



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D. C. 20460

November 4, 1986

SAB-EC-87-008

Honorable Lee M. Thomas  
Administrator  
U. S. Environmental  
Protection Agency  
401 M Street, S. W.  
Washington, D. C. 20460

OFFICE OF  
THE ADMINISTRATOR

Dear Mr. Thomas:

The Science Advisory Board's (SAB) Dioxin Toxic Equivalency Methodology Subcommittee met in public session on September 8 to review a draft document prepared by the Agency's Risk Assessment Forum and entitled "Interim Procedures for Estimating Risk Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans (CDDs and CDFs)." The document sets forth an approach for assessing the hazard of CDD and CDF mixtures relative to the toxicity of the 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) isomer.

The request for SAB review of this Toxic Equivalency Factor (TEF) methodology originated on February 27, 1986 from Assistant Administrator for Air, Craig Potter, who recommended SAB review in relation to his office's ongoing interest in assessing dioxin risks associated with municipal waste combustion. The SAB Executive Committee accepted this request and formed the Dioxin Toxic Equivalency Methodology Subcommittee to carry out the review. The Subcommittee approached its task with the assumption that it was reviewing a generic methodology as opposed to one that was limited solely to the issue of municipal waste combustion.

The Subcommittee's report consists of two sections: 1) its consensus statement on the draft document in its current form, and 2) comments on individual steps that EPA should initiate to improve the document or the scientific data base for toxic equivalency evaluation. The Subcommittee has already forwarded the comments of its individual members to the Agency's staff.

The Subcommittee generally concludes that the draft document represents a successful interim attempt to articulate a scientific rationale and procedures for developing risk management decisions for mixtures which contain CDDs and CDFs related in structure and activity to TCDD. The Subcommittee's major recommendations include: placing greater emphasis on

toxicokinetics, including metabolism; assigning priority to using human data, when available; validating the TEF methodology by selected testing of hypotheses; articulating clearly the decision steps, assumptions and methods of calculation; restating and re-emphasizing the interim nature of the methodology; and addressing the possibility of chemical and toxicological interactions with other types of compounds in complex environmental mixtures.

We appreciate the opportunity to review the TEF methodology and to present our technical evaluation. We request that the Agency formally respond to the scientific advice provided in the attached report.

Sincerely,



Richard Griesemer, Chairman  
Dioxin Toxic Equivalency  
Methodology Subcommittee

Norton Nelson, Chairman  
Executive Committee

Report of the Science Advisory Board's Dioxin Toxic Equivalency  
Methodology Subcommittee Following Its Evaluation  
of EPA's Toxic Equivalency Factor Methodology for CDDs and CDFs

A. Major Subcommittee Conclusions

EPA has proposed interim procedures for estimating health risks for CDDs and CDFs based on the premises that: (a) toxicity equivalence factors can be assigned to untested (or incompletely tested) compounds on the basis of structure/activity relationships; and (b) the toxicity of mixtures of these compounds can be approximated for policy purposes by the sums of their TEF times concentrations. Empirically, the present proposal falls generally between the positions adopted by certain European countries, which rank 2,3,7,8 TCDD far above any other congener in toxicity, and that initially proposed by the state of California, which equates all the dioxin congeners. All have used similar scientific assumptions in developing policy.

The Subcommittee agrees that the congeners of CDDs and CDFs constitute a class of chemical substances that share similar structural relationships and qualitatively similar toxic effects and, therefore, can reasonably be considered together. From the limited toxicologic data available it seems reasonable, too, to consider those tetra- to hexa-chlorinated compounds with chlorine substitutions at the lateral 2,3,7,8 positions as a closely related subclass in terms of biological activity and environmental fate.

The Subcommittee also concurs that the problems in assessing the health risks of dibenzo-p-dioxins and dibenzofurans are two-fold. They include: limited information from human or experimental studies about the hazards from exposure to these compounds (few of the 75 CDDs and 135 CDFs have been tested at all) and even more limited information about their possible interactions in mixtures. Indications of interactions, mostly additive, are found in certain experimental model systems (e.g. binary combinations). Not addressed in the draft document, however, is the possibility of chemical and toxicologic

interactions with other types of compounds in complex environmental mixtures, especially solvents that might affect uptake and retention by the body. EPA should address the latter subject in the TEF document, perhaps with more specific reference to its recently published Risk Assessment Guidelines and to three National Academy of Sciences' reviews on toxicological interactions, the last of which is currently being prepared for EPA and the National Institute of Environmental Health Sciences. The Subcommittee also questions the basis for including or excluding other chemicals with effects similar to CDDs and CDFs, such as chlorinated biphenylenes.

Based upon its review of the draft document, the Subcommittee concludes that the method proposed by EPA is a reasonable interim approach to assessing the health risks associated with exposure to mixtures of CDDs and CDFs for risk management purposes. It is necessary, however, as lessons are learned from toxicologic research and from application, the approach should be re-evaluated systematically by EPA. Moreover, attempts should be made to validate the method by selected experimental testing of hypotheses. For example, more data are needed on in vivo potencies of additional PCDDs and PCDFs to compare with in vitro test results. The assumption of additivity can be evaluated by comparing observed activities with predicted activities in selected tests.

