AN ALTERNATIVE METHOD FOR ESTABLISHING TEFS FOR DIOXIN-LIKE COMPOUNDS. PART 3. DEVELOPMENT OF WEIGHTED DISTRIBUTIONS OF REPS FOR PCB 126 AND 2,3,4,7,8-PeCDF

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Introduction

Currently, regulatory agencies utilize the toxic equivalency factor (TEF) approach to evaluate potential health risks associated with exposure to polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like polychlorinated biphenyls (PCBs). The current TEF methodology has been identified as "interim," and, as such, is subject to periodic review as new information becomes available. When the current World Health Organization (WHO) TEFs were established, the expert panel relied upon a series of decision criteria to assess the relative importance of the underlying relative estimates of potency (REP) in assigning a consensus-based TEF for each congener. However, because this was a qualitative process, it is not possible to characterize the variability and uncertainty inherent in the risk estimates that are based on the WHO TEFs.

It has been recognized for some time now that the REP values represent a heterogeneous data set and range across several orders of magnitude,[1,2,3] yet the TEF values are assigned as single point estimates. To address this limitation, several investigators have proposed developing distributions of REP values for use in probabilistic risk assessments.[2,4] These distributions could potentially be used to establish point estimate TEFs based on a common point on the underlying distribution, thereby ensuring a more uniform degree of conservatism in the TEF values.

Haws et al[4] recently published an updated REP database, the REP_{2004} database. This database is structured in a way that easily allows for the conduct of quantitative analyses. In developing the REP_{2004} database, it was noted that individual REP values were derived from many different types of studies, of different design and using different REP derivation methods. As such, equal weighting of all REP values may not be appropriate when developing distributions of REP values for use in risk assessment. To address this issue, we have undertaken an effort to develop a transparent, reproducible, quantitative weighting scheme, based on the original criteria used by the WHO expert panel during their review in 1997. The quantitative weighting scheme is outlined in a companion paper presented by Haws and coworkers.[5] This preliminary weighting scheme involves several different measures of study quality and relevance, as well as multiple iterations by which the REP distributions can be analyzed. In this paper, we apply the proposed weighting scheme to PCB 126 and 2,3,4,7,8-PeCDF, which are two of the most data-rich congeners in the REP_{2004} database, to evaluate the effect of weighting on REP distributions.

Materials and Methods

The Analytical Hierarch Process (AHP) was selected as the preferred framework for the development of a weighting scheme that could be applied to the REP database as described by Scott et al.[6] The specific study elements and scientific criteria that form the basis of the quantitative weighting scheme are described by Haws et al.[5] Briefly, *in vivo* studies were evaluated based on pharmacokinetic (PK) considerations, REP derivation quality, method of REP derivation and endpoint. *In vitro* studies were evaluated based on the method of REP derivation and REP derivation quality. Multiple iterations of the weighting criteria were applied as follows:

Iteration 1a: *in vivo* only (PK, REP Derivation Quality, REP Derivation Method)
Iteration 1b: *in vitro* only (REP Derivation Quality, REP Derivation Method)

Iteration 1c: *in vivo* only with endpoint (PK, REP Derivation Quality, REP Derivation Method, Endpoint)
Iteration 2: vivo (1a) and vitro (1b) combined
Iteration 3: vivo (1c) and vitro (1b) combined

In addition, both log- and semi-log- scales were used to evaluate each iteration.

Each REP value in the REP_{2004} database was assigned a score for each of the study elements or weighting factors and a total weighting score was calculated in Microsoft Excel. 115 REP values derived from 38 studies were evaluated for PCB 126, 86 of which were based on *in vivo* studies and 29 on *in vitro* studies. For 2,3,4,7,8-PeCDF, 99 REP values derived from 28 studies were evaluated; 82 were based on *in vivo* studies and 17 on *in vitro*. The individual REP weights calculated based on the AHP framework were combined to prepare a cumulative distribution, which was subsequently used to determine the 10th, 25th, 50th, 75th and 90th percentiles of the weighted distribution.

Results and Discussion

Comparisons of the impact that the various weighting iterations and scales had on the REP distributions for PCB 126 and 2,3,4,7,8-PeCDF are shown in Figures 1 and 2. In their analyses of the different decision analysis methods Scott and coworkers[6] noted that when a more aggressive scale is utilized (i.e. log scale) there is a concomitant decrease in variance of REP distributions. The application of the proposed weighting scheme to data for PCB 126 and 2,3,4,7,8-PeCDF in this paper further supports this observation. The range of the weighted REP distributions was reduced when compared to the unweighted distributions for both congeners.

One of the issues that must be addressed in the development of REP distributions for use in risk assessment is the appropriateness of combining *in vivo* and *in vitro* studies. Comparisons of the various iterations used in this study and show that when the *in vivo* and *in vitro* studies are combined, the distributions are very similar to those observed for *in vivo* only suggesting that combining the *in vivo* and *in vitro* REPs may have a little impact on any point estimate TEF derived from the distribution.. This suggests that it is, in fact, appropriate to combine *in vivo* an *in vitro* REPs when developing distributions for each congener. It is important to note that when the *in vivo* and *in vitro* studies are combined in iterations 2 and 3, the *in vivo* REPs are weighted more than the *in vitro* REPs (evaluated on a log and semilog scale in this study) Interestingly, when "endpoint" is included (iteration 3), only very slight changes to the REP distributions were observed.

