ASSESSMENT OF THE IMPACT OF USING WEIGHTED DISTRIBUTIONS OF REPs TO DEVELOP EXPOSURE ESTIMATES FOR DIOXIN-LIKE COMPOUNDS

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Introduction

The current approach for evaluating potential health risks associated with exposure to mixtures of dioxin-like compounds (DLCs) involves use of the toxic equivalency factor (TEF) methodology. TEFs are relative potency estimates (REPs) based on qualitative scientific judgment and reflect single point estimates determined based on all available data describing the REP of a chemical compound compared to TCDD[1,2]. However, because the REPs for any given congener are based on a host of different endpoints, test conditions and derivation methods, they represent a heterogeneous data set and range across several orders of magnitude[1,2,3,4]. Because the TEFs are established using a qualitative process and are presented as a single point estimates, the variability in the underlying REP distributions is not captured and, as a result, it is not possible to characterize the uncertainty inherent in the risk estimates that are developed based on the TEFs.

To address limitation of the TEF methodology, some investigators have proposed developing distributions of REP values that could in turn be used in probabilistic risk assessments[2,3]. During their most recent reevaluation of the TEF methodology, the WHO expert panel indicated that consideration should be given to developing weighted distributions of REP values and these weighted distributions could then be used to establish TEFs for each DLC. Based on this recommendation, we developed an objective, consensus-based weighting framework that could be used to identify and place greater emphasis on REPs relevant for purposes of estimating human health risks[5]. In this study, the weighting framework was applied and the impact of using weighted distributions of REPs was investigated by estimating the intake associated with consumption of catfish containing DLCs using several different approaches.

Materials and Methods

***REP Weighting*:** For each REP, numerical values were assigned to each of the study elements in the framework (Figure 1) and the study elements were then compared against one another to determine the weight for each individual study element. The REP weights were determined using an algebraic solution such that the ratios for all paired comparisons were taken into account simultaneously. The weights for each study element were then combined with each of the different study elements (e.g., PK, REP derivation quality, REP derivation method) being given equal weight, and study type given the most weight, to calculate the overall weight for the REP value based on a log scale[5]. Using this framework, weighted REP distributions were generated for all studies and congeners in the REP_{2006} database[2].

Case Study: In this case study, the impact of using weighted REP distributions was evaluated by comparing estimated intake of DLCs from catfish consumption calculated using three approaches for valuating toxic equivalency: 1) WHO TEFs[1]; 2) point estimate TEFs based on a series of selected percentiles from the weighted and unweighted REP distributions (i.e., deterministic); and 3) using the full weighted and unweighted REP distributions in a monte carlo analysis (i.e., probabilistic assessment). Congener-specific data from catfish collected in Southern

Mississippi[6] were used to calculate the estimated daily intake associated with consumption of DLCs using the following equation:

$$\text{Intake} = \sum (Ci \times IR \times CF \times EF \times ED \times TEFi) / (BW \times AT))$$

where Ci is the exposure point concentration based on the mean value of "all data" (CF is a conversion factor) and TEFi represents the sum of all individual congener TEFs multiplied by the mean fish tissue concentration to derive total risk from all congeners. The ingestion rate (IR) for fish consumption (12 g/day) was based on Finley et al[7]. Exposure frequency (EF) was assumed to be 365 days/year and the averaging time was equal to a 70-year lifetime, along with an exposure duration (ED) of 30 years and a standard body weight (BW) of 70 kg. TEF values, and resulting intake estimates, were calculated using multiple approaches including a deterministic approach utilizing the point estimate TEF values (without REP distributions), a deterministic approach utilizing a constant percentile (50th, 75th and 95th) from unweighted or weighted distributions, and a probabilistic approach which utilized unweighted and weighted distributions to select the 50th, 75th and 95th percentile based on monte carlo techniques (Crystal Ball v5.2.2, 2000).

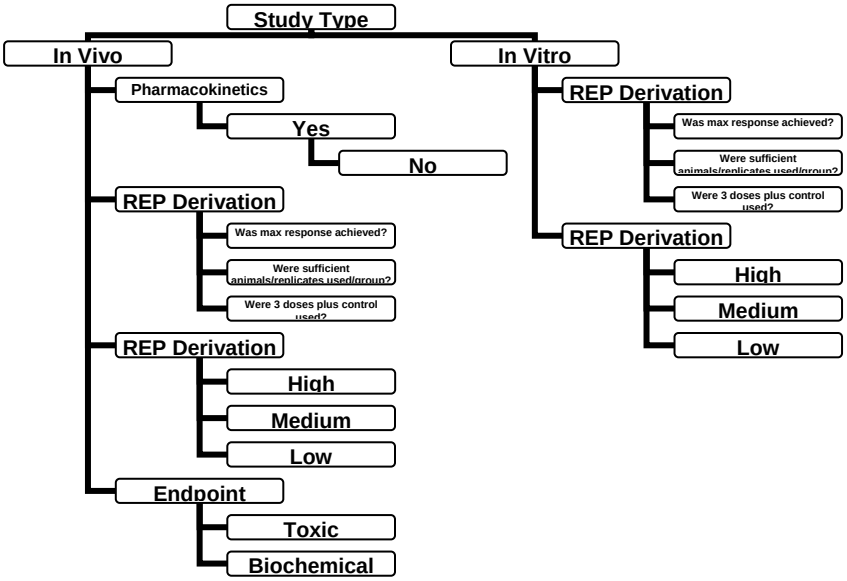

Figure 1. REP weighting framework[5].