The Subcommittee recommends that EPA place more emphasis on the interim nature of the method in the document. The Subcommittee anticipates that, over time, the method will be modified and eventually superseded as more precise data become available. Meanwhile, the general method proposed appears to have utility for this and for other classes of closely related compounds where toxicologic data are incomplete. Application of structure activity relationships is an old and established practice of demonstrated usefulness in pharmacology and toxicology.

However, EPA should not abandon its exploration of other approaches to estimating risks for substances in mixtures. For example, where variability in the composition of environmental samples is not wide, a reference standard approach might be used (similar to those used in toxicology for selecting a reference cigarette or a representative blend of gasolines). As another example, the incorporation of a small amount of radiolabeled test compound into a representative and defined mixture might be one useful way of determining in vivo whether the uptake and metabolism of one congener is greatly modified by the presence of other substances in a mixture.

Some additional technical comments that the Subcommittee wishes to draw to the Agency's attention include: 1) perceptions by many Subcommittee members of an over-reliance upon the postulated mechanisms of the Ah receptor/AHH enzyme induction upon which to gauge relative and absolute toxicity; 2) the need to discuss the work of Matsumura, Rozman, Greenlee, Poellinger and others on additional toxicologically significant effects of the dioxins other than those associated with receptor binding or with cytochrome P-450 induction; 3) observations of a disassociation between AHH induction and cytotoxicity in studies on the gonado toxicity of TCDD; and 4) examination of the extent to which the longer biological half-life of higher chlorinated dioxin isomers, as compared to 2,3,7,8-TCDD, counter-balances their lesser in vivo potency.

#### B. Major Subcommittee Recommendations

The Subcommittee has several recommendations for improving the report. First, the draft report narrative is relatively brief and may not be readily understood by those not familiar with dioxins. For example, four

possible approaches are introduced and one (TEF) selected, but the document does not clarify what the other three approaches are and the reasons for their rejection. The first approach, long-term animal testing, might be appropriate for municipal incinerator fly ash, where analytic data suggest there is a characteristic pattern of composition. The second approach (short-term assays) is not clearly described (not even whether they are in vivo or in vitro). The third approach, additivity of the toxicity of components, is at first rejected in the narrative but then forms the basis for handling the equivalents to 2,3,7,8-TCDD in mixtures.

Because the draft document presents a procedure, it is essential that the decision steps be clearly articulated, the assumptions made explicit, and the mechanics of calculating be illustrated in a stepwise fashion. To approach the subject from the viewpoint of studying the whole class of pollutants and to avoid bias by selecting data, the Subcommittee recommends that the tabular data be enlarged to include all compounds with zero to eight substituted chlorines. Biological activity has been reported for di- and tri-CDDs, and carcinogenicity studies exist for DD and 2,7 DCDD, as examples. Moreover, the activity of brominated and other substituted compounds should also be indicated and a specific effort encouraged to collect data on non-chlorine substituted compounds.

In contrast with the document's first priority on carcinogenic and then on teratologic effects in animals, the Subcommittee recommends that the TEF methodology assign first priority to human data when it exists. In evaluating experimental data, EPA should continue to follow the current

toxicologic practice of evaluating all endpoints, and selecting the ones most reliable, sensitive, and important for risk assessment. Thus, columns should be added to the tables in the document for other important toxic endpoints including immunotoxicity, thymic atrophy, body weight, and enzyme induction in vivo. The limited data points from which TEFs are currently derived (e.g. carcinogenicity of 2,3,7,8-TCDD, 2,3,7,8-Hx CDDs and reproductive effects of those compounds plus 2,3,7,8-TCDF) should be critically re-examined and the range of experimental data and estimated potencies from all studies tabulated. The Subcommittee also recommends that EPA consider assigning higher relative TEFs to CDFs in general, and 2,3,4,7,8-PeCDF in particular.

The Subcommittee strongly believes that EPA should assign greater priority to obtaining and using data on toxicokinetics, including metabolism. The rates of uptake and distribution of compounds alone and in mixtures are important measures of bioavailability and dosimetry. The kinetics of metabolism and excretion, along with those of receptor kinetics and affinities, should be especially useful for interspecies comparisons and for estimating risks for this particular class of compounds.

The Subcommittee wishes to emphasize that the method proposed may lack scientific validity. The associated errors have not been quantified. It is important, therefore, that the Agency make every effort to validate the method. The Subcommittee recommends periodic review and analysis as better data are obtained, and that EPA make systematic efforts to obtain critically important data, including that from in vivo tests on compounds

with representative positional substitutions. Efforts should continue to develop methods for assaying the biologic activity of important mixtures (e.g. fly ash) in in vitro systems, using other cells in addition to hepatocytes and other endpoints in addition to AHH activity. Until the uncertainties are reduced, the interim TEF method should be largely reserved for specific situations where the components of the mixture are known, where the composition of the mixture is not expected to vary much with time, and where the extrapolations are consistent with existing animal data.



U. S. ENVIRONMENTAL PROTECTION AGENCY

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