DEVELOPMENT OF TOXIC EQUIVALENCY FACTORS (TEFs) FOR HALOGENATED AROMATIC HYDROCARBONS

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ABSTRACT

2,3,7,8-TCDD and structurally related compounds elicit a number of common toxic and biochemical responses in laboratory animals and mammalian cells in culture. The major differences between these chemicals are their potencies. The results from several studies on the quantitative structure-activity relationships (QSARs) for 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons have been utilized to derive TEFs (relative to 2,3,7,8-TCDD) for the 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins and dibenzofurans.

INTRODUCTION

2,3,7,8-TCDD has been extensively utilized as a prototype for investigating the mechanism of action of the toxic halogenated aromatic hydrocarbons (1,2). It is apparent that 2,3,7,8-TCDD elicits a diverse spectrum of species-, strain-, age- and sex-dependent biochemical and toxic effects in laboratory animals and the corresponding toxic polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and their bromo- and bromo-/chloro-analogs cause similar responses (1-3). Extensive structure-activity relationships for PCDDs, PCDFs and PCBs have demonstrated that the major differences between the toxic halogenated aromatic hydrocarbons are their relative potencies. These data, coupled with other mechanistic studies, show that 2,3,7,8-TCDD and related compounds act through a common mechanism which involves the initial interaction of the toxins with the cytosolic aryl hydrocarbon (Ah) receptor protein (1,2).

The halogenated aromatic hydrocarbons (HAHs) which have been identified in environmental matrices are complex mixtures of isomers and congeners. Hazard and risk assessment of these mixtures requires toxicity data on the individual compounds present in the mixtures. Thus, TEFs (relative to 2,3,7,8-TCDD) have been determined for several PCDD, PCB and PCDF congeners and these values can be used for assessing the potential hazard and risk of mixtures containing these compounds (4-6). It should be noted that TEFs have been developed to measure "2,3,7,8-TCDD-like" activity and it has been assumed that the interactions of HAHs present in a mixture are additive.

RESULTS AND DISCUSSION

TEFs have been proposed for the 2,3,7,8-substituted PCDDs and PCDFs which contain four or more chlorine groups and this includes ten and seven of the 135 and 75 possible PCDF and PCDD congeners respectively. The potential toxicities of congeners

Table 1. TEF Values for 2,3,7,8-Substituted PCDDs and PCDFs.

Congener	TEF Values NATO-CCMS	Nordic	Revised	Relative Potency Ranges In Vivo Toxicities	In Vitro Results[a]
a. PCDDS					
2,3,7,8-TCDD	1	1	1	-	-
1,2,3,7,8-pentaCDD	0.5	0.5	0.5	0.59-0.053	0.64-0.07
1,2,34,7,8-hexaCDD	0.1	0.1	0.1	0.24-0.013	0.13-0.05
1,2,3,6,7,8-hexaCDD	0.1	0.1	0.1	0.16-0.0152	0.5-0.005
1,2,3,4,7,8,9-hexaCDD	0.1	0.1	0.1	0.14-0.016	0.009
1,2,3,4,6,7,8-hexaCDD	0.01	0.01	0.01	0.0076	.003
OCDD	0.001	0.001	0.001	> 0.0013	0.0006
b. PCDFs					
2,3,7,8-TCDF	0.1	0.1	0.1	0.17-0.016	0.43-0.006
2,3,4,7,8-pentaCDF	0.5	0.5	0.5	0.8-0.12	0.67-0.11
1,2,3,7,8-pentaCDF	0.05	0.01	0.05	0.9-0.018	0.13-0.03
1,2,3,4,7,8-hexaCDF	0.1	0.1	0.1	0.18-0.038	0.2-0.013
2,3,4,6,7,8-hexaCDF	0.1	0.1	0.1	0.097-0.017	0.1-0.015
1,2,3,6,7,8-hexaCDF	0.1	0.1	0.1	-	-
1,2,3,7,8,9-hexaCDF	0.1	0.1	0.1	-	-
1,2,3,4,6,7,8-heptaCDF	0.01	0.01	0.1	0.18-0.009	-
1,2,3,4,7,8,9-heptaCDF	0.01	0.01	0.1	0.17-0.003	-
OCDF	0.001	0.001	0.001	-	-

[a]does not include receptor binding data

with fewer than four lateral chlorine substituents have been ignored by most TEF schemes and this approach may be justified since (a) the 2,3,7,8-substituted PCDDs and PCDFs (Cl_4-Cl_6) are the most toxic members of each class and (b) constitute > 80% of the total PCDDs plus PCDFs present in most environmental samples. Table 1 summarizes the range of relative potencies of the 2,3,7,8-substituted PCDDs and PCDFs and also includes the TEF values recommended by the Nordic countries, an International group (4,5) and by the author (6). It is evident that the experimental TEF values vary considerably, however, with few exceptions, the TEFs suggested by these groups are comparable. The higher TEFs proposed by the author for the heptachlorodibenzofurans (heptaCDFs) are based on recent immunotoxicity studies in C57BL/6 mice (7). It should be noted that the TEF values assigned to individual congeners will change with the addition of new experimental data.

Eadon and coworkers have previously investigated the toxicity of a PCDF/PCDD mixture obtained from PCB fire in the Binghamton state office building (8). The observed 2,3,7,8-TCDD equivalents for the *in vivo* toxicity of this mixture to guinea pigs was comparable to the corresponding value which was calculated from the known composition and their respective TEFs (6). Additional studies are required to further validate the TEF approach for hazard and risk assessment of toxic HAHs.

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.

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