WEIGHTED PCDD/F AND PCB REP DISTRIBUTIONS AND THEIR USE IN PROBABILISTIC RISK ASSESSMENT

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Introduction

Toxic equivalency factors (TEFs) are estimates of the relative potency (REP) of 2,3,7,8-substituted PCDD/Fs and coplanar PCBs. The World Health Organization (W.H.O.) recently proposed a list of updated TEFs for these compounds, based on their review of over 900 REP values from *in vitro* and *in vivo* animal studies[1]. Consistent with previous TEF schemes, the W.H.O. TEFs are point estimates established from a range of REP values for a particular congener.

We recently determined that the degree of conservatism in the W.H.O. TEFs varies considerably amongst the congeners[2]. In general, the PCB TEFs represent the central tendency of the range of REP values, while the PCDD/F TEFs tend to be more representative of upper-bound estimates. Because the range of REP values typically span several orders of magnitude, this disparity can introduce a significant degree of uncertainty in the risk assessment and risk apportioning process, particularly in settings where these chemical classes are co-mingled. To address this inconsistency, we proposed the use of probabilistic distributions for the REP values[2].

In this paper, we extend and refine our initial analysis via the development of "weighted" REP distributions. The studies which comprise the individual REP values for a given congener can vary considerably in quality, ranging from simple *in vitro* receptor binding assays to long-term *in vivo* exposures. Accordingly, it is reasonable to suggest that equal weighting of all studies may not provide an accurate representation of relative potency. The purpose of this analysis is to assess the influence of different (and fairly simplistic) weighting schemes in which greater quantitative emphasis is placed on those individual studies which provide more relevant and substantial potency data, based on standard toxicity-testing principles. The relative influence of each weighting scheme is determined in part via a case study probabilistic risk assessment involving fish consumption. These findings can be used to assess whether and to what degree a weighting analysis will be critical to the development of standard distributions suitable for use in probabilistic analyses.

Methods and Materials

The electronic W.H.O. REP database was used to construct unweighted REP distributions for each congener (see Finley et al, 1999 for details). With one exception, these distributions exhibited a "best fit" to a lognormal distribution. The nature of the studies used to derive each of the REP values was then reviewed, and two different weighting schemes were developed, as summarized in Table 1. In Weighting Scheme 1, the *in vitro* values were simply assigned a relative weighting

equal to one-third of the *in vivo* values. In Scheme 2, *in vitro* values were placed into one of 5 categories; REP values from unknown cell lines received the lowest relative ranking of 1, values from human cell lines in which chemical exposure occurred for < 24 hours received the highest relative ranking of 5. The *in vivo* studies were placed into 12 categories, with relative weightings increasing in a geometric progression from the lowest ranked study type (mortality study) to the highest ranked study type (cancer bioassay).

Table 1. Weighting Schemes for REP Distributions

Study Type	Endpoint	Relative Weighting	
		Scheme 1	Scheme 2
In vivo	Cancer	3	12,288
In vivo	Enzyme	3	6,144
In vivo	Immunotoxicity	3	3,072
In vivo	Vitamin A	3	1,536
In vivo	Liver Weight	3	768
In vivo	Hepatic Lipid	3	384
In vivo	Other Weight	3	192
In vivo	Teratogenicity	3	96
In vivo	Hematology	3	48
In vivo	Thyroid	3	24
In vivo	Hormone	3	12
In vivo	Mortality	3	6
In vitro	Human cell lines, <= 24 hours	1	5
In vitro	Human cell lines, >24 hours	1	4
In vitro	Nonhuman cell lines, <= 24 hours	1	3
In vitro	Nonhuman cell lines, >24 hours	1	2
In vitro	Unknown cell line	1	1

Table 2 presents 50th and 95th percentile values of the unweighted and weighted distributions of the relatively more potent and persistent congeners. A probabilistic analysis of PCDD/F and PCB risk via fish consumption was developed using representative fish and crab tissue data from an industrialized waterway in New Jersey. Generic distributions for total tissue consumption rates, exposure duration, and adult male body weight were taken from Finley et al[3]; site-specific point

estimates of fraction of fish and crab that comprise total tissue intake were taken from Finley et al[4]. The risk estimates associated with the different weighting schemes are summarized in Table 3.

