EPA

United States
Environmental
Protection Agency

Science Advisory
Board (A-101)

EPA-SAB-EPEC-92-024
August 1992

AN SAB REPORT: REVIEW OF RATIONALE FOR DEVELOPMENT OF AMBIENT AQUATIC LIFE WATER QUALITY CRITERIA FOR TCDD (DIOXIN)

PREPARED BY THE DIOXIN ECOTOX SUBCOMMITTEE OF THE ECOLOGICAL PROCESSES AND EFFECTS COMMITTEE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

August 11, 1992

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-EPEC-92-024

Mr. William K. Reilly
Administrator
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

RE: SAB Review of the Rationale for Development of Ambient Aquatic Life Water Quality Criterion for TCDD (Dioxin)

Dear Mr. Reilly,

The Science Advisory Board (SAB) was asked by the Office of Water and the Office of Research and Development to review research proposals to support the development of a water quality criterion for 2,3,7,8 TCDD (dioxin). This SAB activity is being coordinated with the Agency's reevaluation of its dioxin risk assessment. The Ecological Processes and Effects Committee of the SAB established a Dioxin Ecotox Subcommittee which met March 19-20, 1992 to conduct this review.

The Subcommittee was asked to review the proposed plan for its ability to fill data gaps for a dioxin water quality criterion, the adequacy of the endpoints and species evaluated, the consistency of the proposed tests with the Guidelines to establish water quality criteria, and to provide recommendations for research to support the use of a Toxicity Equivalency Factors (TEF).

The Subcommittee commends EPA for its innovative and well-conceived research plan to support the development of a dioxin water criterion. The Subcommittee endorses study of the body burden approach that EPA has proposed and encourages the Agency to continue and expand research that would validate the assumptions of the approach, particularly those related to exposure, dosing parameters, and body burden equilibria. The use of the fish,

Medaka, is inherently controversial and EPA should consider substitute species that are native or modify the guidelines for developing water quality criteria. The Subcommittee also recommends that EPA add tests to evaluate metabolism of dioxin, biomarkers such as immunosuppression and preneoplastic lesions, and improve analytical measurements and verify aqueous concentrations. Such information would support the development and implementation of the criterion. The Subcommittee finds that the TEF approach is promising, but further verification must be done before it can be applied to aquatic life and wildlife. Overall, EPA has presented several alternatives to conventional testing of chemicals which, if verified by additional research, will provide valuable insights about compounds that bioaccumulate. This research may also lead to a new approaches for criteria that should be reflected in the national guidelines for developing water quality criteria. These and other recommendations are elaborated in the attached report.

Finally, the SAB would like to express concern about the limited resources for the ongoing dioxin environmental research effort. We hope that the situation is corrected as soon as possible so this valuable research can continue.

The Science Advisory Board appreciates the opportunity to conduct this important review and we look forward to reviewing the Agency's progress in revising the National Guidelines for Water Quality Criteria and developing an accumulation-based hazard evaluation. For this research plan, we are particularly interested in whether the Agency will be able to include additional test organisms and verify critical assumptions as part of the overall research plan.

Sincerely yours,

Raymond Loehr, Chair
Executive Committee
Science Advisory Board

Kenneth L. Dickson, Chair
Ecological Processes and
Effects Committee

Robert Huggett, Chair
Dioxin Ecotox Subcommittee

U.S. ENVIRONMENTAL PROTECTION AGENCY

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MRS. MARCIA K. JOLLY (MARCY), Secretary to the Designated Federal Official

