A Preliminary Approach to Characterizing Variability and Uncetainty in the Mammalian PCDD/F and PCB TEFs

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Introduction

The current toxic equivalency factors (TEFs) for PCDD/Fs and "dioxin-like" PCBs represent consensus-based values that were recommended by an international panel of experts convened by the World Health Organization (WHO) in June of 1997.[1] As a part of the development of the mammalian TEFs, the WHO expert panel considered an extensive body of *in vivo* and *in vitro* studies compiled into a database of relative potency (REP) values by scientists at the Karolinska Institute in Stockholm Sweden (hereafter referred to as the Karolinska database). In deriving the TEFs from the underlying REP data, the WHO expert panel employed the following qualitative criteria: 1) *in vivo* studies were given greater weight than were *in vitro* studies and/or quantitative structure activity relationship (QSAR) data; 2) chronic studies were given greater weight than subchronic studies, which were given greater weight than subacute studies, which were given more weight than acute studies; and 3) toxic responses were given more weight than biochemical responses (e.g., enzyme induction).[1] In accordance with the procedures for review established by the WHO expert panel, previously established TEFs for PCDD/Fs[2,3] and dioxin-like PCBs[4] were retained unless there were sufficient data to support a change.[1] The final TEFs recommended by the WHO expert panel were determined based on scientific judgment and represent order-of-magnitude estimates of potency for each of the congeners relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

As has been indicated by a number of investigators, the REP values for many congeners are derived from a highly heterogeneous data set, and for most TEFs, the range of underlying REP values often spans several orders of magnitude.[1,5,6,7] However, the degree to which the current "point estimate" TEFs introduce variability and uncertainty into the health risk assessment process cannot be

characterized in a quantitative fashion. Such characterizations may be important in settings where numerous PCDD/F and PCB congeners contribute to potential health risk. We believe that the use of REP distributions, as a supplement to or in place of "point estimate" TEFs, would facilitate such characterizations. Specifically, use of a range of REP values, perhaps with a clearly identified "central tendency" (e.g., 50^{th} percentile) and/or "upper bound" (e.g., 90^{th} or 95^{th} percentile), would permit more informed discussions regarding the degree to which the TEFs contribute to variability and uncertainty in health risk estimates. This is important given the widespread use of the TEFs by numerous governmental agencies and others to regulate or otherwise assess potential health risks associated with exposures to this class of compounds. In this analysis, we describe the derivation of REP distributions for certain PCDD/F and PCB congeners using a "refined" REP database that was developed for this purpose

Methods

The Karolinska database was not intentionally designed or annotated in such a way as to be ideal for development of REP distributions or other quantitative analyses. As described elsewhere,[8] we have developed a refined REP database wherein certain REP values have been removed based on one or more of the following: 1) values were excluded due to procedural errors (e.g., data entry errors, multiple entries of the same REP value published in different studies, etc.); 2) values were excluded because they did not meet the original WHO selection criteria (e.g., lack of a reference compound, use of non-mammalian data, lack of a response, etc.); or 3) values were excluded for other, more subjective reasons (e.g., values derived from QSAR data or a mixtures study, values derived from unpublished studies that were unobtainable, multiple REPs from a single study that used different assays to measure the same response, etc.).[8] This refined database contains 58% and 49% of the PCDD/F and PCB REPs in the original Karolinska database (respectively). In addition, we have corrected and/or updated the study element information (descriptors of study methods and results), as appropriate.

The number of REPs for each congener is highly variable, with as few as a single REP value for 123789HxCDF, 1234678HpCDF, and 1234789HpCDF, to as many as 62 REP values for PCB 126. We chose to develop distributions for those congeners with 10 or more REP values. This criterion is consistent with recommendations regarding calculation of statistically-valid exposure-point concentrations.[9] There are 15 congeners in the refined database that have 10 or more REP values, as shown in Table 1. A preliminary analysis indicated that the REP distributions for these congeners could not be described as parametric distributions based on statistical goodness-of-fit tests (Shapiro-Wilk, Kolmogorov-Smirnov, Chi-Square, and Anderson-Darling). Therefore, we did not assume any specific distributional shape but instead express the distribution empirically in the form of percentiles.