Results and Discussion

Impact of Weighting on REP Distributions: The highest weighted studies did not always cluster around each other, nor did they always cluster around a specific percentile, nor were they generally in the tails of the weighted distribution. Weighting did not significantly impact the overall distribution of REP values; rather it primarily impacted the upper and lower percentiles. For most congeners, weighting generally tightened the distributions. For some congeners, such as PCB 169, widening of the distribution occurred because (a) studies of higher quality and relevance had REP values that were at the extreme end of the distribution and (b) the REP values for different endpoints varied by up to 3 orders of magnitude. Differences were consistently observed in the upper end of the

distributions when unweighted and weighted distributions were compared. This is an important as risk assessments often focus on the upper end of the distributions.

Impact of Weighting on Intake Calculations: Intake estimates varied by approximately two orders of magnitude across the various approaches (Figure 2). In addition, the intake estimates calculated with the WHO TEFs were consistent with the estimates based on the 50th percentile of the weighted and unweighted distributions. Intake estimates based on unweighted distributions were generally higher than those based on weighted distributions, particularly when the upper percentiles were selected. Weighting had a greater impact when percentiles >75th were selected. Apportionment of intake changed substantially when probabilistic methods were applied versus the WHO TEFs (Table 1). The use of distributions had a greater impact on intake calculations than did the weighting process alone.

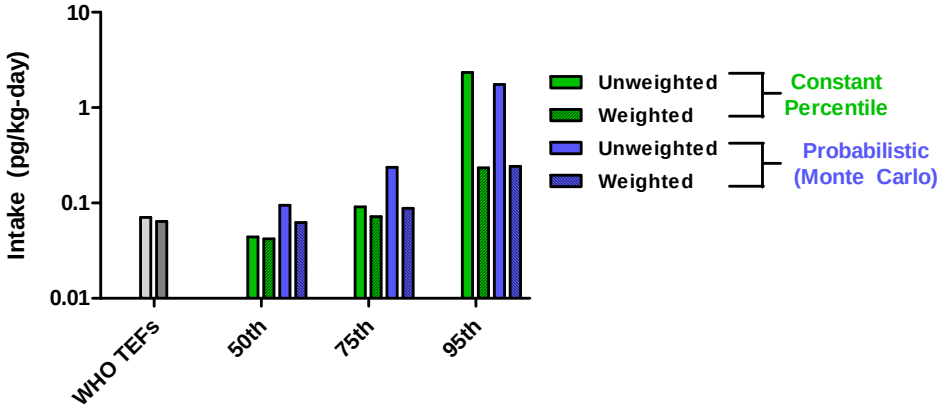

Figure 2: Comparison of intake estimates (TEQ pg/kg-day) using three different approaches to derive TEF values for each DLC congener. Both the "constant percentile" and "probabilistic" methods utilize the full REP distributions.

Findings of this study were consistent with previous efforts to develop a weighting framework for DLC REP estimates. The lack of a significant impact of weighting on REP distributions themselves may be due to the inherent variability in the REP values. Despite this finding, use of weighted REP distributions (rather than point estimates) has the potential to significantly impact exposure and risk calculations, particularly when upper percentiles are used to develop exposure and risk estimates.

Overall, the use of a quantitative weighting scheme (a) provides the WHO with a quantitative method for developing TEFs, (b) enhances the objectivity and transparency in the process for establishing TEFs, and (c) allows for quantitative uncertainty analysis. By using this approach, regulators, the regulated community, risk managers and the general public can reproduce how TEFs are derived and can assess the impact of new data on the REP distributions. Lastly, the use of REP distributions could simplify the process of updating point estimate TEFs and separate risk assessment from risk management procedures.

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Table 1: Apportionment of intake (TEQ pg/kg-day) by chemical group.

Approach	PCB Intake	PCDD/F Intake	Ratio of PCB Intake to PCDD/F Intake
Deterministic			
1998 TEFs	2.56E-04	1.28E-03	0.2
2006 TEFs	3.21E-04	1.28E-03	0.3
Probabilistic			
50th Percentile			
Unweighted Probabilistic	3.85E-02	1.92E-03	20
Weighted Probabilistic	6.41E-03	1.28E-03	5
75th Percentile			
Unweighted Probabilistic	6.41E-03	1.28E-03	5
Weighted Probabilistic	1.28E-03	1.28E-03	1
95th Percentile			
Unweighted Probabilistic	3.85E-03	1.28E-03	3
Weighted Probabilistic	5.13E-04	6.41E-04	0.8

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