

RISK ASSESSMENT

THE UNITED STATES EPA SCIENCE ADVISORY BOARD REPORT (2001) ON THE EPA DIOXIN REASSESSMENT

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Introduction

In April 1991, the United States Environmental Protection Agency (EPA) announced it would conduct a scientific reassessment of the potential health risks posed by exposure to dioxin and related compounds. This report was to be a follow-up of the 1987 assessment of dioxin by EPA. The so-called "reassessment" was issued in draft form in 1994. It was reviewed by the EPA Science Advisory Board (SAB) in 1995.¹ The EPA SAB is comprised primarily of professors and other scientists who are considered expert at various aspects of the environmental sciences.

In 1995, the SAB reviewed the 1994 draft and issued a report (EPA-SAB-EC-95-021) with the following four key findings:

- a) substantive changes were needed to the chapter on dose-response modeling and the risk characterization
- b) EPA should develop a new chapter on toxicity equivalence factors (TEFs)
- c) the health and exposure sections did not require significant changes
- d) the revised chapters on dose response modeling and risk characterization should undergo external peer review prior to the SAB re-review of these issues

The EPA completed its revision of the 1995 document and submitted the revision to a new SAB panel for review in late September, 2000. The SAB met on Nov 1 and 2, 2000 to review the sections noted above. The SAB panel also had conference calls on January 23rd and April 23rd to discuss many issues which they considered relevant. This paper presents a summary of the final report of the SAB which was submitted to the EPA Administrator on June 1st, 2001.² Due to lack of space, the information in this abstract is primarily that which was presented in the Executive Summary of the SAB report. A discussion of the foundation for these conclusions will be presented at the conference.

Conclusions of the SAB

The following are the comments that the SAB asked EPA staff to consider when they revise and finalize their risk assessment of dioxin:

- a) HUMAN CARCINOGEN DESIGNATION: EPA has designated criteria for labeling a substance as a human cancer hazard in its draft revised carcinogen risk assessment guidelines.^{3,4,5} Criteria for designating human carcinogens differ between these two sets of guidelines and the previous 1986 EPA guidelines.

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(i.e. whether statistically significant associations between exposure and cancer could be concluded to be causal), as well as the scientific data demonstrating similar modes of action in humans and laboratory animals.

Almost half of the Panel's Members did not support the classification of TCDD as a human carcinogen, citing what they perceived as: (1) the lack of a consistent carcinogenic response (in terms of dose-response) across the various epidemiological studies; (2) the small relative risks observed in each study over a wide range of exposures; (3) the possible impact of confounders; (4) the lack of understanding of the mechanism of action (as is true for most carcinogens); and (5) the fact that the primary increase demonstrated by EPA is in total number of tumors (a response not heretofore attributed to any chemical carcinogen).

Other Panel Members did, however, support the classification of TCDD as a human carcinogen. They believed that the results from studies of TCDD-exposed workers were persuasive, and that the variety of studies from researchers in different countries provided limited but convincing evidence of TCDD's carcinogenicity in humans, particularly for lung cancer and soft tissue sarcomas. Those Members supporting the classification of TCDD as a human carcinogen (just over one-third of the Subcommittee) cited the fact that an international cohort and four industrial populations with highly exposed sub-cohorts and sufficient numbers in the populations had all shown increased risks of all cancer types associated with TCDD exposure. In two heavily exposed cohorts who had measured body burdens of TCDD, there were modest but significant increases in risk of all cancers with increases in TCDD levels. These Members believe that a single factor other than dioxin exposure can not be identified which could explain the epidemiological findings from multiple countries in multiple industrial settings. It is their position that these data (coupled with the animal data) suggest that, at least in highly exposed groups, TCDD acts as a human carcinogen.

b) **CALCULATION OF CANCER POTENCY FACTOR:** The panel acknowledged that for dioxin, the extrapolation from high experimental exposure doses to low environmental exposures was not as large a challenge as the one EPA generally faces with other chemicals; e.g., the exposure gap is much narrower than usual. However, in light of the considerable uncertainties in the cancer potency factor and of the accuracy of individual TEFs for many of the dioxin-like chemicals (e.g., the PCBs), the majority of Panel Members had concerns about the EPA cancer risk estimates associated with current population exposures (background dose in the diet) and felt that it was not appropriate for the Agency to characterize the risks in such a quantitative manner without providing a similar quantitative estimate of uncertainty.