ABSTRACT

The report represents the conclusions and recommendations of the U.S. Environmental Protection Agency's Science Advisory Board regarding a research proposal entitled "Rationale for the Planned Studies to Develop an Ambient Aquatic Life Water Quality Criterion for TCDD" (January 1992). The Subcommittee commended EPA for its innovative and well conceived research plan to support the development of a dioxin water criterion. The Subcommittee endorses the body burden approach and encouraged the Agency to continue and expand research that would validate the assumptions of the approach. The Subcommittee found that the use of the fish, Medaka, was inherently controversial and recommended that EPA consider either a native substitute species or modify the guidelines for developing water quality criteria. The Subcommittee also recommended that EPA add tests to evaluate metabolism of dioxin, develop additional biomarkers, and improve analytical measurements and verify predicted aqueous concentrations to support the development and implementation of the criterion. The Subcommittee found that the TEF approach was promising but recommended further verification before it could be applied to aquatic life and wildlife. Overall, the Subcommittee found that EPA presented several alternatives to conventional testing of chemicals which, if verified by additional research, will provide valuable insights about compounds that bioaccumulate and depurate slowly. This research may also lead to a new approaches for criteria that should be reflected in the national guidelines for developing water quality criteria.

KEY WORDS: Dioxin, Bioaccumulation, Ah receptors, TCDD, water quality criteria.

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1. EXECUTIVE SUMMARY

The Dioxin Ecotox Subcommittee of the Ecological Processes and Effects Committee of the Science Advisory Board (SAB) met on March 19-20, 1992 to review a draft research plan entitled "Rationale for the Planned Studies to Develop and Ambient Aquatic Life Water Quality Criterion for TCDD" (January 1992).

The numbers of species and endpoints are consistent with the criteria guidelines, but the guidelines were developed for water column exposures, and the research plan under consideration employs a body burden target. The body burden approach is logical in this case but needs to be validated. Exposure to a single concentration using a saturated test solution over four days, followed by exposure to clean water may not be adequate to manifest sublethal or chronic effects comparable to standard toxicity tests. The primary problem is one of methodological resolution.

The research plan for developing a water criterion for 2,3,7,8-TCDD is based on the assumption that bioaccumulated dioxin is the appropriate dosing parameter and that short term exposures which produce tissue concentrations of dioxin in organisms which correlate to toxic effects can be used to evaluate species sensitivity. These assumptions may be correct, but they need to be tested.

The use of the fish, Medaka, in the development of criteria is inherently controversial. On the one hand, Medaka is a well studied model in aquatic toxicology, and the species is suitable for many different types of assessments. However, it is not a native species to North America. This inconsistency needs to be resolved before the Medaka data set can be considered acceptable. Several native fish species are also suggested as substitutes for Medaka. Further chronic studies are recommended for fish and invertebrates as well.

It is commonly believed that chemicals with very large K_{ow}s do not bioconcentrate to the extent that the Kow would predict. There are a number of reasons for this, but the issue of importance for TCDD is one of being confident that all of the model parameters that are used to assess bioaccumulation and bioconcentration for this chemical are thoroughly understood. The Subcommittee recommended that the existing measurements of K_{ow} be critically evaluated to determine their adequacy.

The Subcommittee recommended that EPA conduct additional research on the role of the intestine in dioxin effects and metabolism and evaluate other biomarkers such as

immunosuppressors and neoplasia. They also recommended additional research on methods to quantify dissolved water concentrations of TCDD and its dibenzofuran congeners. Following the development of the methods, they recommended field verification of the K_{ow} estimated concentrations.

2. INTRODUCTION

EPA has committed to reassess the risks of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin) to human health and ecosystems. Although the major public concern over dioxin has been related to human health hazards, recent studies indicate that dioxin and related compounds may be toxic at extremely low concentrations to reproduction of aquatic populations in the Great Lakes. Due to this information, EPA's Duluth Environmental Research Laboratory developed research plans "Rationale for the Planned Studies to Develop an Ambient Aquatic Life Water Quality Criterion for TCDD" (January 1992) and a data base to reassess the risks of dioxin and related compounds to aquatic life and wildlife.

The reassessment will result in a revised ambient aquatic life water quality criterion for dioxin. The approach for evaluating the effects of dioxin deviates from the specific procedures in the "Guidelines for the Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses", hereafter referred to as guidelines for criteria. The deviation occurs in the hazard assessment which is based on accumulation rather than exposure concentrations and in the use of a non-native species for testing.