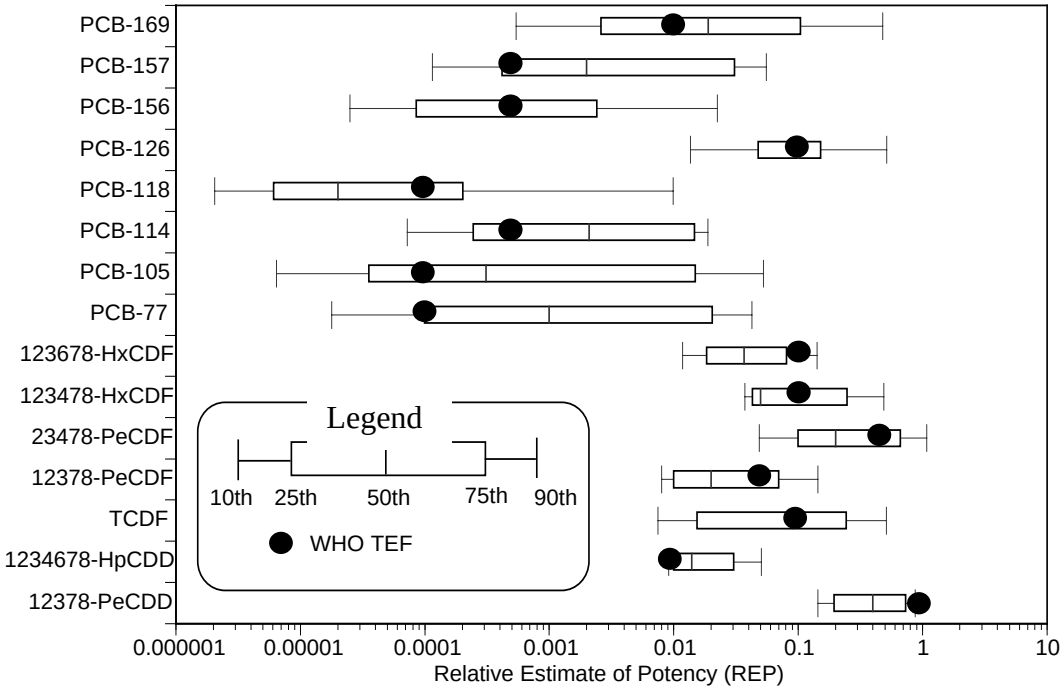
Table 1
Congeners with a Sufficient Number of Valid REP Values

PCDD/PCDF Congeners	PCB Congeners
12378 PeCDD	PCB 77
1234678 HpCDD	PCB 105
TCDF	PCB 114
12378 PeCDF	PCB 118
23478 PeCDF	PCB 126
123478 HxCDF	PCB 156
123678 HxCDF	PCB 157
	PCB 169

Results and Discussion

As can be seen in Figure 1, REP values for a given PCDD/F congener typically range across 1–3 orders of magnitude, while the REP values for any given PCB congener were found to range across 3–6 orders of magnitude. An evaluation of the REP distributions for each congener showed that the WHO consensus-based TEFs for PCDD/Fs are generally consistent with the upper bound of the distributions, whereas the consensus-based TEFs for the dioxin-like PCBs are generally more representative of the central tendency or lower range of the underlying distributions (Table 2). These findings are consistent with earlier studies conducted using the original Karolinska database.[10]

Figure 1
Distributions of REP Values



Although distributions were not developed for those congeners with fewer than 10 REP values, basic summary statistics were developed (Table 3). As was observed for those congeners having 10 or more REP values, the data in Table 3 indicate that there was greater variability in the range of REP values for the dioxin-like PCBs than for the PCDD/Fs. With the exception of OCDF, there was generally about an order of magnitude difference between the minimum and maximum REP values for the PCDD/Fs, while the difference for PCBs was about three orders of magnitude. Additionally, there were three congeners (123789 HxCDF, 1234678 HpCDF, 1234789 HpCDF) with only a single REP value in the refined database. It is important to note that while the REP data set for these three congeners is limited, they are only minor contributors to the overall background human body burden and do not typically drive regulatory action. With regard to the other congeners that have fewer than 10 REP values, only 123678-HxCDD has been found to contribute significantly to the overall background human body burden based on the current WHO TEFs. However, because there appear to be inconsistencies in the degree of conservatism in the TEFs established for individual congeners, this picture could change. In addition, although some of these congeners may appear to be minor contributors on an individual basis, when taken together in an assessment of cumulative risk, they may, in fact, tip the balance in favor of regulatory action.

