TEFs: Alternatives and Future Directions

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Since Toxic Equivalency Factors were first proposed over a decade ago, the use of this methodology has been debated in the United States. The TEF methodology has been described as an interim method and its use was recommended until a better methodology could be developed. In the 11 years since the USEPA adopted the interim use of TEFs (1), few if any new methods have been proposed. During this period, the use of TEFs has expanded beyond human risk assessment to use in ecological risk assessment. With the expanded use of the TEF methodology perhaps it is time to re-evaluate the use of the TEF methodology and to consider potential alternatives.

One of the toughest questions is what do we want from the TEF methodology? Presently, the TEF methodology can adequately predict the TCDD equivalents of a complex mixture. It is possible that the TEF methodology could predict some toxic responses, but it is unlikely to predict all responses. Exposures, both human and ecological, are complex and consist of both dioxin-like chemicals and non-dioxin-like chemicals. It is the combined exposure that creates not just the potential health effects but is also responsible for many of the difficulties in predicting these health effects following exposure to mixtures. The TEF methodology can estimate the TCDD equivalents of the mixture. However, it is our limited understanding of the interactive effects of TCDD with non-dioxin-like chemicals that causes our greatest uncertainties.

The difficulty in predicting responses of complex mixtures stems from the multiple mechanisms or pathways with which chemicals act to produce their toxicities. Because of the multiple pathways available, many of the toxicities may not be predicted based on the TEF methodology. The TEF methodology focuses solely on toxicities mediated by activation of the Ah receptor. One example of a response not readily predicted is hypothyroidism (9). Studies in rats exposed to a complex mixture of PCDDs, PCDFs and PCBs determined that the TEF methodology adequately predicted hepatic EROD activity. In these same animals, the dose that decreases serum thyroxine was over predicted by almost 2 orders of magnitude. The mono-ortho PCBs present in this mixture decrease serum thyroxine by multiple

mechanisms of which an Ah receptor mediated pathway is but one. Similar greater than additive effects have been observed for increases in hepatic porphyrins (10). There is also some evidence for non-additive interactions on tumor promotion following exposure to dioxin-like and non dioxin-like chemicals (11). Focusing future studies on the interactions of dioxin-like chemicals with non-dioxin-like chemicals is imperative if estimating the total risk of these mixtures is to be improved.

If we examine the uncertainties in risk assessment of dioxin-like chemicals, one could ask do the uncertainties in the TEF methodology increase or decrease uncertainty in the overall risk assessment process? In order to answer this we have to think of viable alternatives to the TEF methodology. One is to ignore all chemicals but TCDD. Another is to consider all chemicals as equally potent to TCDD. These two options clearly increase uncertainty and are inappropriate. Another alternative is to determine total PCBs and make the assumption that this mixture is equivalent to one of the commercial PCB mixtures tested. It is not likely that every environmental sample will have the same make-up as Aroclor 1254, hence the alternative to estimate risk on total PCBs also has significant uncertainties. Thus, it is clear that the use of the TEF methodology decreases uncertainty in risk assessments.

Another way of examining the TEF methodology is to ask whether the uncertainty in the TEF methodology is greater or less than uncertainties in other areas of risk assessment, such as exposure or dose-response relationships. Different regulatory agencies throughout the world have assigned either tolerable daily intakes or virtually safe dose estimates for TCDD. These estimates range at least 3 orders of magnitude if not more. Examination of the extensive literature base testing complex mixtures of dioxin-like chemicals indicates that the TEF methodology predicts the response of mixtures in experimental systems to well within a factor of five for responses as diverse as enzyme induction, immunotoxicity and tumor promotion.

Over the last decade we have developed an understanding for what factors are important for the relative potency of a dioxin-like chemical. Clearly Ah receptor binding and activation are critical (4,5) as are pharmacokinetic parameters (6). Physiologically-Based Pharmacokinetic Biologically Based Dose Response models (PBPK/BBDR) have used these types of data to model the effects of TCDD in experimental animals. These models have proved to be quite accurate in their predictive abilities (7). As one alternative to the TEF methodology, it may be possible to develop PBPK/BBDR models that can estimate the dose and responses following exposures to complex mixtures. These models may even account for interactions between dioxin-like and non dioxin-like chemicals. There are some drawbacks to this procedure. Extensive and perhaps expensive studies would be required on the pharmacokinetics for every congener of interest, in addition to the response studies. The types of models that have been developed focus predominately on single chemicals and no models are available for use with complex mixtures found in environemental samples. While there is a strong base of knowledge on the development of PBPK/BBDR models, there are no models available that have the complexity to describe the exposures and effects of simultaneous exposure to all the chemicals included in the TEF methodology.