c) **ESTIMATED NON-CANCER RISKS:** EPA was congratulated for assembling a sprawling and diversified literature on the topic of non-cancer effects into a coherent document. EPA's conclusions were that adverse non-cancer effects were likely to be within or close to the range of current human body burdens. The panel noted that EPA used human data as qualitative support for the concern about non-cancer effects. They acknowledged that laboratory animal data had not been used to calculate MOEs or any other quantitative measure of toxicity for dioxin. Given the uneven quality of the available human data and some seemingly conflicting findings, most Members of the Panel believe that this level of integration was appropriate. Most Panel participants were concerned that the Reassessment

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Document provided insufficient emphasis on the potential non-cancer risks posed by these chemicals.

d) **NON-CANCER RISK ASSESSMENT METHODOLOGY:** In the present draft report, the Panel felt that fundamentally different approaches were used for cancer and non-cancer endpoints.

The Panel was concerned that presentation of quantitative estimates of risk only for cancer might focus disproportionate attention upon cancer at the expense of non-cancer risks. Consequently, the Panel recommends that in future re-evaluations the Agency develop a similar approach for all adverse effects of dioxin, to the extent that such methods become feasible.

The Panel discussed what this common risk assessment approach should be and believed it would ideally be most useful for risk managers to have quantitative estimates of the cancer and non-cancer risk from low exposures, provided such estimates could be made in a reliable manner. However, the Panel believed the information base for dioxin does not allow such estimates to be reliably developed at present.

The Panel therefore recommended that, in addition to the point of departure, an RfD also be calculated. Such a calculation could provide a useful societal exposure goal, could provide a useful perspective on potential dioxin risks, could facilitate comparisons with other substances for which a RfD has been calculated, while not precluding use of the MOE approach.

e) **TEFs:** Most Members of the Panel believe that the TEF methodology, given the inherent uncertainties stemming from the lack of data, is a reasonable and widely accepted way of dealing with the joint effects of dioxin-like compounds on human health. The majority of the Panel noted that the TEF approach is well accepted internationally. Moreover, because only about five chemicals of the 30 account for 70% of the TEQ in the diet, the data available for this small group tend to limit the uncertainties to a more manageable level. Some Panel Members remain concerned about various aspects of the TEF methodology and are much less convinced that it adequately portrays the toxicity of joint exposures where the TEQ dose is not dominated by 2,3,7,8-TCDD.

f) **DOSE METRICS:** The Panel agreed that dose metrics, such as body burden, steady-state blood level, or areas under the curve (AUC) were superior to using the traditional mg/kg-day metric. However, the majority of this Panel recommended that a better justification for using a specific dose metric was needed. The Panel urged EPA to provide more explicit examples of how different dose metrics might apply to specific toxic endpoints. For example, whereas lifetime average body burden (LADD) or AUC may be more appropriate than peak exposure for predicting cancer risks, some measure of peak exposure during pregnancy would be more appropriate for predicting the likelihood of an adverse effect upon the developing fetus. The panel suggested that this concept deserved a much more complete discussion than was presented in the draft reassessment.

g) **MARGIN OF EXPOSURE APPROACH:** In setting its range of 10 -50 ng/kg body burden as a "point of departure" for calculating MOE for non-cancer effects, the Agency

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appropriately evaluated data on a variety of responses, including both biochemical and whole-organ endpoints. However, in their numerical treatment of these data the Agency relied solely upon a definition of the ED₀₁, which could be subject to large variation in the estimated value depending on the input data and/or specific model assumptions. Since the effect of this approach upon the point of departure is not clear, the Panel recommended that other EDs be calculated using other definitions that are consistent with Agency guidance. Also, since the ED₁₀ has been applied to other chemicals by the Agency, for comparison purposes these values should also be presented. Regardless of the outcome of this re-analysis, the Panel also recommends that the Agency give additional thought to the justification regarding its selection of a method for condensing these ED into a recommended range.

Finally, the SAB concluded that the Agency's description of its calculation of ED₀₁ was not sufficiently detailed to permit the calculations to be repeated. They recommended that a clear and complete description of this calculation would significantly improve the transparency and accessibility of the Reassessment.

h) EXPOSURE: Overall, the panel concluded that the estimates of background exposures were clearly and reasonably characterized. Moreover, they believed that the Reassessment document was thorough and provided an important international resource for assessing exposure to dioxin-like compounds. The data on concentrations in food had been expanded significantly since the 1995 draft. However, the Panel recommended that additional work on the exposure assessment section was needed.

i) BODY BURDEN. EPA provided information on body burdens of dioxin. However, it would be beneficial to also provide additional information on how body burdens vary with age, on how body burden varies in females depending on the number of offspring, etc. The panel suggested that EPA should identify important data gaps in this area and highlight research opportunities.

