Development of a Relative Estimate of Potency Distribution for 2,3,7,8-TCDF

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INTRODUCTION

Recently the possible benefits associated with the use of Relative Estimate of Potentcy, REP, distributions in probabilistic analyses involving mixtures of PCDD/F and PCB congeners have been discussed[1]. The REP distributions have been proposed as a supplement or alternative to the "point estimate" 1998 W.H.O. TEFs that are typically employed in environmental risk assessments. Preliminary suggestions regarding weighting schemes for the REP values have also been proposed [1]. A "revised" REP database was recently presented after it was determined that several of the individual 936 values considered by W.H.O. did not meet the original inclusion criteria or were duplicative [2]. The impact of these revisions to the REP distributions suggested previously [1] has not been characterized. The purpose of this paper is to develop a weighted REP distribution for 2,3,7,8-TCDF using a revised REP database that is similar to that proposed by others [2].

METHODS

The W.H.O. REP database for 2,3,7,8-TCDF contains 31 REPs derived from in vivo studies and 14 REPs from in vitro studies. A "revised" set of 27 2,3,7,8-TCDF REP values was taken from the original W.H.O REP database. In addition, we incorporated 8 REP values from 6 different 2,3,7,8-TCDF studies that met the W.H.O.'s inclusion criteria[3] but were either not considered by W.H.O. or were published after 1998. As summarized in Table 1, a total of 35 REP values are considered in this analysis; 20 of the REPs are from in vivo studies and 15 REPs are from in vitro studies.

The quantitative factors used to weight the individual REP values are summarized in Table 2. Consistent with the approach used by W.H.O. to derive the 1998 TEFs, in vivo studies were given increased weight (factor of 3) relative to in vitro studies. In vivo REP values also received increased weight as a function of exposure duration, route of exposure, and number of doses. The different weighting factors were multiplied together to form a single aggregate weighting factor for each REP. Under this scheme, the greatest possible aggregate weighting factor (value of 48) would be assigned to a 2-year feeding study with multiple doses.

Development of distributions was carried out as described previously [1]. Briefly, the weighted and unweighted TCDF REPs were tested for distribution fit using the D'Agostino test and the Kolomogrov-Smirnov (K-S) test with Lilliefors's modification [4]. The fit tests indicated that the unweighted TCDF REP data best fit a truncated lognormal distribution. The distribution fit test p values for the K-S test with Lilliefors Modification and the D'Agostino Test were 0.53 and 0.93, respectively, indicating that these data fit a lognormal distribution.

While probability plots indicate that the weighted data appear to have a Weibull or lognormal distribution, subsequent distribution testing using the K-S test for a Weibull distribution, and Lilliefors and D'Agostino tests for a lognormal distribution indicate that the weighted data do not fit either distribution type ($p<0.00001$). Therefore, the percentiles of the weighted REP data were used to define an empirical distribution in Crystal Ball®, a Monte Carlo simulation program [5]. To define a final REP distribution, this empirical distribution was simulated in Crystal Ball using the Monte Carlo sampling method for 10,000 iterations.

RESULTS

As shown in Table 1, the individual REP values spanned approximately two orders of magnitude (0.006 to 0.5). The lognormal mean of the unweighted REP distribution was 0.08. When the unweighted REP data were segregated into in vivo and in vitro values, the lognormal means were 0.075 and 0.10, respectively. The mean of the weighted REP distribution was 0.059. When the weighted REP data were segregated into in vivo and in vitro values, the means were

0.056 and 0.10, respectively.

Figure 1 illustrates the unweighted and weighted distributions over a range of percentiles. Except for between the 85th and 95th percentiles, the percentile values associated with the unweighted REP distribution are approximately 2-fold greater than in the weighted distribution. For example, the 25th, 50th, and 75th percentiles of the unweighted distribution are 0.02, 0.045, and 0.1, respectively while these percentiles for the weighted distribution are 0.01, 0.023, and 0.05, respectively.

DISCUSSION

The TCDF REPs used in this analysis cover a broad range of adverse and biochemical effects, including: lethality, developmental effects, inhibition of body weight gain, and P450 induction. However, there is a clear lack of studies that examined cancer related endpoints, which introduces some uncertainty into current estimates of the true carcinogenic potential of TCDF.

