The Toxicity Equivalency Factor (TEF) Method: Decision Criteria for Determining Applicability*

By
Frederick W. Kutz[1], Donald G. Barnes[1], David P. Bottimore[2], and Erich W. Bretthauer[1].

[1]U.S. Environmental Protection Agency.
401 M Street S.W.,
Washington, DC 20460

[2]Versar, Inc.
6850 Versar Center
Springfield, VA 22151.

ABSTRACT

The toxicity equivalency factor (TEF) method is an interim procedure for estimating the toxicological significance of complex mixtures of chemicals. TEFs provide a measure of relative potency among chemicals, usually referenced to a particular chemical of known toxicity. The method has been developed for several groups of chemicals, however, the method is not suitable for use with all chemicals. As a result, generalized criteria have been developed to determine the applicability of the TEF method.

INTRODUCTION

The TEF method is a practical tool for risk assessors and risk managers in estimating the toxicity of complex mixtures of environmental pollutants. TEF schemes have been used widely by scientists and regulatory agencies in addressing the 210 chlorinated dibenzo-*p*-dioxins and dibenzofurans (CDDs and CDFs). The method facilitates risk communication by reducing into one number large volumes of data for individual compounds. Multiplication of the concentration of a chemical in a mixture by its TEF converts the concentration of that congener into an equivalent concentration of a reference chemical. For the CDDs and CDFs, the reference chemical is 2,3,7,8-TCDD. One of the most widely used TEF systems is the International Toxicity Equivalency Factor (I-TEF) Method of Risk Assessment for Complex Mixtures of Dioxins and Related Compounds (CCMS, 1988a,b). The I-TEF method has been officially adopted by numerous nations as the preferred interim method for CDDs and CDFs (U.S. EPA, 1989; Kutz et al, 1989a).

Given the widespread acceptance and acknowledged utility of the TEF method for CDDs and CDFs, many have urged the development of TEF methods for other mixtures of chemical pollutants. Some of the other groups of chemicals for which TEF approaches have been

*Although the research described in this article has been funded by the United States Environmental Protection Agency partially through Contract No. 68-D9-0166 to Versar, Inc., it has not been subjected to Agency review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

developed include polychlorinated biphenyls (PCBs) and polyaromatic hydrocarbons (PAHs). These schemes have been based roughly on the TEF methods for CDDs and CDFs. The use of consistent criteria for TEF development and assignment of values contributes to the credibility of approaches and comparability of different schemes. These criteria also facilitate revision of TEF methods as additional toxicity data are generated.

Although the TEF approach is based on scientific data, the method has only limited scientific validation. TEFs for the CDDs and CDFs have been developed using a limited data base of *in vivo* and *in vitro* toxicity data generated from a variety of toxic endpoints in different animals. As a result, there are acknowledged limitations to TEF methods. These limitations are results of both procedural and scientific methodologies used to develop the methods and assign the TEF values. In addition, TEF approaches must be considered as interim methods because they can and should be revised as more definitive toxicity data are generated on complex mixtures (or their individual components). Additional data can be used (in accordance with the criteria used originally to develop the method) to improve or eventually replace the TEF method with methods that measure directly the toxicity of unique chemical mixtures. Accordingly, generalized criteria are necessary to facilitate consistency in TEF development and revision. The criteria described below were developed to assist in determining if the TEF approach is suitable for a complex mixture (group of chemicals) (Kutz et al. 1989b; Versar, 1990).

CRITERIA FOR DEVELOPMENT OF TEFs

Because of the limitations of the TEF method, their development and use should be viewed critically or even skeptically. Therefore, it is important to determine under what conditions one should consider TEFs for complex mixtures. These criteria are intended to provide a basic framework for TEF development and not to restrict the procedure. In fact the relative emphasis given to the different criteria should be made on a case-by-case basis.

- There should be a demonstrated need for a TEF approach.
- Any particular set of TEFs should be limited to a sharply defined group ("family") of chemicals.
- A broad, but probably incomplete, base of toxicity data on the individual members of the family of chemicals should be developed.
- The TEF scheme should identify "an index chemical" whose toxicity has been relatively well characterized.
- The relative toxicity of compounds to the "index chemical" should be reasonably consistent across a variety of toxic endpoints.
- Available *in vivo* results should support predictions made from *in vitro* test results.
- A general additivity (or modest antagonism, but no synergism) of toxicity among the congeners should be demonstrated.

- There should be some plausible mechanistic explanation available to rationalize the TEF approach.

- There should be a mechanism for gaining consensus and moving toward implementation.

