Peer Review Workshop of
Dioxin Reassessment-Chapter 9: Toxicity Equivalency Factors for Dioxin and Related Compounds and the Revised Integrated Summary and Risk Characterization Document

CHARGE TO THE REVIEWERS

Introduction and Background

In April 1991, the U.S. Environmental Protection Agency (EPA) announced it would conduct a scientific reassessment of the health risks of exposure to dioxins. This reassessment was initiated in response to emerging scientific knowledge of the biological, human health, and environmental effects of dioxin. Significant advances have occurred in the scientific understanding of mechanisms of dioxin toxicity, of the carcinogenic and other adverse health effects of dioxin in people, of the pathways to human exposure, and of the toxic effects of dioxin to the environment.

EPA's reassessment activity led to the publication of a 1994 draft multi-volume document titled Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. This 1994 draft was reviewed by the agency's Science Advisory Board (SAB) in May 1995. Their review and subsequent Fall 1995 report had four key recommendations:

- The review provided substantive comments on two sections in the reassessment documents-the chapter on Dose Response Modeling (chapter 8) and the Risk Characterization document (identified as chapter 9 in a previous draft).

- The review recommended development of a new chapter on toxicity equivalent factors (TEF) for the purpose of gathering in one place the discussion and scientific information on the complex issue and use of TEFs for dioxin and dioxin-like compounds.

- The review approved the health and exposure sections (chapters 1-7) without the need for further SAB review, provided EPA updated these sections with any relevant new information before finalizing.

- The review recommended that the revised chapters on Dose Response Modeling and Risk Characterization and the new chapter on TEFs should undergo external peer review prior to the SAB's re-review.

To date, EPA has addressed the first three SAB recommendations listed above and conducted an external peer review on the revised Dose-Response Modeling analysis (chapter 8), but the agency has not yet conducted an external peer review of the updated Integrated Summary and Risk Characterization or the new Chapter 9-Toxicity Equivalency Factors (TEF) for Dioxin And Related Compounds. The scientific rigor of these documents is the subject of this peer review.

During this peer review, EPA seeks expert opinions on several key questions that pertain to the content of the documents, Integrated Summary and Risk Characterization and the Toxicity Equivalence Factors (TEF) for Dioxin and Related Compounds. The questions are classified into twelve general topics, listed on the following pages. Further, EPA welcomes insights on additional topics relevant to these documents, but not explicitly addressed in the other questions. Following the workshop, ERG will prepare a summary report that documents the reviewers' responses to these questions. The reviewers will then be asked to review the ERG report for accuracy, after which ERG will submit the final peer review meeting report to the agency.

General Instructions When Preparing Written Comments

When addressing the questions to which you have been assigned, please make sure that you have addressed the following general questions in your responses: Are the assumptions and uncertainties clearly and adequately expressed?

- Are the key issues, statements, and conclusions clearly stated?
- Are the conclusions in the Integrated Summary and Risk Characterization supported with sufficient data, information, arguments, and references?
- Are the discussion points clear? How would you suggest improving the clarity of the text?
- Please make specific recommendations on improvements that can be made to the document to improve it.

REVIEWER ASSIGNMENTS

ASSIGNED CHARGE QUESTIONS

TOPIC 1: BODY BURDENS

In Section 5.1 of the Integrated Summary and Risk Characterization report, EPA concluded that body burden is a better metric for assessing inter-species scaling (animal to human) than are other methods (e.g., daily dose information combined with an uncertainty factor for pharmacokinetics, or 3/4 power body weight scaling).

Question 1:
Primary Reviewer-Brent Kerger
Secondary Reviewer-Richard Dickerson

Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based upon daily dose?

TOPIC 2: USE OF A "MARGIN-OF-EXPOSURE APPROACH" TO EVALUATE RISKS

EPA has recommended the use of margin-of-exposure (MOE) to evaluate the potential for health effects from dioxin. This approach expresses exposure as a percent additivity to background and recommends that it is a policy decision as to whether such increments reach significance for decision making. EPA decided not to apply the RfD/RfC methods to dioxin because of the relatively high background compared to effect levels and because these methods are most useful for evaluating increments of exposure from specific sources when background exposures are low and insignificant. EPA's decision to use an MOE approach differs from the approaches taken by the Agency for Toxic Substances and Disease Registry (ATSDR 1999) and WHO (1998), who calculate a minimal risk level (MRL) of 1 pg/kg/day and tolerable daily intake (TDI) of 1 - 4 pg/kg/day, respectively.

Question 2
Primary Reviewer-Colin Park
Secondary Reviewer-Richard Dickerson, Lorenz Rhomberg

How might the rationale be improved for EPA's decision not to calculate an RfD/RfC, and for the recommended MOE approach for conveying risk information? Is an MOE approach appropriate, as compared to the traditional RfD/RfC? Should the document present an RfD/RfC?