The current W.H.O. TEF of 0.1 is representative of the 75th percentile of the unweightedREPs considered in this analysis. When the individual REPs are weighted, the TEF falls at approximately the 82nd percentile of the distribution. This shift occurs due to the increased weighting of the in vivo TCDF studies, which tend to exhibit a lower relative potency than the in vitro studies.

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Table 1: Summary of Weighting Factors Applied to REP Values in Development of a TCDF REP Distribution

Study	REP	Weight 1 In Vivo vs In Vitro	Weight 2 Study Duration	Weight 3 Multiple vs. Single Dose	Weight 4 Relevant Exposure Route	Total Weight
van Birglen et al. 1996[a]	0.25	3	3	2	2	36
Waern 1995 [a]	0.07	3	2	1	2	12
Davis & Safe 1988 [a]	0.2	3	1	1	1	3
Mason et al 1985 [a]	0.025	3	2	1	1	6
Mason et al 1985 [a]	0.006	3	2	1	1	6
Mason et al 1985 [a]	0.016	3	2	1	1	6
Mason et al 1985 [a]	0.0065	3	2	1	1	6
Weber et al 1985 [a]	0.03	3	2	1	2	12

Weber et al 1985 [a]	0.03	3	2	1	2	12
Weber et al 1985 [a]	0.03	3	2	1	2	12
Harris et al 1990 [a]	0.5	3	1	1	1	3
McKinney et al 1985 [a]	0.29	3	2	1	2	12
DeVito et al 1997 [a]	0.012	3	3	2	2	36
DeVito et al 1997 [a]	0.0077	3	3	2	2	36
DeVito et al 1997 [a]	0.014	3	3	2	2	36
DeVito et al 1997 [a]	0.0076	3	3	2	2	36
DeVito et al 1993 [a*]	0.0325	3	2	2	2	24
DeVito et al 1993 [a*]	0.05	3	2	2	2	24
DeVito et al 1993 [a*]	0.047	3	2	2	2	24
Takagi et al 2003 [a*]	0.0667	3	1	1	2	6
Clemens & van DerHeuvel 1994[b]	0.03	1	NA	NA	NA	1
Clemens & van DerHeuvel 1994 [b]	0.4	1	NA	NA	NA	1
Bandiera et al 1984 [b]	0.0185	1	NA	NA	NA	1
Bandiera et al 1984 [b]	0.091584	1	NA	NA	NA	1
Bandiera et al 1984 [b]	0.243902	1	NA	NA	NA	1
Mason et al 1985 [b]	0.018	1	NA	NA	NA	1
Mason et al 1985 [b]	0.092	1	NA	NA	NA	1
Mason et al 1985 [b]	0.24	1	NA	NA	NA	1
Tillitt and Glesy 1991 [b]	0.007	1	NA	NA	NA	1
Wiebel et al 1996 [b]	0.09	1	NA	NA	NA	1
Wiebel et al 1996 [b]	0.12	1	NA	NA	NA	1
Brown et al 2001 [b*]	0.067	1	NA	NA	NA	1
Li et al 1999 [b*]	0.15	1	NA	NA	NA	1
Krishnan & Safe 1996 [b*]	0.03	1	NA	NA	NA	1
Gierthy & Crane 1985 [b*]	0.1	1	NA	NA	NA	1

[*] Study either not in original W.H.O database or published after 1998

[a] In vivo study

[b] In vitro study

Table 2: Summary of Weighting Factors

Weighting Categories	Weights
In Vivo Study	3
In Vitro Study	1

In Vivo Study Duration (less than 1 week)	1
In Vivo Study Duration (less than 1 month but more than 1 week)	2
In Vivo Study Duration (more than 1 month but less than 2 years)	3
In Vivo Study Duration (2 years or greater)	4
In Vivo Route of Exposure (gavage)	2
In Vivo Route of Exposure (i.p.)	1
In Vivo Number of Doses (single)	1
In Vivo Number of Doses (multiple)	2

Figure 1: Comparison of unweighted and weighted REP distributions for 2,3,7,8-TCDF