The Research Plan (January, 1992 draft) summarized the studies planned and on-going and the rationale for using these studies in the reassess of criteria for aquatic life and wildlife. The plan also included a brief list of pertinent literature related to the assumed mode of action of dioxin, the occurrence of aryl hydrocarbon receptors in different taxonomic groups, and preliminary information on reproductive effects in fish. This Research Plan will contribute to a preliminary assessment of ecological risks associated with dioxin in aquatic ecosystems.

2.1 Charge for the Review

The SAB was asked by the Office of Water to review the research plan developed by ORD for the reevaluation of the water quality criterion for dioxin. The charge for this Subcommittee was to review the research plans and evaluate the endpoints and test procedures that were proposed for consistency with the National guidelines for developing water quality and whether the suite of tests is adequate. This Subcommittee will also address questions on the use of Toxicity Equivalent Factors that were posed to the SAB as part of the review of the Great Lakes Water Quality Initiative. The charge for this review were as follows:

1) Are the species and the endpoints selected appropriate?

2) Will the research plan fill the data gaps for the establishment of aquatic-based water quality criterion?

3) Are there any other tests that should be included in the plan? If so, can the information be gathered within the specified time frame (by the summer of 93)?

4) Are the proposed tests consistent with the Guidelines for the establishment of water quality criteria to protect aquatic ecosystems? If not, or if there is uncertainty, are they sufficient to develop a "scientifically defensible" water quality criterion for use in State standards and ultimately, to develop effluent limitations?

5) What research should be undertaken to support the use of Toxicity Equivalency Factors (TEF) for aquatic life and wildlife?

2.2 Subcommittee Review Procedures

The Subcommittee met on March 19-20, 1992 to receive briefings and review the research plan. Oral and written public comments were received from four groups. The research plan was characterized as a working draft, which represented both plans and studies in progress. In response to some of the recommendations made by the panel at the review, EPA agreed to modify its plan. In addition, the Subcommittee heard a presentation from the Wisconsin Department of Natural Resources on their development of wildlife criteria as part of the Great Lakes Water Quality Initiative. This panel had two members in common with

the Great Lakes Water Quality Subcommittee which was reviewing the initiative guidance. The final question in the charge was modified to address the concerns of the Great Lakes Initiative as well as this dioxin research program. The Subcommittee also noted that the approach for using TEFs with dioxin must also be consistent with the human health risk assessment approach which is scheduled to be reviewed later.

The Subcommittee provided a summary of its preliminary findings at the conclusion of this review and writing assignments were made at the meeting. Written materials were compiled and edited by the Designated Federal Official and the Subcommittee Chair. working documents were reviewed by the Subcommittee through the mail, revised and one draft was provided to the public, EPA and the Executive Committee of the SAB at the same time.

3. EVALUATION OF THE RESEARCH PLAN

3.1 Selection of Species and Endpoints

The numbers of species and endpoints are consistent with the criteria guidelines, but the guidelines were developed for water column exposures, and the research plan under consideration employs a body burden target. The body burden approach is logical in this case but needs to be validated. Exposure to a single concentration using a saturated test solution over four days, followed by exposure to clean water may not be adequate to manifest sublethal or chronic effects comparable to standard toxicity tests. The primary problem is one of methodological resolution.

We applaud the program's efforts to include wildlife species which are dependent on aquatic environments. We understand that time, cost and lack of preliminary data and experience limit the scope of work that can be performed on avian and/or mammalian models. However, it is important that research applied to taxa such as mink or piscivorous birds be conducted to make the application of the criteria to wildlife species more meaningful. The Subcommittee believes that a chronic test should be performed most likely on mink. We encourage coordination of this aspect of the aquatic criteria program with the Great Lakes Water Quality Initiative in its research on effects of 2,3,7,8 TCDD, especially on minks. The program should also consider wildlife species from other regions. Collaborative planning should make data gained from these studies valuable to both programs.

