Thus, based on these mechanistic considerations, a TEF approach has been adopted by most regulatory agencies for the risk assessment of PCDDs and PCDFs^{10,11}. All the relevant individual congeners have been assigned a TEF value which is the fractional toxicity of the congener relative to a standard toxin, namely TCDD. Thus, if the ED₅₀ 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 ED₅₀ (TCDD)/ED₅₀ (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-dependent¹⁰. 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 1) 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 which are used for protecting human and environmental health. It should be noted that proposed TEFs are interim values which should be reviewed and revised as new data becomes available^{10,11}.

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

There are reports which indicate that the single value TEF approach for PCDDs and PCDFs can be successfully used to predict the toxicity of complex mixtures of PCDFs and PCDDs/PCDFs in laboratory animals^{10,12}. 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 non-additive interactive effects are minimal. The major application of the TEF approach has been the conversion of quantitative analytical data for PCDD/PCDF mixtures into TCDD or toxic equivalents (TEQ) where [PCDF_i] and [PCDD_i] represent the concentrations of the individual congeners, TEF_i is their corresponding TEF and n is the number of congeners. Thus, the concentrations of a complex mixture of PCDDs and PCDFs in a sample can be reduced to a single TEQ value which represents the calculated concentration of TCDD 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 tissue¹⁰. 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/person¹³. The estimated total daily intake was 130 pg/person and only 15% of this total was due to TCDD alone. The daily intake of PCDDs/PCDFs was estimated as 2 pg/kg/day (TEQs). This value is within the 1 to 10 pg/kg/day range of acceptable daily intakes recommended by most regulatory agencies with the exception of the U.S. Environmental Protection Agency which has utilized a value of 0.006 pg/kg/day. The significant differences between the USEPA and other regulatory agencies are based on their calculation methods and assumptions^{14,15}. For example, the USEPA assumes that TCDD is a complete carcinogen¹⁶ 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 ¹⁶⁾ 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 USEPA value of 0.006 pg/kg data and the current intake of 2 pg/kg/day of TEQs is of concern and is currently being reevaluated by the agency.

2. Development of TEFs for Coplanar and Monoortho Coplanar PCBs

Safe ¹⁰⁾ has previously reviewed the QSAR studies for the coplanar and monoortho coplanar PCBs which are known to bind to the Ah receptor and induce TCDD-like responses. In some of these studies, the comparison of the toxic and biochemical potencies of the coplanar PCBs with TCDD are not given. The biochemical and toxic potencies and the derived TEF values for the coplanar 3,3',4,4'-tetraCB, 3,3',4,4',5-pentaCB, and 3,3',4,4',5,5'-hexaCB congeners are summarized in Tables 2 and the range of experimentally-derived TEF values varied considerably. These variations were not totally unexpected for 3,3',4,4'-tetraCB since this congener is rapidly metabolized in rats and many of the lowest TEFs were observed in this species. 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 the 0.01 value proposed by Safe may be useful as an interim TEF ¹⁰⁾. The assignment of a final TEF value for 3,3',4,4',5,5'-hexaCB should await the results of further studies; however, the proposed TEF ⁴⁾ of 0.05 may be useful on an interim basis. A TEF of 0.1 was originally assigned to the 3,3',4,4',5-pentaCB ^{4,10)} and this value appears to be consistent with the data base for this compound.

The relative potencies and TEFs for several monoortho coplanar PCBs are also summarized in Table 2. 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 ¹⁰⁾ 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 2. Mean TEFs of 0.00098 ± 0.002 , 0.000088 ± 0.000096 and 0.00040 ± 0.00043 were observed for 2,3,3',4,4'-pentaCB (10 responses), 2,3',4,4',5-pentaCB (11 responses) and 2,3,3',4,4',5-hexaCB (14 responses), respectively. The following interim TEFs are proposed for the monoortho coplanar PCBs ⁴⁾: 0.001, 0.0001 and 0.0004 for the 2,3,3',4,4'-pentaCB, 2,3',4,4',5-pentaCB and 2,3,3',4,4',5-hexaCB congeners, respectively. In addition, the mean TEFs for 2,3,3',4,4',5-hexaCB, 2',3,4,4',5-pentaCB and 2,3,4,4',5-pentaCB were 0.00029, 0.00005 and 0.00019, respectively, and the suggested TEFs for these compounds are 0.0003, 0.00005 and 0.0002, respectively. A WHO committee ¹⁷⁾ has also recommended TEFs for PCB congeners and these are summarized in Table 2.