Question 3
Primary Reviewer-Lorenz Rhomberg
Secondary Reviewer-Mark Harris

The SAB commented that previous dose-response modeling was too limited to biochemical endpoints (CYPIA1, IA2, ...), Are the calculations of a range of ED01 body burden calculations for non-cancer effects in rodents responsive and clearly presented? Please comment on the weight-of-evidence interpretation of the body burden data associated with a 1% response rate for non-cancer effects that is presented in Chapter 8, Appendix I and Figure 8-1 (where EPA considers that the data best support a range estimate for ED01 body burdens between 10 ng/kg to 50 ng/kg).

TOPIC #3: MECHANISMS AND MODE OF ACTION

The scientific community has identified and described a series of common biological steps that play a role in most, if not all, observed dioxin-related effects in vertebrates, including humans. Biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on many of these endpoints do not generally exist for other congeners. The discussion in Part III indicates that our understanding of mechanisms of toxic action of TCDD is limited, but that a generalized mode-of-action can be discussed in light of these uncertainties.

Question 4
Primary Reviewer-Mark Harris
Secondary Reviewer-Matti Viluksela

How might the discussion of mode-of-action of dioxin and related compounds be improved?

Question 5
Primary Reviewer-Mark Harris
Secondary Reviewer-Matti Viluksela

Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?

TOPIC #4: TOXICITY EQUIVALENCY FACTORS

Dioxin and related compounds exist in nature as complex mixtures, the biological activity of which can be estimated using relative potency values and an assumption of dose additivity. Such an approach has evolved over time and has been characterized as a useful interim procedure to assess complex mixtures. The TEF approach has been accepted by numerous countries and several international organizations. In 1995, the Science Advisory Board supported "... EPA's use of Toxic Equivalencies for exposure analysis ...", but suggested that the Agency describe the history and application of the TEF process more explicitly.

Question 6
Primary Reviewer-Peter deFur
Secondary Reviewer-Mark Harris

Is the history, rationale and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? Did EPA clearly describe its rationale for recommending adoption of the 1998 WHO TEFs?

Question 7
Primary Reviewer-Brent Kerger
Secondary Reviewer-Matti Viluksela

Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?

TOPIC #5: NON-CANCER EFFECTS

Based on the information presented in Part II of the reassessment, Health Assessment for 2,3,7,8-TCDD and Related Compounds, EPA believes that adequate evidence supports the inference that humans are likely to respond with a broad spectrum of non-cancer effects from exposure to dioxin and related compounds. These effects will likely range from biochemical changes at or near background levels of exposure to adverse effects with increasing severity as body burdens increase above background levels.

Question 8
Primary Reviewer-Richard Dickerson
Secondary Reviewer-Allan Smith

Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the non-cancer endpoints discussed in the reassessment?

Question 9
Primary Reviewer-Richard Dickerson
Secondary Reviewer-Peter deFur

Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?

TOPIC #6: CANCER EFFECTS

A weight-of-the-evidence evaluation suggests that mixtures of dioxin and related compounds are strong cancer promoters and weak direct or indirect initiators, and thus are likely to present a cancer hazard to humans. Although uncertainties remain regarding quantitative estimates of upper bound cancer risk from dioxin and related compounds, the reassessment uses various data sources to evaluate the slope of the dose-response curve at the low end of the observed range (using the LED01). This approach uses a simple proportional (linear) model and a calculation of both upper bound risk and margin of exposure (MOE) based on human equivalent background exposures and associated body burdens.

Question 10
Primary Reviewer-Allan Smith
Secondary Reviewer-Brent Kerger, Curtis Travis

Do you agree with the characterization in this document that dioxin and related compounds are carcinogenic hazards for humans?

Question 11
Primary Reviewer-Allan Smith
Secondary Reviewer-Brent Kerger

Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the LED01 as a point of departure), as described in the EPA "Proposed Guidelines for Carcingenic Risk Assessment" (EPA/600/P-92/003C; April 1996)? Is this approach equally as valid for dioxin-like compounds.

Question 12
Primary Reviewer-Holly Hattemer-Fry
Secondary Reviewer-Colin Park

Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient, or should more weight be given to specific data sources?

TOPIC #7: BACKGROUND AND POPULATION EXPOSURES

The term "background exposures" is used to describe dioxin exposures for the general population (i.e., individuals who are not exposed to readily identifiable point sources of dioxin-like compounds). Current adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to average 45 and 25 pg TEQDFP-WHO98/day, respectively, for a daily total intake of 70 pg TEQDFP-WHO98/day (~1 pg/kg/day). The estimated current average adult body burden of 5 ng TEQDFP-WHO98/kg is substantially less than levels measured in the late 1980s/early 1990s (~14 ng TEQDFP-WHO98/kg), yet still reflects intakes from past exposure levels which are thought to be higher than current levels. Considerable variability around these means exists due to both the quantity and types of foods consumed. For instance, EPA has estimated that background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean, based on normal variability in human diet and behavior. Beyond this variability, EPA notes the existence of special populations that may be exposed to higher levels, such as individuals living near discrete local sources, subsistence or recreational fishers consuming more highly contaminated species, and nursing infants.

Question 13
Primary Reviewer-Myrto Petreas
Secondary Reviewer-Holly Hattemer-Fry, Christopher Rappe

Have the estimates of background exposure been clearly and reasonably characterized?