One model that examines the effects of TCDD on thyroid hormones has many of the complexities that would be required of a model for mixtures (8). However, this model has

196 differential equations and almost as many variables that are either fixed or fitted by the model. The addition of kinetic models for the dioxin-like chemicals will only add to the complexity of this model. It is not clear that a model this sophisticated will actually provide accurate predictive capabilities for human risk assessment given the uncertainties in estimating many of the parameters required in the model. The development and use of sophisticated PBPK/BBDR models examining complex mixtures may be years away.

Another alternative method proposed using a Toxic Equivalency *Function* (TE Function) on the assumption that the relative potencies of these chemicals are a function of dose and that their relative potencies are different at high doses compared to lower environmental concentrations (2). An advantage of this method is that it may be able to account for partial agonists. While there may be some data supporting this hypothesis, it is difficult to adequately test and may be even more difficult to implement. The dose response relationship of two chemicals acting through the same mechanism are parallel at least from the 20 - 80% response range (3). Parallel dose response curves imply that the relative potencies can be described as a factor. For most responses examined in the typical experimental design, response rates lower than 20% are not readily measurable or easily discriminated from controls. Because these low responses are difficult to determine, testing the hypothesis that the relative potency is dose-dependent may be unattainable. These low dose extrapolations are not unique to dioxin-like chemicals but are perplexing problems that toxicologists and risk assessors have grappled with for decades with no clear resolution in sight.

However, even if the issue of low dose extrapolation could be resolved, implementing the TE Function methodology may be quite difficult. Dose response curves are typically "S" shaped with two inflection points. In order to adequately describe the dose-response curve and discriminate differences between high and low dose-response relationships, multiple dose levels (8 or more) for each chemical for each endpoint would be required. This methodology is data intensive and for developmental, carcinogenic and subchronic toxicities, the cost would most likely be prohibitive. Aside from the cost, there are additional complexities to overcome. The dose-response relationship or function for TCDD is different for every endpoint in a particular species. It is not clear that the dose-response relationship for a single endpoint would be equivalent for all species. If these functions are not equivalent across speciess, which species do we use to compare the functions of the chemicals when extrapolating to humans? In addition, the use of the method in human risk assessment requires an understanding of the human dose response relationship. With the limited data available in humans, this last point becomes a major obstacle.

The TEF methodology, while highly criticized, is the only viable method to estimate potential health or ecological effects for risk assessments of complex mixtures of dioxin-like chemicals. While this method has its faults, it decreases the overall uncertainties in risk assessments. In addition, there are other areas of the risk assessment process that contribute to much greater uncertainty that the TEF methodology. The present state of knowledge supports the continued use of TEFs.

References

1. US EPA March 1987. Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-p-dioxin and -dibenzofurans (CDDs and CDFs). EPA/6225/3-89/016.
2. Putzrath, RM; *Regul. Toxicol. Pharmacol.* 1997, 25, 68.
3. Holford NG and Sheiner, LB *CRC Crit. Rev. Bioeng.* **1981**;5, 273
4. Safe, S. *CRC Crit. Rev. Toxicol.* **1990** 21, 51.
5. Birnbaum LS; Prog. Clin. Biol. Res; 1994; 387, 139.
6. DeVito MJ and Birnbaum, LS; *Fundam. Appl. Toxicol.*; **1995**; 24, 145.
7. Wang X, Santostefano, MJ, Evans, MV, Richardson, VM, Diliberto, JJ and Birnbaum, LS; *Toxicol. Appl. Pharmacol.;* **1997**; 147, 151.
8. Kohn, MC, Sewall, CH, Lucier, GW and Portier, CJ; *Toxicol. Appl. Pharmacol.*; **1996**;165, 29.
9. Van Birgelen, APJM, Visser, TJ, Kaptein, E, Kodavanti, PRS, Derr-Yellin, EC, DeVito, MJ and Birnbaum, LS; *Organohalogen Compounds;***1997**; 34, 270.
10. Van Birgelen APJM, DeVito, MJ, Akins, JM, Ross, DG, Diliberto, JJ and Birnbaum, LS; *Organohalogen Compounds*;**1996**; 26, 211.
11. Van der Plas, SA, Haag-Gronlund, M, Scheu, G, and Warngard, L; *Toxicol. Sci.* **1998**;42,134.