j) SPECIAL POPULATIONS/AGE-SPECIFIC EXPOSURES. Populations at increased risk from exposure to dioxin and dioxin like compounds include those subgroups that may be at the high end of the exposure distributions as well as the biologically more susceptible. The Panel agreed that EPA has appropriately identified several populations as having the potential to be highly exposed. These populations include nursing infants, individuals with unique diets, occupationally exposed individuals, cigarette smokers, and individuals who may live near significant sources. The panel acknowledged that the Native American population, and other groups, may be more highly exposed than other populations because of their culture and diet. Women of childbearing age, as well as younger females, are a special population of concern because any exposure they receive may be passed to their children through breast milk. The panel concluded that the document did a credible job of identifying those at increased risk because of demographic characteristics; there was very limited information available on genetic susceptibility. EPA should include, if possible, a description of all "special populations" in the Summary Document.

k) RELATIVE RISKS OF BREAST FEEDING. EPA summarized relevant data from studies of infants who had been breast fed and calculated dioxin intakes for nursing infants. It also calculated changes in body burdens over a one year nursing scenario. The Panel found the

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characterization of cancer risks to nursing infants was adequate (with a few caveats delineated in the text). However, the Panel felt the non-cancer health risks for infants and children were insufficiently characterized, particularly concerning the data available on the developmental and reproductive effects of dioxin. It was recommended that EPA extend the breastfeeding exposure scenarios beyond one year to include the subgroup of committed breast-feeders and other women that extend breastfeeding beyond one year. Furthermore, the SAB suggested that EPA evaluate non-health cancer risks for nursing infants to the extent practicable.

l) **RISKS DUE TO NATURALLY OCCURRING CHEMICALS THAT BIND TO AH RECEPTORS:** Some Members believed that, because some naturally occurring chemicals that bind to the Ah receptor can be found in the diet, and possibly in blood and tissue, EPA should consider the magnitude of their biological activity when appropriate data become available in the published literature. In particular, the panel also suggested that EPA study the transplacental transport of these chemicals and their ability, *in utero*, to interfere with reproductive development, as has been documented for TCDD itself.

m) **NON-MONOTONIC DOSE RESPONSE FUNCTIONS:** The panel concluded that there was some evidence that very low doses of dioxin may result in decreases in some adverse responses, including cancer, but can produce other adverse effects at the same or similar doses. The Panel recommended that the totality of evidence concerning this phenomenon continue to be evaluated by the Agency as studies become available. The panel suggested that EPA should carefully examine the evidence for any "U-shaped" dose response curves.

n) **NEED FOR FURTHER INVESTIGATION AND PERIODIC REASSESSMENT:**

In undertaking production of this document, the EPA was faced with a difficult task, but carried it out with considerable care. Its primary problem, despite the amount of research already devoted to dioxins, remains continued information gaps relevant to risk assessment despite extensive study.

Discussion

Over the course of the six months from the time our panel met until the issuance of the final report, we wrestled with many difficult issues associated with dioxin. During this period, there were at least five different drafts of our report that were circulated, critiqued and edited by various panel members. As is evidenced by the language in the report, the panel failed to reach a consensus view on many of the points that are considered important in regulatory decision-making. Nonetheless, the panel believes that we assembled important suggestions that, if incorporated into the final document, will enhance its completeness and stature.

The paper which will be presented at the conference will provide additional rationale for some of the decisions reached by our panel for some of the more difficult topics addressed here.

References

1. SAB (Science Advisory Board) U.S. Environmental Protection Agency. (1995). EPA-SAB-EC-95-021. Washington, D.C.

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2. SAB (Science Advisory Board) U.S. Environmental Protection Agency. (2001). EPA-SAB-EC-01-006. Washington, D.C.
3. EPA (Environmental Protection Agency). (1996). *Federal Register*, 61,79:17960
4. SAB (Science Advisory Board) U.S. Environmental Protection Agency. (1999). EPA-SAB-EC-99-0014. Washington, D.C.
5. SAB (Science Advisory Board) U.S. Environmental Protection Agency. 1999. Review of the EPA's Draft Revised Cancer Risk Assessment Guidelines (EPA-SAB-EC-99-0014).

Note: The author, although a member of the EPA SAB panel which evaluated the dioxins, has based this abstract on the views expressed in the final report but does not claim that it represents all of the views expressed in the report or the multitude of views held by various panel members. Every attempt has been made to capture the conclusions of the report. The views expressed at the meeting will be those of the author rather than an attempt to speak on behalf panel