FRAMEWORK FOR APPLICATION OF THE TOXICITY EQUIVALENCE METHODOLOGY FOR POLYCHLORINATED DIOXINS, FURANS AND BIPHENYLS IN ECOLOGICAL RISK ASSESSMENT

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Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and biphenyls (PCBs) commonly occur as complex mixtures in the environment, including in animal tissues. For more than a decade, the U.S. Environmental Protection Agency (EPA) and other organizations have estimated the combined risks that such mixtures pose to human health using a method known as the toxicity equivalence methodology. Application of this methodology in ecological risk assessments has proceeded more slowly, in part because of the variety of species from different taxonomic classes that need to be considered. As both data and experience with the methodology have accumulated, experts have reached consensus that the toxicity equivalence methodology can strengthen ecological risk assessments[1,2]. Based on recommendations from a 1998 workshop[2] sponsored by EPA and the U.S. Department of the Interior, the *Framework for Application of the Toxicity Equivalence Methodology for Polychlorinated Dioxins, Furans and Biphenyls in Ecological Risk Assessment* (heretofore referred to as the Framework) has been developed.

Materials and Methods

The Framework, prepared by a Technical Panel under the auspices of EPA's Risk Assessment Forum, promotes scientific consensus on risk assessment issues and to ensure that this consensus is incorporated into appropriate risk assessment guidance. To accomplish this, the Risk Assessment Forum assembles EPA experts in a formal process to study and report on these issues from an Agency-wide perspective. With the intent to assist EPA scientists in using the methodology in ecological risk assessments that involve PCDDs, PCDFs and PCBs, as well as to inform EPA decision makers, other agencies, and the public about this methodology, the Framework is organized in accordance with EPA's *Guidelines for Ecological Risk Assessment*[3].

Results and Discussion

Terminology. To date, many different terms and acronyms have been used to describe the concept

of the potency of individual PCDDs, PCDFs and dioxin-like PCBs, relative to 2,3,7,8-TCDD. Inconsistency in terms and abbreviations associated with the toxicity equivalence methodology has led to recommendations to further clarify terminology and acronyms[2]. In response to these recommendations, the Framework establishes a clear, systematic and unified terminology scheme for the toxicity equivalence methodology, building on the terminology adopted at the 1997 World Health Organization (WHO) international consensus meeting[1]. The WHO meeting report[1] introduced the term *relative potency* (REP) to refer to estimates of the potencies of individual PCDD, PCDF, and PCB congeners, relative to 2,3,7,8-TCDD, to cause a particular toxic or biological effect as determined in a single study. The Framework adopts the WHO terminology and definition, except that the acronym "ReP" is used rather than "REP". The Framework also adopts the WHO definition of toxicity equivalence factors (TEFs) as estimates of the relative potencies of individual dioxins, furans and PCBs, relative to 2,3,7,8-TCDD, derived using careful scientific judgment after considering all available data. Additionally, the Framework extends the WHO terminology by introducing the term *relative potency factor*, abbreviated RPF, as an intermediate between ReP and TEF. An RPF refers to an estimate based on one or more studies of the potency, relative to 2,3,7,8-TCDD, of an individual chemical to cause dioxin-like toxicity or biological effects. Hence, the term relative potency factor (RPF) is directly analogous to TEF, but an RPF is derived in the context of a specific risk assessment rather than by international expert consensus. Finally, TEFs or RPFs, when multiplied by concentrations of AhR agonists in appropriate media (tissues or food), can be used to calculate a toxicity equivalence concentration (TEC). The Framework recommends against direct application of TEFs or RPFs to concentrations in abiotic media because the resulting TECs will be inconsistent with most dose-response relationships.

Selection of Appropriate Relative Potency Factors. The Framework acknowledges, that in most cases, it is reasonable to use the WHO consensus TEFs[1] in ecological risk assessments. They reflect careful scientific judgment following expert review of the existing database of relative potency studies. Use of the TEFs minimizes the effort required by a risk assessor in selecting appropriate RPFs. In addition to considering the consensus TEFs, risk assessors may explore the selection and use of RPFs. For example, if RPFs can be derived from ReP data for relevant effects to a particular species of concern in an ecological risk assessment, they may be more accurate in calculating toxicity equivalence concentrations than the TEFs, which are consensus values for entire taxonomic classes of organisms. Risk assessors will need to consider the potential reductions in uncertainty that may be achieved by using specific RPFs as alternatives to corresponding TEFs. While increased effort is involved in identifying and selecting the appropriate values, a number of benefits may be accrued: (1) increased confidence that TEF values are most appropriate; (2) description of ranges of uncertainty through alternative calculations of Toxicity Equivalence Concentrations (TEFs vs. RPFs); (3) provide capability for inclusion of AhR agonists without assigned TEFs; (4) identification of new ReP data not utilized in the 1997 WHO effort to set TEFs; and (5) increased risk assessor knowledge of the pros and cons of alternative RPFs.