The use of the fish, Medaka, in the development of criteria is inherently controversial. On the one hand, Medaka is a well studied model in aquatic toxicology, and the species is suitable for many different types of assessments. However, it is not a native species to North America, and the National Guidelines specify the use of native species. If it is discovered that the Medaka plays a pivotal role in the establishment of the criteria (e.g. if it were the most sensitive species), a criterion including Medaka data would generate unfavorable public comment. Furthermore, the data on Medaka that are presently available contain inconsistencies (one set of larvae shows nearly perfect survival, a second set shows significant mortality). These inconsistencies need to be resolved before the Medaka data set can be considered acceptable. There are also some native fish species which may be useful substitutes for Medaka, including rainbow trout, brown bullhead, mummichog, and mangrove rivulus. Further there are several introduced species (particularly livebearers) for which

histopathological data are available, including the guppy, platyfish, top minnow (Poeciliopsis sp.), and zebra danio.

The proposed research includes tests with the frog genus, Rana. While amphibians may be good models for the study of developmental effects, the Agency has almost no experience with these species. Caution should be exercised until their sensitivity and applicability for the intended use is ascertained. Should an amphibian be used, the Subcommittee recommends consideration of Xenopus over Rana because there is an existing method for determining developmental effects (i.e., the Frog Embryo Teratogenicity Assay Xenopus-FETAX). It is recognized that Xenopus is also a non-native species and carries all the potential problems associated with Medaka. For Xenopus, the choice can be defended because there is already extensive scientific literature on its response to a variety of chemicals, the test system has been independently validated in several laboratories, and standardized protocols and an atlas of abnormalities have been developed which may facilitate interpreting the results. In light of the previous discussion of Medaka and Xenopus, the Subcommittee recommends that EPA consider revising the National Guidelines to allow use of using non-native species.

Several other conclusions of the Subcommittee relative to selection of species and endpoints are given below:

1. The Subcommittee also recommends the addition of chronic toxicity tests on a benthic feeding fish, if it can be done within the time frame. At least one bullhead species has shown tumors in dioxin-contaminated waters.
2. The reduced suite of invertebrate acute toxicity tests may be appropriate, but some verification of chronic invertebrate effects should be made by conducting at least one standard invertebrate chronic study.
3. The Subcommittee recommends using a freshwater bivalve for assessing bioaccumulation rather than the proposed snails (Aplexa hypnorum or Heliosoma sp.), because bivalves are efficient chemical accumulators. Although effects data are limited for dioxin, the bivalve could be an ideal organism to establish direct tissue effects of exposures to TCDD via histopathology.

3.2 Does the Plan fill data gaps?

The research plan for developing a water criterion for 2,3,7,8-TCDD is based on the assumption that bioaccumulated dioxin is the appropriate dosing parameter and that short

term exposures which produce tissue concentrations of dioxin in organisms which correlate to toxic effects can be used to evaluate species sensitivity. These assumptions may be correct, but they need to be tested. The proposed research assumes that the exposure concentration and duration of exposure are irrelevant for the production of the effect as long as the combination of concentration and duration of exposure result in a body burden high enough to produce the effect. It also assumes that both dietary and water exposures can be used to derive the residue-based water quality criterion. This has never been done before and there is only limited data which support the concept that whole body residues can be correlated with toxic effects in a consistent manner across a range of exposure levels. The proposed studies must demonstrate the validity of this approach by showing a strong correlation of effects with residues and demonstrating that effects occur at the same residue level independent of exposure route. The Subcommittee questions whether the planned four day exposure to dioxin will be sufficient to elicit sublethal effects. Therefore, a longer exposure may be necessary. Additionally, the validity of using laboratory-derived residue based effects for evaluating residues in field collected species will be very difficult to demonstrate. This is important if the approach is to have credibility and utility.