Results and Discussion

As shown in Table 2, for most congeners, increased emphasis on *in vivo* studies had little influence on the central tendency and upper bound values of the REP distribution. Most REP distributions still exhibited a "best fit" to a lognormal distribution under either weighting scheme, and in general the 50th and 95th percentiles of the distributions changed by less than an order of magnitude. This may be due to the fact that, for any given congener, the *in vivo* data are not disproportionately representative of upper- or lower-bound values, i.e., they tend to be homogenously distributed throughout the REP distribution. Significantly increased weighting of the *in vivo* data therefore does not significantly alter the 50th/95th percentile values.

Table 2. Summary of REP Probability Distribution Percentiles

Congener	Weighting Scheme					
	Unweighted		Scheme 1		Scheme 2	
	50th	95th	50th	95th	50th	95th
12378PeCDD	0.50	0.91	0.40	1.04	0.50	0.91
123478HxCDD	0.08	0.61	0.07	0.61	0.07	0.61
123679HxCDD	0.031	0.220	0.031	0.220	0.031	0.220
123789HxCDD	0.042	0.70	0.42	0.070	0.042	0.070
1234678HpCDD	0.014	0.060	0.018	0.10	0.020	0.060
2378TCDF	0.070	0.50	0.30	0.50	0.019	0.500
12378PeCDF	0.023	0.750	0.018	0.20	0.015	0.100
23478PeCDF	0.20	1.44	0.20	1.44	0.13	0.70
123478HxCDF	0.050	3.98	0.050	0.490	0.014	0.050
123678HxCDF	0.050	0.150	0.063	0.100	0.014	0.100
234678HxCDF	0.120	0.320	0.100	0.320	0.015	0.015
1234678HpCDF	0.100	0.320	0.100	0.320	0.040	0.100
PCB 126	0.10	0.77	0.10	0.67	0.06	0.55
PCB 169	0.01	0.74	0.01	0.71	0.01	0.71
PCB 77	0.0003	0.0360	0.0001	0.0360	0.0000	0.0360
PCB 157	0.00025	0.00500	0.00042	0.01800	0.00042	0.01800
PCB 156	0.00017	0.00460	0.00018	0.00460	0.00017	0.00250
PCB 105	0.00005	0.00230	0.00004	0.00170	0.00003	0.00050
PCB 118	0.00004	0.00080	0.00004	0.00067	0.00005	0.00067

As shown in Table 3, use of distributions yields results that are qualitatively and quantitatively different from those obtained with point estimates. Specifically, use of distributions tends to yield higher risk estimates for PCBs, and decreased risk estimates for PCDD/Fs. This is a result of the fact that the W.H.O. PCB TEF point estimates are representative of central tendency values, while the PCDD/F TEF point estimates are more representative of upper-bound values. Use of

distributions "corrects" for this disparity. Although the changes in the 95th percentile risk estimates are not dramatic, it is interesting to note that the most significant contributor to total risk is different under deterministic (PCBs) vs. probabilistic (PCDD/F) conditions. This suggests that risk apportionment in areas where these two chemical classes are present might depend on whether deterministic or probabilistic risk analyses are employed.

Table 3. Comparison of 95th Percentile Risk Estimates Associated with Different Weighting Schemes

Analysis	PCB Risk	PCDD/F Risk
Deterministic with W.H.O. Point TEFs	2.25E-04	2.71E-04
Probabilistic with Unweighted TEF PDFs	2.64E-03	2.81E-04
Probabilistic with Weighting Scheme 1 TEF PDFs	2.54E-04	8.23E-05
Probabilistic with Weighting Scheme 2 TEF PDFs	2.97E-04	8.65E-05

The results described here are preliminary; we present a simplistic weighting scheme that does not attempt to weight the *quality* of the individual studies. As noted in by Starr et al[5], a rigorous weighting analysis might account and correct for departures from parallelism of the dose-response curves and high dose data that are not relevant to environmental exposures. However, these preliminary findings suggest that a more in-depth analysis may yield distributions that are not significantly different from unweighted or simplistically weighted distributions.

References

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