3. Application of TEFs Derived for PCBs

TEFs for PCDDs/PCDFs have been extensively used to determine TEQs in industrial, commercial and environmental mixtures of these compounds. Tanabe and coworkers ^{18,19)} 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 cells²⁰). 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 9 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^{4,10}).

4. 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 mice²¹⁻²⁵) and it is conceivable that for PCB mixtures the interactions would also decrease coplanar PCB-induced toxicity. These potential inhibitory interactions between different structural classes of PCBs would result in overestimation of the toxicity of PCB mixtures using the TEF approach. Davis and Safe²³) 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 3. 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); however, these values can be used to estimate the TEQs for these four congeners in Aroclors 1016, 1242, 1254 and 1260 since the analysis of the coplanar and monoortho coplanar PCBs in these has been determined^{19,26}). 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. $TEQ = \sum [PCB_i \times TEF_{i,n}]$). The results in Table 4 summarize the calculated TEQs and ED₅₀ values for the immunotoxicity of the commercial PCBs using TEQs derived from only four of the coplanar and monoortho coplanar PCBs. The calculated ED₅₀s are maximum values since the contributions from Ah receptor agonists other than the compounds noted above have not been included in the calculation. In all cases, the calculated ED₅₀ values are significantly lower than the observed ED₅₀ values and the ratios of ED₅₀ (observed)/ED₅₀ (calculated) were 7.1, 22.5, 364 and ∞ for Aroclors 1260, 1254, 1242 and 1016. 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 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^{23,24}).

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 ED₅₀ values were 137, 84, 51, 92 and 343 mg/kg (for AHH induction) and 678, 346, 251, 137, 442 mg/kg (for EROD induction), respectively²⁷). Since the induction-derived TEF values for the coplanar and monoortho coplanar PCB congeners in rats have been determined and their concentrations in Aroclors 1242, 1254, 1260 are also known (Table 3) then the TEQ values can be readily calculated (Table 5). The results show that with one exception there was less than a 2-fold difference between the observed versus calculated ED₅₀ values; these data suggest that for AHH and EROD induction in the rat by the commercial PCBs, the

interactive effects were minimal. Using a similar approach, it has been shown that for the induction of AHH and EROD activity by PCB mixtures in rat hepatoma H4II-E there were also minimal interactive effects^{19,20}. 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 non-additive interactions among the PCBs, PCDDs and PCDFs. The results obtained in mice and rats for PCB mixtures illustrate that there are significant species and possibly response-specific differences in the non-additive antagonist interactions between PCBs and other Ah receptor agonists. Analysis of the data in rats supports the TEF approach for several responses (AHH and EROD induction, body weight loss and thymic atrophy); however, it is possible that there may be response-specific differences within the same animal species.

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

5. References

1. Dewailly, E., Weber, J. P., Gingras, S., and Laliberte, C. (1991) Coplanar PCBs in human milk in the province of Quebec, Canada -are they more toxic than dioxin for breast fed infants. *Bull. Environ. Contam. Toxicol.* 47:491-498.
2. Jensen, A. A. (1989) Background levels in humans. In: *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, edited by R. D. Kimbrough and A. A. Jensen. Elsevier Science Publishers. p. 345
3. Safe, S. (1991) Polychlorinated dibenzo-*p*-dioxins and related compounds: sources, environmental distribution and risk assessment. *Environ. Carcin. Ecotox. Reviews* 9:261-302.
4. Safe, S. (1994) Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *C. R. C. Crit. Rev. Toxicol.* 24:87-149.
5. Tarhanen, J., Koistinen, J., Paasivirta, J., Vuorinen, P. J., Koivusaari, J., Nuuja, I., Kannan, N., and Tatsukawa, R. (1989) Toxic significance of planar aromatic compounds in Baltic ecosystem - new studies on extremely toxic coplanar PCBs. *Chemosphere* 18:1067-1077.
6. Goldstein, J. A. and Safe, S. (1989) Mechanism of action and structure-activity relationships for the chlorinated dibenzo-*p*-dioxins and related compounds. In: *Halogenated Biphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, edited by R. D. Kimbrough and A. A. Jensen. Amsterdam, Elsevier-North Holland. p. 239-293.
7. Poland, A., Greenlee, W. F., and Kende, A. S. (1979) Studies on the mechanism of action of the chlorinated dibenzo-*p*-dioxins and related compounds. *Ann. N. Y. Acad. Sci.* 320:214-230.
8. Poland, A. and Knutson, J. C. (1982) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and related