It should be pointed out that bioaccumulation is expected to occur largely in adipose tissue. Existing theories on the mechanism of TCDD effects claim that the toxicological effects of dioxins are largely dependent upon interactions with the aryl hydrocarbon (Ah) receptor. There is good reason to suspect that the kinetics of dioxin with respect to the Ah receptor would be different than those involving the storage of dioxins in lipids. Therefore, there is good reason to expect that the proportion of dioxins reaching the Ah receptor would be influenced by the rate at which the dioxin is administered to the organism. Without a clear demonstration of the irrelevance of duration of exposure for effects and the overwhelming dependence of chronic effects upon body burden, the validity of the research program will be questionable. The above assumptions must be verified because they are the linchpins upon which the residue approach is postulated for TCDD. The Subcommittee believes that these points are very important. Therefore, the Subcommittee recommends that before the data and methodology are utilized in a criterion, this approach and supporting demonstration data should be carefully reviewed since it will set a precedent for chemicals with log K_{ow}s greater than 6.0.

It is commonly believed that chemicals with very large K_{ow}s do not bioconcentrate to the extent that the Kow would predict. There are a number of reasons for this, but the issue of importance for TCDD is one of being confident that all of the model parameters that are used to assess bioaccumulation and bioconcentration for this chemical are thoroughly understood.

Understanding this relationship will ultimately increase the validity of Bioaccumulation factor (BAF) models that are based on lipid normalization and the use of K_{ow}. In order to reduce the error associated with this estimate an accurate measurement of the K_{ow} is needed. It is recommended that the existing measurements of K_{ow} be critically evaluated to determine their adequacy.

Understanding exposure is key to explaining dose response and bioaccumulation data. Currently it is believed that both toxicity and bioaccumulation can be directly correlated with the dissolved "free" fraction of the total chemical present in a water exposure study. Additionally it is believed that the organic carbon content of sediments provides a normalizing factor for calculating the bioavailable fraction of the total chemical present in sediments from different sites. One or more of the EPA proposed BAF models that could be used for assessing the bioaccumulation of TCDD incorporates the use of the bioavailable (dissolved) fraction of the total TCDD present. These models also normalize TCDD concentrations to sediment organic carbon content and to organism lipid content. The Subcommittee recommends that the mechanisms controlling bioavailability of TCDD in water and sediment be evaluated in order to support BAF models that will be used to evaluate TCDD environmental risk and set water quality criteria. Recent work by EPA suggests that concentrations of organic contaminants in interstitial waters are closely related to observed biological effects. A well defined set of experiments where residues are measured and compared with the sorbed, dissolved, and total TCDD concentrations during exposure are appropriate. Predicted and measured residues could be compared and the theory on bioavailability could be verified.

3.3 Additional Test Recommendations

The Subcommittee recommends that the following tests be considered for the research plan. In some cases, they can be conducted within the time frame (spring 1993) established for this research. These tests are in addition to the research which the Subcommittee strongly recommends to verify the underlying assumptions of the current approach for the dioxin criterion.

A. Biomonitoring Tests

1) The fish intestine may play an important role in the effects and metabolism of TCDD. This tissue has an Ah receptor, induced cytochrome P-450s, and induced EROD (7-ethoxyresorufin-O-deethylase) activity. Thus the intestine and liver of fish should be assayed for the various endpoints.

2) Other biomarkers to be considered should include immunosuppression/immunotoxicity, preneoplastic lesions,and neoplasia.

B. Monitoring

1) At this time it does not appear possible to analytically quantitate dissolved ambient water concentrations of chlorinated TCDD and TCDF congeners. It does not appear impossible, however to develop the analytical methodologies to allow for such determinations. It is recommended that the proposed research plan be modified to include project(s) which will lead to the ability to quantify the dissolved fraction of most hazardous chlorinated dioxins and dibenzofurans in natural waters.

2) After development of analytical methodologies, the predicted aqueous concentrations of TCDD should be verified by actual measurements.

3) EPA should recommend the methods by which monitoring is to be performed. For example, should measurements in water or biota be performed?

The development of water quality criterion will ultimately require an estimation of the concentration in water that will produce toxic effects. The research program is totally oriented towards developing the data needed to support the residue approach. Eventually EPA must calculate the water concentration which should not be exceeded. Development and verification of the model(s) that will be used are, perhaps, as important at the bioaccumulation studies. The Agency should focus on this aspect of developing a water quality criterion while the bioaccumulation/toxicity studies are in progress.