Ideally, chemical-specific RPFs based on both the species and endpoint of concern should be selected by risk assessors. In the absence of such data, a decision must be made as to which TEFs or RPFs provide the most accurate measure of relative potency for use in calculating TECs from

chemical-specific residue data. In essence, the decision involves choosing between the uncertainty introduced by species-, endpoint-, and dose metric-dependent differences in RePs. In many cases, more than one type of uncertainty may be present. Common sense suggests that one should select the RPFs or TEFs that represent the best (i.e., most accurate) information available. However, since the magnitude of the uncertainty or potential error inherent in a given RPF or TEF choice often can not be quantified, the choice frequently requires best professional judgment.

Visualization and Application of Criteria for Selection of Optimum RPFs. Data limitations do not negate the need to consider uncertainties and make optimum RPF/TEF decisions for the particular problem formulation, species, and effects of concern. To this end, a three dimensional matrix model (Figure 1) is provided for evaluating the applicability of different ReP data associated with TEFs or RPFs that may be available (or that could be derived) and the types of uncertainty inherent to each. Using this concept, selection of TEFs or RPFs can be based on a three dimensional hierarchical approach involving use of the best available information relative to the ideal choice which would be a species-specific RPF for the endpoint of concern based on optimum dose metrics. Currently, the ReP matrix model's primary value is to allow visualization of the complex factors that influence the applicability of potentially diverse relative potency data for specific risk assessment scenarios. This could include enhancement of efforts to describe uncertainties associated with RPF selections.

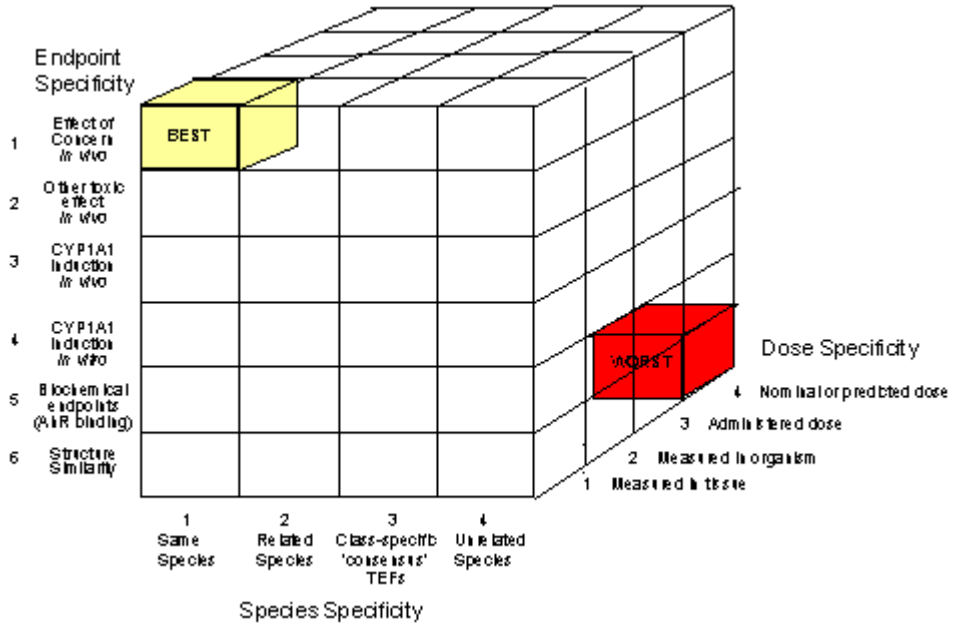
Because the three dimensional matrix model for selecting RPFs from ReP data is realistic but is unlikely to evolve into a purely quantitative and unambiguous model in the future, any number of questions concerning specific data may arise with its application in risk assessments. A few examples of such questions are presented in the Framework to assist in understanding how the approach can be used to consider and select RPFs from the types of ReP data available.

Uncertainty. The Framework also summarizes uncertainties associated with the toxicity equivalence methodology and more specifically, uncertainties associated with application of the methodology in ecological risk assessment. The relative importance of uncertainties inherent to the toxicity equivalence methodology versus those endemic to all risk assessments depends on the particular assessment. The decision matrix model for selection of RPFs provides some considerations for ordering uncertainties underlying particular elements of the methodology.

Conclusions

Use of the toxicity equivalence methodology has several implications for ecological risk assessment. The primary implication addressed in the Framework is that the ecological risk assessor must select appropriate potency factors for PCDDs, PCDFs, and PCBs. As demonstrated in the Framework, practical approaches exist for selecting potency factors. International consensus TEFs (currently, WHO-TEF_{98}s) have been established for mammals, birds, and fish classes and they represent reasonable values for estimating the TEC. The Framework also presents a matrix to facilitate the selection of assessment-specific RPFs as alternatives to TEFs that may enhance the accuracy of risk estimates using the toxicity equivalence methodology. The selection matrix is a useful tool in optimizing the application of the toxicity equivalence methodology and encouraging the appropriate use of new potency information as it becomes available.

Figure 1. Three dimensional matrix model for selection of RPFs or TEFs. Selection of appropriate TEFs or RPFs involves consideration of how similar a tested species is to the species of concern (x-axis), a tested endpoint is to the endpoint of concern (y-axis), and a reported dose is to the dose of concern (z-axis).



Acknowledgements

The Risk Assessment Forum Framework described in this short paper is currently in draft form for external review purposes and does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

References

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