Median values were only changed slightly in some of the iterations. When comparing median REP values from 2,3,4,7,8-PeCDF iteration 2, the median REP value decreased from an unweighted value of 2.2 E-1 to 2.0 E-1 when a log scale was applied but increased to 2.4E-1 when the semi-log scale was applied. A similar trend was noted in iteration 3 for 2,3,4,7,8-PeCDF, but no changes were observed to the median value for iterations 1a & b. For PCB 126, median REP values were not altered by more than 0.001 in any iteration except for iteration 1a which resulted in a 0.002 decrease in the REP median value.

The 1998 WHO TEF values are also plotted along with the weighted and unweighted REP distributions in Figures 1 and 2. For PCB 126, the WHO TEF values fall close to the 50^{th} percentile for all of the REP distributions containing the *in vivo* data set. For 2,3,4,7,8-PeCDF, the TEF value falls above the 75^{th} percentile REP value for all REP distributions containing the vivo data set. This preliminary assessment of the distributions indicates that the WHO consensus-based TEFs for PCDDs/PCDFs are consistent with the upper bound of the distributions while the TEFs for dioxin-like PCBs are more representative of the central tendency of the REP distributions. This is consistent with findings for unweighted distributions reported by Haws et al[4].

In conclusion, this preliminary assessment, using the two most data rich congeners, suggests that weighting has very little impact on the overall distribution of REPs. The results of this study are consistent with findings observed following application of different weighting schemes to earlier version of the database.[2,4] Despite the development and application of an intricate mathematical process which controls for key evaluation criteria with respect to

determining relative potencies, major changes in resulting REP distributions were not observed. One possible explanation for this lack of impact on the overall distribution of REP values is that the variability in the REP values is much larger than the variability accounted for in the weighting scheme. Nonetheless, the use of a quantitative weighting scheme may serve to further enhance the transparency in the process for establishing TEFs.