3.4 Consistency with the Guidelines

The proposed use of bioaccumulated dioxins as a surrogate for dioxin exposure in water appears to fall within the philosophy espoused by the criteria derivation process. The method applied to dioxins does not generate a Final Acute Value (FAV) required in the National Guidelines and therefore does not derive a Criterion Maximum Concentration (CMC). The method only derives Criterion Continuous Concentrations (CCC) values in terms of bioaccumulated dioxin concentrations in aquatic biota. The derivation of the CCC is complicated by the fact that the species sensitivity appear to be dichotomously distributed between sensitive and insensitive species. This can seriously distort the derivation of the 5th percentile downward if regression techniques are applied.

With the existing inability to measure aqueous environmental levels of TCDD and our resulting ignorance of its partitioning in the environment, the criteria will not lead to scientifically defensible effluent limits. Typical effluent limits for water soluble chemicals with low hydrophobicity directly apply water quality criteria for receiving waters into permits. The proposed criteria development method for TCDD will result in aquatic life tissue residue concentration above which ecological effects could occur. There is great uncertainty in "back" calculating a residue concentration into an ambient water concentration. Such a calculation would need to be specific for species to be protected and as mentioned previously, would require an accurate measurement of dissolved TCDD. There would be site-specific consideration for species which would require lipid normalization of the criteria, adjustment for K_{oc} (transfer from sediment) and consideration for route of exposure to "fish". The process by which the residue-based criteria would be applied to an effluent discharge is uncertain and EPA is requested to carefully consider and propose/develop a workable procedure. The existing bioaccumulation models available for calculating an ambient water concentration need further peer review and testing before they will be defensible.

The "National Guidelines" require all collected data to be evaluated for minimum acceptability before inclusion in data bases for criteria development. The procedures for "collection of data" (p.21-22) set acceptability requirements. EPA should comply with these criteria in TCDD criteria development. Under such constraints, they should be aware that some data presented at the briefing would have been rejected.

The documentation for much of the proposed research is based on previous work done at the Duluth Environmental Research Laboratory. Since many of the proposed efforts will take place at the same laboratory and will be performed by some of the same investigators, some may question whether the program is too provincial and whether its hypotheses have received peer review. The Subcommittee therefore recommends that every effort be made to include peer reviewed references and documentation from other researchers (both academic and stakeholders) which are pertinent to the development of dioxin criteria and its research plan.

3.5 Toxicity Equivalency Factor Research Needs

The TEF approach appears promising but it must be investigated further. The TEF data obtained for lake trout eggs suggest that this approach may work for aquatic species and that the values are different than values calculated by Safe (1990). Whole organism TEF or at least target organ TEF with species of interest (birds, mammals, fish) may be the best way

to use the TEF. However, a cause and effect relationship between blue sac disease and TCDD was not adequately demonstrated by the data presented. Blue sac disease appears to be a general stress syndrome that can be caused by 20 specific causes, including, infectious physiological genetic and physico-chemical agents. The Subcommittee strongly recommends that the effect with TCDD be verified with appropriate broodstock replication.

For TEF to be used for aquatic life and wildlife, more studies are needed to show phylogenetic variability. An assumption is made that a similar Ah receptor in various animal groups is responsible for various biological effects observed in fish. Also, the assumption is made that metabolism of dioxin is of little importance in fish. The activated complex (dioxin-Ah receptor) translocating protein in the cell nucleus induces the production of certain cytochrome P-450s. Certain electrophilic metabolites of dioxin produced by the induced P-450 are thought to initiate cancer. This brings up the question, are the reproductive effects of dioxin in fish due to dioxin or to dioxin metabolites? Are fish quite different with respect to metabolism of dioxin than other wildlife?

At present the Subcommittee concludes that there are insufficient data available to judge the reliability and accuracy of the proposed TEF approach. Perhaps the question can be evaluated more fully in combination with the ORD report on the effects of TCDD on human health in another SAB review.

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