- halogenated aromatic hydrocarbons. Examinations of the mechanism of toxicity. *Annu. Rev. Pharmacol. Toxicol.* 22:517-554.
9. Safe, S. (1986) Comparative toxicology and mechanism of action of polychlorinated dibenzo-*p*-dioxins and dibenzofurans. *Annu. Rev. Pharmacol. Toxicol.* 26:371-399.
 10. 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.
 11. Bellin, J. S. and Barnes, D. G. (1989) *Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-Dioxins and -Dibenzofurans (CDDs and CDFs)*. Washington, D.C. U.S. E.P.A.
 12. Eadon, G., Kaminsky, L., Silkworth, J., Aldous, K., Hilker, D., O-Keefe, P., Smith, R., Gierthy, J. F., Hawley, J., Kim, N., and DeCaprio, A. (1986) Calculation of 2,3,7,8-TCDD equivalent concentrations of complex environmental contaminant mixtures. *Environ. Health Perspect.* 70:221-227.
 13. Beck, H., Dross, A., and Mathar, W. (1992) PCDDs, PCDFs, and related contaminants in the German food supply. *Chemosphere* 25:1539-1550.
 14. Paustenbach, D. J., Wenning, R. J., Lau, V., Harrington, N. W., Rennix, D. K., and Parsons, A. H. (1992) Recent developments on the hazards posed by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in soil: implications for setting risk-based cleanup levels at residential and industrial sites. *J. Toxicol. Environ. Health* 36:103-149.
 15. Shu, H. P., Paustenbach, D. J., and Murray, F. J. (1987) A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Regulat. Toxicol. Pharmacol.* 7:57-88.
 16. Kociba, R. J., Keyes, D. G., Beger, J. E., Carreon, R. M., Wade, C. E., Dittenber, D. A., Kalnins, R. P., Frauson, L. E., Park, C. L., Barnard, S. D., Hummel, R. A., and Humiston, C. G. (1978) Results of a 2-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in rats. *Toxicol. Appl. Pharmacol.* 46:279-303.
 17. Ahlborg, U. G., Becking, G. C., Birnbaum, L. S., Brouwer, A., Derks, H. J. G. M., Feeley, M., Golor, G., Hanberg, A., Larsen, J. C., Liem, A. K. D., Safe, S., Schlatter, C., Wærn, F., Younes, M., and Yrjänheikki, E. (1994) Toxic equivalency factors for dioxin-like PCBs. *Chemosphere* 28:1049-1067.
 18. Kannan, N., Tanabe, S., and Tatsukawa, R. (1988) Potentially hazardous residues of non-*ortho* chlorine substituted coplanar PCBs in human adipose tissue. *Arch. Environ. Health* 43:11-14.
 19. Kannan, N., Tanabe, S., and Tatsukawa, R. (1988) Toxic potential of non-*ortho* and mono-*ortho* coplanar PCBs in commercial PCB preparations: 2,3,7,8-T₄CDD toxicity equivalence factors approach. *Bull. Environ. Contam. Toxicol.* 41:267-276.
 20. Sawyer, T. and Safe, S. (1982) PCB isomers and congeners: induction of aryl hydrocarbon hydroxylase and ethoxyresorufin O-deethylase enzyme activities in rat hepatoma cells. *Toxicol. Lett.* 13:87-94.
 21. Bannister, R., Davis, D., Zacharewski, T., Tizard, I., and Safe, S. (1987) Aroclor 1254 as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist: effects on enzyme activity and immunotoxicity. *Toxicology* 46:29-42.
 22. Biegel, L., Harris, M., Davis, D., Rosengren, R., Safe, L., and Safe, S. (1989) 2,2',4,4',5,5'-Hexachlorobiphenyl as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist in C57BL/6J mice. *Toxicol. Appl. Pharmacol.* 97:561-571.
 23. Davis, D. and Safe, S. (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.
24. Davis, D. and Safe, S. (1990) Immunosuppressive activities of polychlorinated biphenyls in C57BL/6 mice: structure-activity relationships as Ah receptor agonists and partial antagonists. *Toxicology* 63:97-111.
 25. Haake, J. M., Safe, S., Mayura, K., and Phillips, T. D. (1987) Aroclor 1254 as an antagonist of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicol. Lett.* 38:299-306.
 26. Schulz, D. E., Petrick, G., and Duinker, J. C. (1989) Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detection. *Environ. Sci. Technol.* 23:852-859.
 27. Harris, M., Zacharewski, T., and Safe, S. (1993) Comparative potencies of Aroclors 1232, 1242, 1248, 1254 and 1260 in male Wistar rats - assessment of toxic equivalency factor (TEF) approach for polychlorinated biphenyls (PCBs). *Fund. Appl. Toxicol.* 20:456-463.
 28. Sawyer, T. W., Vatcher, A. D., and Safe, S. (1984) Comparative aryl hydrocarbon hydroxylase induction activities of commercial PCBs in Wistar rats and rat hepatoma H-4-II E cells in culture. *Chemosphere* 13:695-701.