Question 14
Primary Reviewer-Myro Petreas
Secondary Reviewer-Holly Hattemer-Fry, Christopher Rappe

Has the relationship between estimating exposure from dietary intake and estimating exposure from body burden been clearly explained and adequately supported?

Question 15
Primary Reviewer-Myrto Petreas
Secondary Reviewer-Holly Hattemer-Fry, Christopher Rappe

Have important "special populations" and age specific exposures been identified and appropriately characterized?

TOPIC #8: CHILDREN'S RISK

Federal agencies are obliged to consider risks to children in their regulatory decisions, with risks that differentially impact children being particularly important. Based on the weight of evidence, EPA considers that risks to children from dioxin and related compounds may be increased compared to the general population, but acknowledges that more data are needed to fully address this issue. EPA's conclusion is based on the spectrum of higher dose toxicity evident in the Yusho/Yu-Cheng and Seveso incidents and on the contemporary epidemiological literature which has shown structural and developmental effects associated with low dose/background exposure to dioxin TEQ levels in various children's cohorts. EPA has concluded that these human developmental effects are consistent with those seen in animal bioassays and in in vitro studies, as well as with dioxin's mechanism of action on cellular differentiation. However, the relative paucity of data has prevented EPA from determining if children are differentially sensitive compared to adults, and the extent to which such differential sensitivity occurs.

Question 16
Primary Reviewer-Matti Viluksela
Secondary Reviewer-Richard Dickerson, Allan Smith

Is the characterization on increased or decreased childhood sensitivity to possible cancer and non cancer outcomes scientifically supported and reasonable? Is the weight of evidence approach appropriate?

TOPIC #9: RELATIVE RISKS OF BREAST FEEDING

Based on estimates that human breast milk contains 35 ppt TEQDFP-WHO98 and a six month nursing scenario, the average daily dioxin intake (on a TEQ basis) for an infant is about 100 times higher than an adult-a notable finding given that infants' exposures occur during sensitive developmental stages. However, the differences in body burden between infants and adults are expected to be much less than differences in the daily intakes, primarily because (1) the long half-life and cumulative nature of the body burden, (2) equilibration throughout the infant's body, and (3) rapid growth in size of the infant.

Question 17
Primary Reviewer-Curtis Travis
Secondary Reviewer-Lorenz Rhomberg

Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?

TOPIC #10 RISK CHARACTERIZATION SUMMARY STATEMENT

Based on the data reviewed in this reassessment and on scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at general population background levels, particularly among more highly exposed groups or special populations, with the spectrum of effects, and their potential to be adverse, increasing as body burdens rise.

Question 18
Primary Reviewer-Peter deFur
Secondary Reviewer-All

Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals, represent effects of unknown clinical significance, but that may be early indicators of toxic response? (Refer to pages 84-86.)

Question 19
Primary Reviewer-Colin Park
Secondary Reviewer-All

Has the short summary statement in the risk and hazard characterization on page 107 adequately captured the important conclusions, and the areas where further evaluation is needed? What additional points should be made in this short statement?

TOPIC # 11: SOURCES

Many Dioxin sources have been identified and emissions to the environment are being reduced. EPA's detailed inventory of dioxin emission sources quantifies, to the extent possible,the emissions for 1987 and 1995 from the majority of known sources in the United States, and provides preliminary estimates of emission factors for other sources where the data are too preliminary to be used to provide national averages. This inventory is presented in Part I of the dioxin reassessment, and has undergone peer review by the SAB. The inventory and other exposure information provide evidence that environmental levels of dioxin-like substances are being reduced through direct and indirect emission control methods. The present information also suggests that reservoir sources in the environment may be important factors to evaluate human exposures.

Question 20
Primary Reviewer-Christopher Rappe
Secondary Reviewer-Curtis Travis

Are these sources adequately described and are the relationships to exposure adequately explained?

Question 21
Primary Reviewer-Peter deFur, Colin Park
Secondary Reviewer-All

Please provide any other comments or suggestions relevant to the two review documents, as interest and time allow.

REVIEWER ASSIGNMENTS: PRIMARY, SECONDARY, AND ALL

REVIEWER	PRIMARY REVIEWER FOR QUESTIONS:	SECONDARY REVIEWER FOR QUESTIONS:	ALL REVIEWERS ADDRESS QUESTIONS:
DeFur	6, 18, 21	9	19
Dickerson	8, 9	1, 2, 16	18, 19 & 21
Harris	4, 5	3, 6	18, 19 & 21
Hattemer-Frey	12	13, 14, 15	18, 19 & 21
Kerger	1, 7	10, 11	18, 19 & 21
Park	2, 19, 21	12	18
Petreas	13, 14, 15		18, 19 & 21
Rappe	20	13, 14, 15	18, 19 & 21
Rhomberg	3	2, 17	18, 19 & 21
Smith	10, 11	8, 16	18, 19 & 21
Travis	17	10, 20	18, 19 & 21
Viluksela	16	4, 5, 7	18, 19 & 21