THE NEED FOR TEFs BASED ON INTERNAL MEASURES OF DOSE: AN ASSESSMENT OF BODY BURDEN TEQS

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Introduction

The human health risk assessment of dioxins is undergoing a methodological shift, wherein *internal measures of dose* are replacing the traditional use of dose metrics expressed as an *intake* or *administered dose* (e.g., mg/kg-day). This is due in part to the fact that the use of internal dose metrics minimizes the species-related differences in pharmacokinetics[1]. In the U.S. EPA's recent Draft "Dioxin Reassessment" (U.S. EPA 2000), human health risk estimates are calculated on the basis of body concentrations (e.g., serum lipid concentrations) rather than a daily intake. In addition, scientists have expressed the opinion that accumulated body concentration is the best predictor of toxicity for TCDD[2].

The use of an internal dose metric has some implications for the PCDD/F and PCB TEF scheme. None of the current W.H.O. TEFs are based on internal dose data; they are all derived from *in vitro* or applied dose information. However, it would seem that use of an internal measure of human dose in conjunction with TEFs that are not based on such a metric would introduce a large degree of uncertainty into a process that is already very highly uncertain. Finley et al.[3] has noted that the range of relative potency (REP) estimates that underlie many of the TEFs can span more than four orders of magnitude. Furthermore, many of the W.H.O. TEFs have been selected from the upper-bound of the REP range[3]; this can lead to a significant degree of compounded conservatism if a mixture of numerous congeners is being evaluated. We believe that use of internal dose REP data only would yield TEFs that contain less variability and would be consistent with the use of internal dose metrics in risk assessment.

The current W.H.O. database contains over 900 REP values, and a subset of the *in vivo* REP data would readily support the derivation of internal dose REPs and TEFs. In this analysis we assemble internal dose TEFs from the published literature and conduct a comparative analysis of body burden TEQ in the general population using W.H.O. TEFs and internal dose TEFs.

Methods

Approximately 80% of the background TEQ tissue concentrations in humans is comprised of TCDD, 1,2,3,7,8-PeCDD (PeCDD), 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PeCDF (PeCDF), and PCB126[4]. Data from Patterson et al.[5] indicate that 1,2,3,7,8,9-HexaCDD is also a significant (i.e., >5%) contributor to the TEQ body burden. We used the body fat data from Patterson et al.[5] to represent background TEQ levels in the general population. These data are from subjects who had no known exposures to PCDD/Fs or PCBs. The literature was reviewed to locate studies for these congeners from which internal dose REPs could be developed. Internal dose REP information was

available for PeCDD[6], PeCDF[6], and PCB 126[7]; but not the HxCDD congeners. For these two congeners, we used *in vitro* data from human cell lines[8].

Results and Discussion

As shown in Table 1, internal dose REPs developed from either tissue concentration or human cell culture data are lower than the corresponding administered dose REPs and/or the W.H.O. TEFs. For the PeCDD and PeCDF congeners, the internal dose REPs are approximately 6-14-fold lower than the respective administered dose REPs, and approximately 7-70-fold lower than the respective W.H.O. values. The human cell line REPs for the HxCDD congeners are about half their respective W.H.O. TEF values, and the internal dose REP for PCB 126 is 10-fold lower than the administered dose TEF and the W.H.O. TEF. It is reasonable to expect that for congeners that accumulate in tissue to a greater extent than TCDD, the tissue-concentration-based REP will be lower than the REP based on the administered-dose. This appears to hold for PeCDD and PeCDF, which have a higher degree of chlorination than TCDD, and therefore, would generally be thought to accumulate to a greater extent. However, the net effect of differences in the absorption, distribution, metabolism, and excretion are likely to be more complex and can be the product of competing influences. The octa-chlorinated CDD/Fs have long biological half-lives relative to TCDD; however, DeVito et al. [9] found that the internal dose REP estimated for OCDF was nearly 230-fold *higher* than the REP based on administered dose. The authors speculated that this unexpected result was due to the poor absorption of OCDF, relative to TCDD.

As shown in Table 2, use of the internal dose REP values yields an estimate of body burden TEQ that is about three times lower than that obtained with the W.H.O. TEFs[10].

Table 1. Comparison of W.H.O. TEFs versus Internal Dose REPs

	WHO TEFs	Tissue Concentration REPs		Human Cell Line REPs
Congener		Administered Dose	Internal Dose	Short-term *in vitro*
1,2,3,7,8-PeCDD	1.0	0.8[a]	0.14[a]	
2,3,4,7,8-PeCDF	0.5	0.1[a]	0.007[a]	
1,2,3,6,7,8-HxCDD	0.1	--	--	0.04[b]
1,2,3,7,8,9-HxCDD	0.1	--	--	0.07[b]
PCB 126	0.1	0.1[c]	0.01[c]	

[a] Tumor promotion data from Wærn et al.[5]
[b] EROD activity data from Lipp et al.[7]
[c] Tumor promotion study of Hemming et al.[6]

Table 2. Comparison of Body Burden TEQs Based on Current WHO TEFs versus Internal Dose-TEFs

		WHO TEQs		Internal Dose TEQs	
Congeners	Conc. in Human Adipose [a] (ppt-lipid)	WHO TEF	TEQ	ID- TEF	TEQ
2,3,7,8-TCDD	4.4	1	4.4	1	4.4
1,2,3,7,8-PeCDD	11.6	1	11.6	0.14	1.62
1,2,3,6,7,8-HxCDD	94.2	0.1	9.42	0.04	3.77
1,2,3,7,8,9-HxCDD	16.9	0.1	1.69	0.07	1.18
2,3,4,7,8-PeCDF	3.7	0.5	1.85	0.007	0.026
PCB 126	46.9	0.1	4.69	0.01	0.47
TOTALS			**35.3**		**11.5**

[a] Patterson et al. 1994

The internal dose REPs presented in Table 1 are based on steady-state liver concentrations, consistent with the fact that liver was the target organ in these studies. The use of liver concentration-based REPs to calculate the TEQ body burden in humans (i.e., fat concentration) is a possible source of uncertainty. However, the relationship between liver and fat concentrations in humans has been examined for a series of PCDD/F congeners[11]. This study found that for the majority of congeners, including TCDD, PeCDD, PeCDF, HxCDD, and HxCDF, the accumulation in liver and body fat were proportionally similar. Hence, the aforementioned uncertainty is likely to be minimal.

Overall, these findings suggest that the use of internal dose TEFs may yield consistently lower estimates of body burden and associated risk. We suggest that the W.H.O. REP database should be further examined to assess whether internal dose data exist that would support the development of other internal dose TEFs. REPs from *in vitro* data might be considered as a surrogate for internal dose data from *in vivo* studies, which is presently limited; the data from cell culture studies represent chemical doses that are in direct contact with the target tissue, and therefore, are pharmacologically similar to an internal dose measured *in vivo*. We are currently evaluating the possibility of modeling tissue concentrations for individual congeners in rodents, which would allow hundreds of REPs in the W.H.O. database to be converted to values with an internal dose basis.

Exposure duration is one criterion that would need to be considered in selection of the appropriate data. A significant time-dependent influence on the magnitude of the REPs has been noted[9,12]. The observed differences in REPs from long-term studies is not completely understood and may be in part due to the autoinduction by certain congeners (i.e., capacity of a congener to induce its own metabolism)[13,14]; which, not surprisingly, appears to be dose-dependent[9,12]. Until these time-dependencies are more clearly understood, these REP data may best be handled with some type of quantitative weighting scheme[15], or the development of REPs based on chronic and acute endpoints separately.

References

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