Table 1. Proposed TEFs for the 2,3,7,8-substituted PCDDs and PCDFs ¹⁰⁾.

| Congener | Relative Potency Ranges | | TEF |
|------------------------|------------------------------|-------------------------------|-------------------------------------|
| | <i>In Vivo</i> Toxicities | <i>In Vitro</i> Toxicities | |
| A. PCDDs | | | |
| 2,3,7,8-TCDD | --- | --- | 1.0 |
| 1,2,3,7,8-PentaCDD | 0.59 - 0.053 | 0.64 - 0.07 | 0.5 |
| 1,2,3,4,7,8-HexaCDD | 0.24 - 0.013 | 0.13 - 0.05 | 0.1 |
| 1,2,3,6,7,8-HexaCDD | 0.16 - 0.0152 | 0.5 - 0.005 | 0.1 |
| 1,2,3,7,8,9-HexaCDD | 0.14 - 0.016 | 0.009 | 0.1 |
| 1,2,3,4,6,7,8-HeptaCDD | 0.0076 | 0.003 | 0.01 |
| OCDD | > 0.0013 | 0.0006 | 0.001 |
| B. PCDFs | | | |
| 2,3,7,8-TCDF | 0.17 - 0.016 | 0.43 - 0.006 | 0.1 |
| 2,3,4,7,8-PentaCDF | 0.8 - 0.12 | 0.67 - 0.11 | 0.5 |
| 1,2,3,7,8-PentaCDF | 0.9 - 0.018 | 0.13 - 0.003 | 0.1 ^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 ¹⁰⁾.

^b Currently used TEFs ⁴⁾.

Table 2. Proposed TEFs for coplanar and selected monoortho coplanar PCBs.

| Congener | Relative Potency Range (<i>in vivo</i> and <i>in vitro</i>) | Mean TEF (\pm SD) (n) ^a | TEF ⁴⁾ | TEF (WHO) |
|-----------------------|--|--|-------------------|--------------|
| 3,3',4,4',5-PentaCB | 0.003 - 0.77 | 0.19 \pm 0.22 (21) | 0.1 | 0.1 |
| 3,3',4,4',5,5'-HexaCB | 0.00059 - 1.1 | 0.053 \pm 0.089 (13) | 0.05 | 0.01 |
| 3,3',4,4'-TetraCB | 0.000007 - 0.13 | 0.017 \pm 0.030 (19) | 0.01 | 0.0005 |
| 2,3,3',4,4'-PentaCB | 0.000034 - 0.0012 | 0.00098 \pm 0.002 (10) | 0.001 | 0.0001 |
| 2,3,3',4,4',5-HexaCB | 0.0011 - 0.000013 | 0.0004 \pm 0.00043 (14) | 0.0004 | 0.0005 |
| 2,3',4,4',5-PentaCB | 0.0000089 - 0.00026 | 0.000088 \pm 0.000096 (11) | 0.0001 | 0.0001 |
| 2,3,3',4,4',5'-HexaCB | 0.0006 - 0.00006 | 0.00029 \pm 0.00019 (7) | 0.0003 | 0.0005 |
| 2',3,4,4',5-PentaCB | 0.00013 - 0.000014 | 0.00005 \pm 0.000044 (6) | 0.00005 | 0.0001 |
| 2,3,4,4',5-PentaCB | 0.00044 - 0.00005 | 0.00019 \pm 0.00014 (6) | 0.0002 | 0.0005 |

^a Number of responses.

