Development, Validation and Limitations of the Toxic Equivalency Factor (TEF) Approach for Halogenated Aromatic Hydrocarbons

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ABSTRACT

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and related toxic halogenated aryl hydrocarbons (HAHs) have been identified as complex mixtures of environmental contaminants in almost every environmental matrix. The relative toxic potencies of individual HAH congeners compared to 2,3,7,8-TCDD have been determined and toxic equivalency factors (TEFs) have been assigned to most of the toxic HAHs. The applications and limitations of the TEF approach for the hazard and risk assessment of HAH mixtures will be discussed.

INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs) are industrial compounds or by-products which have been identified as contaminants in almost every component of the global ecosystem including fish, wildlife, human adipose tissue, serum and milk. Invariably these compounds occur as complex mixtures of isomers and congeners which can only now be identified and quantitated by high resolution analytical techniques. The hazard and risk assessment of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) initially focused on the levels of a single congener, namely 2,3,7,8-TCDD, which is the most toxic member of this class of compounds. However, it was evident that 2,3,7,8-TCDD was a relatively minor component of most industrial and environmental mixtures containing PCDDs and PCDFs and several studies have also reported that many of the 2,3,7,8-substituted congeners were also highly toxic.[1-3] It is generally accepted that the mechanism of action of 2,3,7,8-TCDD and related compounds involves initial binding to the cytosolic aryl hydrocarbon (Ah) receptor protein and this is supported by the correlation between the structure-receptor binding and structure-toxicity relationships for several different structural classes of HAHs.[1-3] Based on their common receptor-mediated mechanism of action and structure-activity relationships, the toxic equivalency factor (TEF) approach for PCDDs and PCDFs has been

developed by several regulatory agencies and a similar approach is being considered for the PCBs.[4,5] Since 2,3,7,8-TCDD is the most toxic HAH, this congener is assigned a TEF value of 1.0 and all other compounds are given TEFs which reflect their potencies relative to 2,3,7,8-TCDD. The individual TEF values can be used to estimate the toxicity of a complex mixture of PCDDs and PCDFs since the Σ [PCDD or PCDF congener](TEF) is equal to the 2,3,7,8-TCDD or toxic equivalents (TEQs) for this mixture. This transformation of a complex array of analytical data into a single TEQ provides a numerical value which has toxicological significance and can be used for hazard and risk assessment of the mixture. The TEF approach is based on a number of assumptions which include the following: (i) the TEFs and TEQs can only be used to assess Ah receptor-mediated responses; (ii) the toxicities of the individual congeners in the mixture are essentially additive, and (iii) a single TEF value can be used to predict relative potencies for all responses.

RESULTS AND DISCUSSIONS

Several different sets of TEF values have been proposed for the 2,3,7,8-substituted PCDDs and PCDFs and these are summarized in Table 1.[3-5] With the exception of 1,2,3,7,8-pentaCDF, most regulatory agencies have adopted the same TEF values for most of the congeners. In addition, recent studies have reported unexpectedly high immunotoxicity for the 1,2,3,4,6,7,8- and 1,2,3,4,7,8,9-heptaCDF and Safe has recommended a TEF of 0.1 for these isomers. A discussion of the validation of the TEF approach for PCDD and PCDF mixtures has been reported[3] and the results suggest that there was good correspondence between the observed and predicted toxic potencies of these mixtures.

The structure-activity relationships for PCBs as Ah receptor agonists have been well documented[3,6] and the most toxic compounds are the coplanar 3,3′,4,4′-tetra-, 3,3′,4,4′,5-penta- and 3,3′,4,4′,5,5′-hexaCB congeners. In addition, the monoortho coplanar homologs also exhibit TCDD-like activity. Like the PCDDs and PCDFs, the TEFs for the individual coplanar and monoortho coplanar PCBs encompass a broad range of values which are dependent on the response and the target organ or cell line. Safe[3] has proposed the following highly conservative TEFs for 3,3′,4,4′-tetraCB, 3,3′,4,4′,5-pentaCB, 3,3′,4,4′,5,5′-hexaCB and the monoortho coplanar PCBs, namely 0.01, 0.05, 0.01 and 0.001, respectively. Utilization of these TEFs or those derived from *in vitro* enzyme induction data has shown that for most extracts of environmental samples, the TEQs for PCBs are significantly higher than those for the PCDDs and PCDFs.[3,7,8]

Previous studies have reported that some PCB congeners and commercial PCB (Aroclor) mixtures exhibit "anti-dioxin" activity.[3,9,10] For example, PCB-inhibition of 2,3,7,8-TCDD-induced monooxygenase enzyme induction activity, immunotoxicity and teratogenicity has been reported. The results in Table 2 summarize the calculated ED_{50} values for the immunotoxicity of several commercial PCB mixtures. (Note: these values were calculated using the conservative TEFs

noted above and the concentrations of the individual coplanar and monoortho coplanar PCBs in the commercial Aroclors.) The observed ED_{50} values for the immunosuppression of the plaque-forming cell response to sheep red blood cells were considerably higher than the calculated values. Two possible explanations for these results are (i) the proposed TEF values for the PCBs are too high and (ii) there are significant antagonistic interactions among the different classes of PCB congeners. Thus before the TEF approach is used for the hazard and risk assessment of PCBs, research on the TEFs for individual congeners and the nature of the interactive effects of PCBs with other classes of HAHs must be determined. (Supported by the National Institutes of Health P42-ES04917).

Table 1. Proposed TEFs for the PCDDs and PCDFs.[3-5]

Congener	TEF
PCDDs	
2,3,7,8-TCDD	1.0
1,3,7,8-pentaCDD	0.5
1,2,3,4,7,8-hexaCDD	0.1
1,2,3,6,7,8-hexaCDD	0.1
1,2,3,7,8,9-hexaCDD	0.1
1,2,3,4,6,7,8-heptaCDD	0.01
OCDD	0.001
PCDFs	
2,3,7,8-TCDF	0.1
2,3,4,7,8-pentaCDF	0.5
1,2,3,7,8-pentaCDF	0.1 (0.05, 0.01)
1,2,3,4,7,8-hexaCDF	0.1
2,3,4,6,7,8-hexaCDF	0.1
1,2,3,6,7,8-hexaCDF	0.1
1,2,3,7,8,9-hexaCDF	0.1
1,2,3,4,6,7,8-heptaCDF	0.1 (0.01)
1,2,3,4,7,8,9-heptaCDF	0.1 (0.01)
OCDF	0.001

Table 2. Limitations of the TEF Approach - Immunotoxicity in C57BL/6 Mice.[a]

Mixture	Calculated ED_{50}[a] (mg/kg)	Observed ED_{50}[b] (mg/kg)
Aroclor 1232	19	464
Aroclor 1242	10	391
Aroclor 1248	not available	190
Aroclor 1254	6	118
Aroclor 1260	33	104

[a] calculated by Dr. S. Hamilton, General Electric, using the coplanar and monoortho coplanar PCB levels.
[b] see reference 9.

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