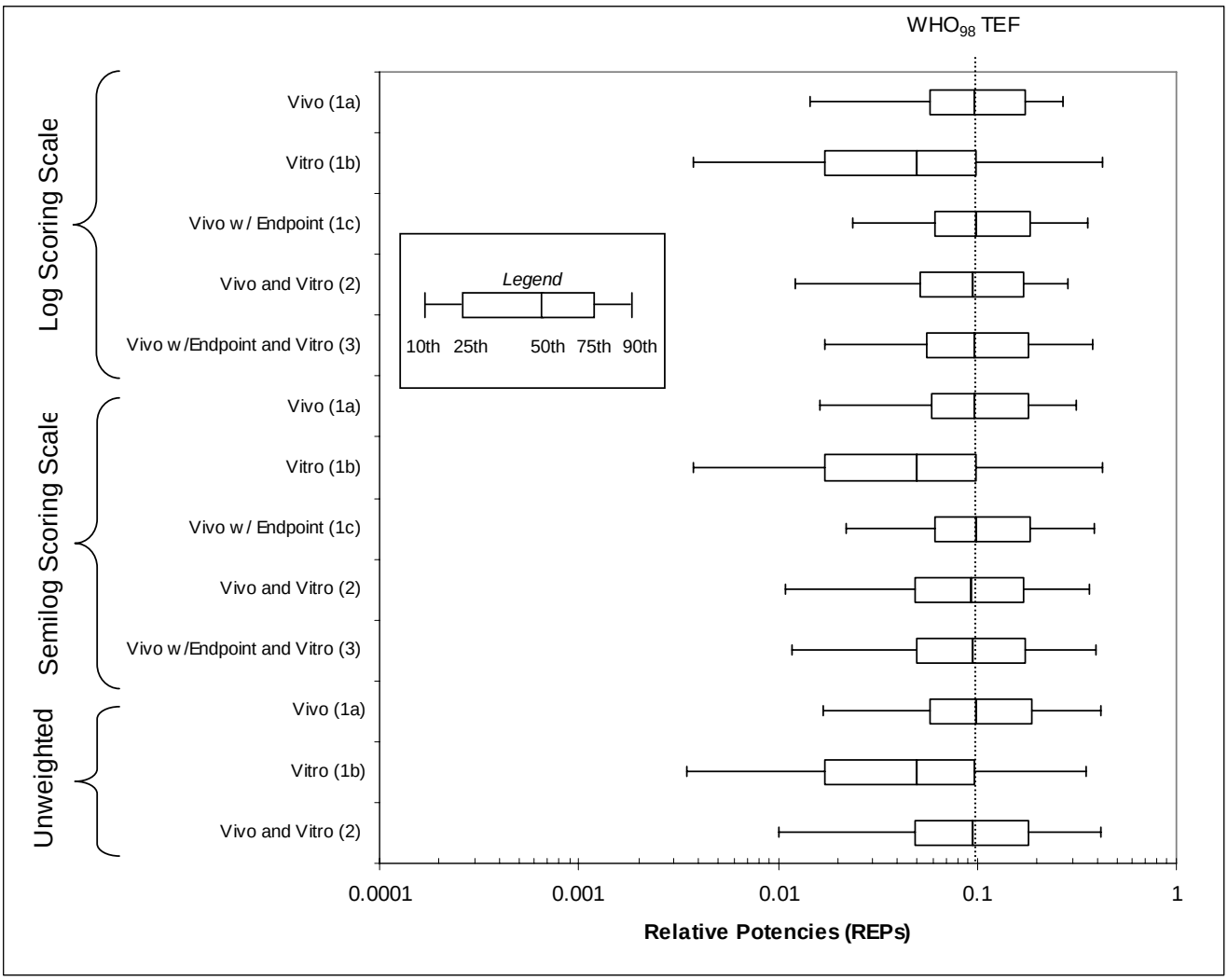

Figure 1. Summary of Weighted and Unweighted Distributions for PCB 126 and Comparison to 1998 WHO TEF

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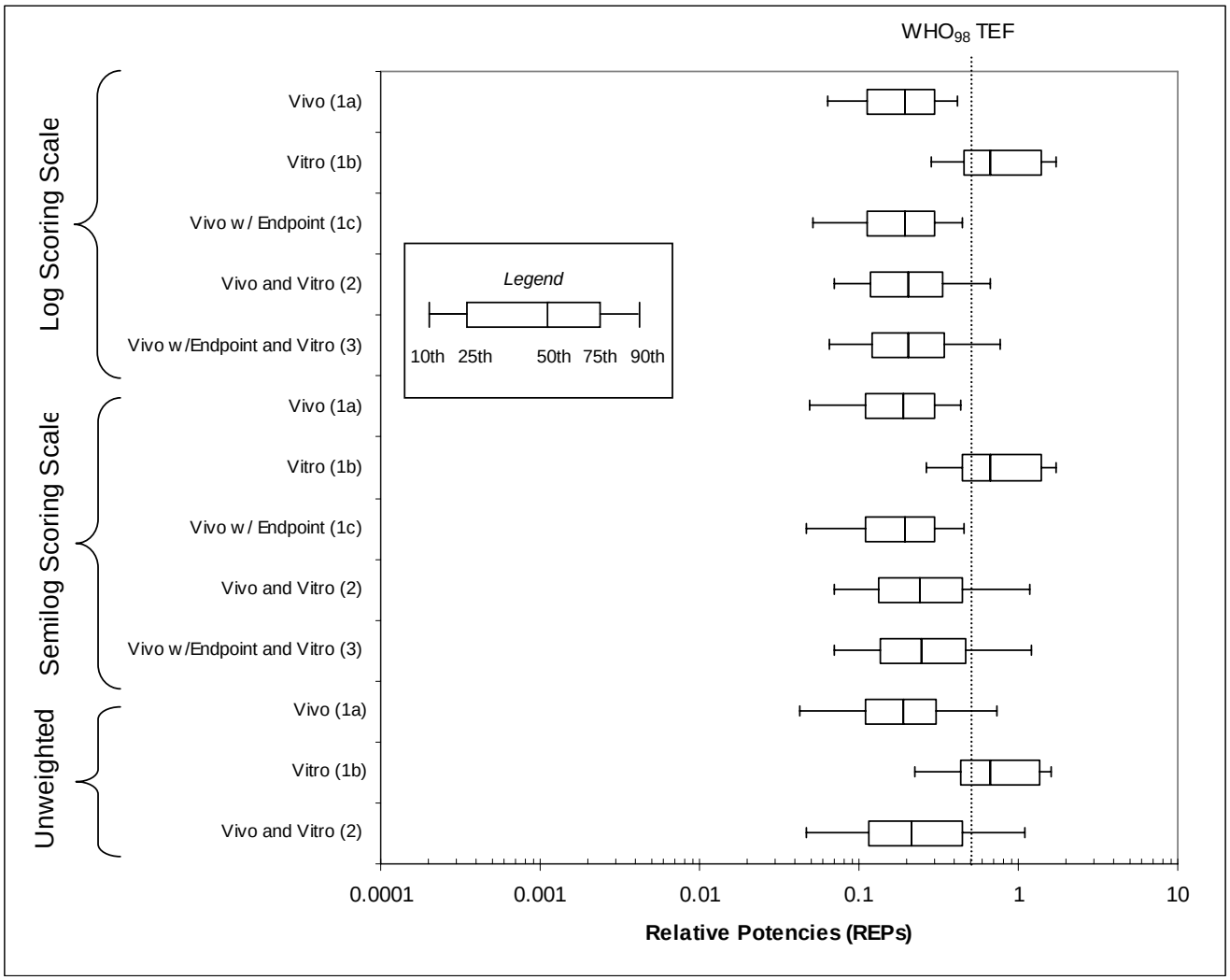

Figure 2. Summary of Weighted and Unweighted Distributions for 2,3,4,7,8-PeCDF and Comparison to 1998 WHO TEF

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