Table 3. Concentrations of coplanar and monoortho coplanar PCBs in Aroclors 1016, 1242, 1254 and 1260^{19,26)}

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

^a Concentrations of monoorthocoplanar PCBs.

^b Concentrations of coplanar PCBs.

Table 4. Application of the TEF approach for calculating the immunotoxicity of Aroclors 1016, 1242, 1254 and 1260 in C57BL/6 mice: comparison of observed²³⁾ versus calculated ED₅₀ 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 derived⁴⁾

Table 5. Application and validation of the TEF approach for predicting the induction activities of Aroclors 1242, 1254 and 1260 in male Wistar rats²⁷⁾.

| 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 |

APPENDIX

In December 1993, the WHO-European Centre for Environment and Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS) held a consultation in Bilthoven, The Netherlands, at which the available data were discussed to derive TEFs for dioxin-like PCB. TEFs were recommended for 3 *non-ortho*-, 8 *mono-ortho*- and 2 *di-ortho*-substituted PCBs (Table 1) *. To illustrate the consequences of the recommended WHO/IPCS TEFs a comparison is made between the application of earlier TEFs (Safe 1990, Ahlberg et al. 1992) and the present recommendation (Table 2).

Table 1. WHO/IPCS interim TEFs for human intake.

| Type | Congener | | TEF |
|-------------------|-----------|-----------------------|------------------------|
| | IUPAC No. | Structure | |
| <i>Non-ortho</i> | 77 | 3,3',4,4'-TCB | 0.0005 |
| | 126 | 3,3',4,4',5-PeCB | 0.1 |
| | 169 | 3,3',4,4',5,5'-HxCB | 0.01 |
| <i>Mono-ortho</i> | 105 | 2,3,3',4,4'-PeCB | 0.0001 |
| | 114 | 2,3,4,4',5-PeCB | 0.0005 ^{1, 2} |
| | 118 | 2,3',4,4',5-PeCB | 0.0001 |
| | 123 | 2',3,4,4',5-PeCB | 0.0001 |
| | 156 | 2,3,3',4,4',5-HxCB | 0.0005 ² |
| | 157 | 2,3,3',4,4',5'-HxCB | 0.0005 ² |
| | 167 | 2,3',4,4',5,5'-HxCB | 0.00001 ¹ |
| | 189 | 2,3,3',4,4',5,5'-HpCB | 0.0001 ¹ |
| <i>Di-ortho</i> | 170 | 2,2',3,3',4,4',5-HpCB | 0.0001 ¹ |
| | 180 | 2,2',3,4,4',5,5'-HpCB | 0.00001 ¹ |

¹ Based on very limited data.

² IUPAC 114, 156, and 157 are expected to have similar TEF-values based on similar responses. Although the data is limited, the determination of TEFs for these congeners is supported by their structural similarity.

* Ahlberg U.G., G.C. Becking, L.S. Birnbaum, A. Brouwer, H.J.G.M. Derks, M. Feeley, G. Golor, H. Hanberg, J.C. Larsen, A.K.D. Liem, S.H. Safe, C. Schlatter, F. Waern, M. Younes, and E. Yrjänheikki (1994): Toxic Equivalency Factors for Dioxin-like PCBs. *Chemosphere* **28**, 1049-1067

Table 2. Toxic equivalents (TEQs) calculated for fish, cow's milk and human milk samples using the present interim WHO/IPCS TEFs are compared to the previously used TEFs by Safe 1990, Safe 1994 and Ahlborg et al 1992a. Chemical data for the human milk are from Norén & Lundén 1991, data on cow's milk are from WHO/EURO 1994 and data on salmon are from Great Lakes Health Effects Division, Health and Welfare Canada (unpublished data).