Although TEF development is based on limited data, good candidate families are those which have congener-specific toxicity data for many different endpoints (both *in vivo* and *in vitro*) and in different animal test systems. The credibility of any TEF approach is strengthened by a general consistency of relative toxicity for a variety of endpoints. For example, in the case where limited carcinogenicity data are supported by subchronic or *in vitro* test results. For the CDDs and CDFs, there exists a relative dearth of long-term data on most of the compounds other than 2,3 7,8-TCDD. In the case of CDDs, CDFs, and PCBs, the potential effects of long-term chronic exposure are of most concern (cancer, reproductive effects, etc.). Toxicity data for most of the other 209 CDDs/CDFs, however, are generally available for short-term toxic effects such as developmental toxicity, thymic atrophy, reduced body weight gain, lethality, and immunomodification.

For the CDDs and CDFs there is a growing body of *in vitro* data (e.g., enzyme induction and cell transformation) which appear to be well correlated with the *in vivo* biological effects. Although the mechanism of toxicity of these compounds is not well understood, it has been hypothesized that there exist relationships between the abilities of CDDs/CDFs to bind to a cytosolic receptor and induction of enzymes [e g , aryl hydrocarbon hydroxylase(AHH)], and the manifestation of toxicity such as thymic atrophy, body weight loss, lethality, carcinogenicity, reproductive/teratogenic effects, and other toxic responses. These findings have been reported by numerous investigators and demonstrate a utility of *in vitro* data in predicting *in vivo* biological responses. While the doses necessary to elicit the toxic response differs for each toxic endpoint, the relative potency of the different CDD/CDF compounds (compared to 2,3,7,8-TCDD) is generally consistent from one endpoint to the other. This general consistency of relative potency for the same CDDs/CDFs using different endpoints and animal systems gives added credence to the TEF concept for these compounds.

The TEF approach considers a wide range of toxicity data in assigning the factors for individual compounds, however, a data hierarchy is used to give priority to results from long-term, whole animal tests such as carcinogenicity. Under ideal conditions, the assessment of toxicity is most accurately accomplished by directly measuring the toxic effects of chronic exposure to a chemical mixture. Since these long-term data are limited for most chemicals, short-term, whole animal studies (such as reproductive effects) and/or subchronic effects data (thymic atrophy, reduced body weight gain, etc.) are used. Acute toxicity studies such as lethality are also used in the assignment of TEFs As stated

previously, the emphasis is placed on *in vivo* test data when they are available. In many cases, however, *in vitro* enzyme induction data (such as AHH induction) are useful for TEF assignment because of the strong correlation with the *in vivo* biological responses. Generally, however, these data are used to confirm and refine the assignment of values based on the *in vivo* data described above.

CONCLUSION

The criteria described have been outlined to assist in future development of TEF schemes for groups of environmental pollutants. Although there are limitations to TEF approaches, they serve as practical tools that can be used in exposure and risk assessment processes. Given the limitations of the approach, it is prudent to use a generalized criteria to strengthen the applicability of the method. The decision criteria provide guidelines for considering the method, determining if it is applicable to a group of chemicals, and making assignments of TEF values.

REFERENCES

CCMS. 1988a. Committee on the Challenges of Modern Society. International Toxicity Equivalency Factor (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds. Pilot Study on International Information Exchange on Dioxins and Related Compounds. North Atlantic Treaty Organization/Committee on the Challenges of Modern Society. Report Number 176. August 1988.

CCMS. 1988b. Committee on the Challenges of Modern Society. Scientific basis for the International Toxicity Equivalency Factor (I-TEF) method of risk assessment for complex mixtures. Pilot Study on International Information Exchange on Dioxins and Related Compounds. North Atlantic Treaty Organization/Committee on the Challenges of Modern Society. Report Number 178. December 1988.

Kutz, F.W., D.G. Barnes, D.P. Bottimore, H. Greim, and E.W. Bretthauer. 1989a. The International Toxicity Equivalency Factor (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds. Presented at Dioxin '89, Toronto, Canada, September 1989. Chemosphere (in press).

Kutz, F.W., D.G. Barnes, D.P. Bottimore, and E.W. Bretthauer. 1989b. The toxicity equivalency factor (TEF) method for estimating risks associated with exposures to complex mixtures. Presented at the Total Exposure Assessment Methodology Conference, Las Vegas, Nevada, November 1989 (in press).

USEPA. 1989. U.S. Environmental Protection Agency. Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-*p*-dioxins and dibenzofurans (CDDs and CDFs) and 1989 update. Washington, DC: U.S. Environmental Protection Agency. EPA/625/3-89/016.

Versar, 1990. Draft Report: A PCB/TEF Feasibility Study. Prepared by Versar, Inc. for U.S. Environmental Protection Agency Office of Research and Development-Risk Assessment Forum. April 11, 1990.