Table 2
Distributions of REP Values Based on Our Refined Database

Congener	N	Min.	Max.	50th %'ile	75th %'ile	90th %'ile	WHO TEF	WHO TEF %'ile Rank
12378 PeCDD	29	0.095	1.1	0.40	0.72	0.84	1	94th
1234678 HpCDD	20	0.0045	0.10	0.014	0.030	0.048	0.01	11th
TCDF	25	0.0060	1.2	0.090	0.24	0.46	0.1	60th
12378 PeCDF	21	0.0027	0.95	0.02	0.06	0.13	0.05	65th
23478 PeCDF	49	0.0065	3.7	0.20	0.66	1.0	0.5	73rd
123478 HxCDF	11	0.014	0.49	0.050	0.23	0.49	0.1	63rd
123678 HxCDF	12	0.01	0.15	0.037	0.078	0.14	0.1	82nd
PCB 77	50	2.0E-06	0.41	0.0010	0.020	0.041	0.0001	20th
PCB 105	34	4.7E-07	0.18	0.00031	0.014	0.050	0.0001	36th
PCB 114	10	7.0E-05	0.025	0.0021	0.014	0.018	0.0005	34th
PCB 118	24	4.2E-07	0.19	2.0E-05	0.00015	0.0067	0.0001	74th
PCB 126	62	0.00069	0.86	0.10	0.11	0.47	0.1	51st
PCB 156	47	2.0E-06	0.16	0.00053	0.0023	0.016	0.0005	43rd
PCB 157	13	4.0E-05	0.175	0.0020	0.031	0.045	0.0005	26th
PCB 169	35	7.0E-05	0.77	0.019	0.10	0.42	0.01	47th

N=total number of REP values; Min.=minimum REP value for the specific congener;
Max.=maximum REP value for the specific congener

With additional refinement, REP distributions such as those described in Table 2 could ultimately be used directly in a probabilistic analysis of risk and/or as a basis for establishing a consistent TEF point estimate (e.g., 50th, 75th, 90th, or 95th percentile) for use in deterministic analyses. One shortcoming of the approach described herein is that all REP values were treated equally. Equal weighting of all REP values may not provide an accurate estimate of relative potency. The development and application of a quantitative weighting scheme would allow more emphasis to be placed on those studies that are of better quality and provide more relevant data. In its review of the USEPA Dioxin Reassessment, the Science Advisory Board concluded that a weighting approach had merit and should be considered in future updates to the TEF scheme.[11] We are currently evaluating a number of different quantitative weighting schemes that could be applied during the development of distributions to place greater emphasis on those REPs from studies that are of higher quality or are expected to be more reliable. These efforts refine and extend the preliminary weighting schemes described by Finley et al.[10,12] and Connor et al.[13] The development of a transparent quantitative weighting scheme, in conjunction with the development of distributions, will also facilitate the addition of new studies as they become available, thereby minimizing the need to reconvene an expert panel.

Table 3
Summary Statistics for Congeners with Fewer Than 10 REP Values

Congener	# REP Values	Range of REP Values	Median REP Value
123478 HxCDD	8	0.050-0.061	0.084
123678 HxCDD	5	0.031-0.20	0.043
123789 HxCDD	4	0.0054-0.070	0.052
OCDD	8	0.00029-0.0032	0.0012
123789 HxCDF	1	0.20-0.20	0.20
234678 HxCDF	7	0.015-0.32	0.21
1234678 HpCDF	1	0.010-0.010	0.010
1234789 HpCDF	1	0.018-0.018	0.018
OCDF	7	4.0E-06-0.0028	0.00011
PCB 81	8	4.18E-050.020-	0.0071
PCB 123	9	3.41E-05-0.027	0.00089
PCB 167	6	2.0E-06-0.0052	0.00032
PCB 189	7	1.0E-05-0.022	0.00018

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