| IUPAC | TEF-system | | | | Human milk | | | | | Cow's milk | | | | | Salmon | | | | |
|--------------------------------|--------------|---------|--------------|--------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------|---------|--------------|--------------|-----------------------------|--------------|---------|--------------|--------------|
| | WHO/ IPCS | Ahlborg | Safe 1990 | Safe 1994 | Conc. pg/g fat | TEQ | | | | Conc. pg/g fat | TEQ | | | | Conc. pg/g wet weight | TEQ | | | |
| | | | | | | WHO/ IPCS | Ahlborg | Safe 1990 | Safe 1994 | | WHO/ IPCS | Ahlborg | Safe 1990 | Safe 1994 | | WHO/ IPCS | Ahlborg | Safe 1990 | Safe 1994 |
| 77 | 0.0005 | 0.0005 | 0.01 | 0.01 | 27 | 0.01 | 0.01 | 0.3 | 0.3 | 3.4 | 0.002 | 0.002 | 0.03 | 0.03 | 930 | 0.5 | 0.5 | 9.3 | 9.3 |
| 126 | 0.1 | 0.1 | 0.1 | 0.1 | 98 | 9.8 | 9.8 | 9.8 | 9.8 | 23.3 | 2.3 | 2.3 | 2.3 | 2.3 | 660 | 66.0 | 66.0 | 66.0 | 66.0 |
| 169 | 0.01 | 0.01 | 0.05 | 0.05 | 47 | 0.5 | 0.5 | 2.4 | 2.4 | 9.9 | 0.1 | 0.1 | 0.5 | 0.5 | 120 | 1.2 | 1.2 | 6.0 | 6.0 |
| 105 | 0.0001 | 0.0001 | 0.001 | 0.001 | 6000 | 0.6 | 0.6 | 6.0 | 6.0 | 590 | 0.06 | 0.06 | 0.6 | 0.6 | 120000 | 12.0 | 12.0 | 120.0 | 120.0 |
| 114 | 0.0005 | 0.0005 | 0.001 | 0.0002 | NA ¹ | | | | | NA | | | | | ND ² | | | | |
| 118 | 0.0001 | 0.0001 | 0.001 | 0.0001 | 25000 | 2.5 | 2.5 | 25.0 | 2.5 | 3000 | 0.3 | 0.3 | 3.0 | 0.3 | 240000 | 24.0 | 24.0 | 240.0 | 24.0 |
| 123 | 0.0001 | 0.0001 | 0.001 | 0.00005 | NA | | | | | NA | | | | | ND | | | | |
| 156 | 0.0005 | 0.001 | 0.001 | 0.0004 | 14000 | 7.0 | 14.0 | 14.0 | 5.6 | NA | | | | | 20000 | 10.0 | 20.0 | 20.0 | 8.0 |
| 157 | 0.0005 | 0.001 | 0.001 | 0.0003 | NA | | | | | NA | | | | | ND | | | | |
| 167 | 0.00001 | | 0.001 | | NA | | | | | NA | | | | | 17000 | 0.2 | | 17.0 | |
| 189 | 0.0001 | | 0.001 | | NA | | | | | NA | | | | | 6500 | 0.6 | | 6.5 | |
| 170 | 0.0001 | | 0.00002 | | NA | | | | | NA | | | | | 62000 | 6.2 | | 1.2 | |
| 180 | 0.00001 | | 0.00002 | | 64000 | 0.6 | | 1.3 | | 3600 | 0.04 | | 0.07 | | 210000 | 2.1 | | 4.2 | |
| Sum of TEQ for non-ortho PCBs | | | | | | 10.3 | 10.3 | 12.5 | 12.5 | | 2.4 | 2.4 | 2.8 | 2.8 | | 67.7 | 67.7 | 81.3 | 81.3 |
| Sum of TEQ for mono-ortho PCB | | | | | | 10.1 | 17.1 | 45.0 | 14.1 | | 0.4 | 0.4 | 3.6 | 0.9 | | 46.8 | 56.0 | 403.5 | 152.0 |
| Sum of TEQ for di-ortho PCBs | | | | | | 0.6 | | 1.3 | | | 0.04 | | 0.07 | | | 8.3 | | 5.4 | |
| Total TEQ for all PCBs | | | | | | 21.0 | 27.4 | 58.8 | 26.6 | | 2.8 | 2.8 | 6.5 | 3.7 | | 122.8 | 123.7 | 490.2 | 233.3 |
| Sum of TEQ for PCDDs and PCDFs | | | | | | 20.6 ³ | 20.6 ³ | 20.6 ³ | 20.6 ³ | | 5.6 | 5.6 | 5.6 | 5.6 | | 56.0 | 56.0 | 56.0 | 56.0 |

¹ NA = Not analyzed

² ND = Not detected

³ Not all 2,3,7,8-penta, hexa and hepta substituted congeners were measured.