



**Comments from Lorenz R. Rhomberg, Ph.D. F.A.T.S. on the Draft SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments**

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Thank you for the opportunity to provide these written comments on the occasion of the Chartered SAB's crucial review of the draft SAB report, "SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments," as provided for in 76FR26290 (May 6, 2100). I am Lorenz Rhomberg, a Principal at the consulting firm Gradient, based in Cambridge, MA. The following comments are my own, but I received support to develop them from the American Chemistry Council.

My comments focus on five areas of concern and are as follows:

1. Concerns About the Adequacy of Methodology for Weight of Evidence and Transparency

**The review expresses important methodological concerns about adequacy of methodology for weight of evidence and transparency of the basis for conclusions. The SAB should emphasize that these are reiterated from earlier reviews and apply to other chemicals' assessments.**

In its review of the EPA dioxin draft reassessment, the dioxin SAB committee makes some clear findings that the basis for weight of evidence judgments in the EPA analyses needs to be better explained, with more concrete and specified methods, including the critically important basis for including and excluding studies and for choosing the particular studies that become the focus of quantitative analysis. The SAB review also calls for development of nonlinear as well as linear dose-response approaches and an evaluation of the relative merits of these by considering the broader understanding of mode of action for dioxin carcinogenicity. The review also strongly calls for the EPA to conduct meaningful quantitative uncertainty analysis of its dose-response modeling.

It is noteworthy that the review makes these points unequivocally and firmly, in the face of arguments presented in the current EPA draft assessment that it is impossible or inappropriate to do these things. Clearly, these are more than just recommendations to the agency about things that could be considered, they are the SAB committee's judgments about what is required for a satisfactory and supportable analysis. These are affirmations of the similar calls that came from the NAS review of the previous version of the EPA document in 2006; yet, the EPA continues to fail to address these critical elements of the dioxin assessment.

These findings by the SAB review committee are important and needed. I urge the Chartered SAB to provide a clear endorsement of their inclusion in the final SAB review document. Indeed, the findings could be made more pointedly in view of the recent chapter entitled 'Roadmap for Revision' in the NAS Review of EPA's formaldehyde assessment..

SAB reviews of other agency assessments in recent years have made the same set of points, as have reviews by NAS panels. Most notably, the recent NAS panel review of EPA's formaldehyde assessment called for a better, more systematic, and more transparent process for explaining how the agency has come to weight-of-evidence judgments in the face of incompletely dispositive and even contradictory data. That panel made clear that it was addressing these comments not only to the agency's analysis of formaldehyde, but to the broader risk assessment process as conducted by the agency. The NAS review set out a "roadmap" – a broad set of recommendations and illustrations of possible approaches that would help to address the questions that have been the subject of recurrent criticism by NAS and SAB panels. The illustrative approaches were set out explicitly to refute the claims in the EPA formaldehyde assessment that no appropriate methodology for uncertainty analysis exists.

In short, returning to the present question of the SAB committee's review of the revised dioxin document, the committee's findings apply not only to this document, but more broadly to the assessment process as currently being carried out at the EPA. The questions are less dioxin-specific (although they are motivated by extensive data on dioxin mode-of-action and pharmacokinetics) than they are methodological. They are less about the soundness of individual inferences than about the soundness and transparency of the inferential process itself. They are about adherence to the letter and spirit of principles of defensible risk assessment that are set out in existing guidance and risk science policy.

What the Chartered SAB decides on this particular case has implications beyond the immediate dioxin assessment. Whether or not the SAB has sought it, because of the confluence of similar methodological questions raised in reviews of several important chemicals, we now have on the table several important larger questions: the characterization of uncertainty, the transparency of evaluation of strengths and weaknesses of scientific judgments, and the serious entertainment of candidate alternative analyses. I respectfully submit that the Chartered SAB's role is not simply to review the products of individual committees, it is to ensure consistency among reviews and to foster, with prodding as appropriate, the application of sound risk assessment practices and policies in all the EPA actions it reviews. Whether the questions as they apply to dioxin are construed narrowly to this case or more broadly, and whether findings are suggested tentatively or asserted firmly, will be consequential for all of the SAB's business, and for the EPA's.

## 2. EPA Has Not Conformed To Its Own Guidance and Policies for Uncertainty Analysis and Weight of Evidence

**EPA has not held to its own extensive guidance and stated science policies regarding the characterization of uncertainty and weight of evidence. The SAB should refer the agency to this guidance and urge that it be followed.**

In previously submitted written comments<sup>1</sup> provided jointly with Gail Charnley of HealthRisk Strategies, I quoted extensively from existing EPA guidance documents to demonstrate that the agency has in place as its stated policy to forthrightly characterize uncertainty, to evaluate plausible alternative analyses of the data and feature their implications for characterization of potential risks, and to be transparent in the arguments used to justify science policy choices. I shall not repeat them here but only note that the previous comments quoted from the 2000 Risk Characterization

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<sup>1</sup> Comments to the EPA Science Advisory Board on the 2010 Dioxin Risk Reassessment. September 15, 2010. HealthRisk Strategies and Gradient.

Handbook,<sup>2</sup> 2002 Information Quality Guidelines,<sup>3</sup> 2003 Assessment Factors Handbook,<sup>4</sup> 2004 Risk Assessment Principles and Practices documentation,<sup>5</sup> and 2005 Guidelines for Carcinogen Risk Assessment.<sup>6</sup> One could also cite the recommendations of the National Academy of Sciences committee that reviewed EPA's 2003 dioxin reassessment.

A true weight-of-evidence analysis should explicitly present the criteria for inclusion and exclusion of studies so that *all* relevant information is included and so that biases toward inclusion of certain outcomes (e.g., only positive outcomes) are avoided. That is, negative or inconsistent results are important to address because their existence will have to be part of the overarching explanation of the array of results on hand. It is important to be explicit about what results are being drawn from each study and not focus just on positive outcomes. Methodologic strengths and weaknesses of each study should be noted without respect to study outcome in order to better assess similarities and differences in study outcomes. The goal is to be able to interpret possible reasons for disagreement, not to select the "best" study and rely on it even if it is contradicted by other study results.

If agency assessments had only made a greater effort to adhere to this existing and established policy, much of the criticism that the current dioxin draft has received could have been obviated. I urge the chartered SAB to call EPA's attention to this existing guidance and to judge agency assessments, including the dioxin assessment, according to whether that guidance is forthrightly followed.

### 3. Choice of Dataset for Basis of Quantitative Characterization Is a Weight-of-Evidence Problem

**The choice of a dataset on which to base quantitative characterization of risks is itself a weight-of-evidence problem and should be treated as such. Chosen datasets should be evaluated for how well they represent and embody understanding of the toxicity endpoints they measure, not just on quality-rating or amenability to modeling.**

I am gratified that the SAB review document has favorably cited a review paper on human studies of dioxins' effects on thyroid hormones in early development (Goodman *et al.* 2010)<sup>7</sup> that I wrote with colleagues at Gradient. I wonder, however, if a larger lesson of this review has been fully grasped; namely the critical role of an endpoint-specific weight-of-evidence evaluation for a particular noncancer toxicity when choosing studies on which to base an RfD calculation.

Clearly, it is important that a study chosen as a basis for an RfD be of sufficient quality and that its data can be reliably modeled to provide the quantitative insights needed. Although these are the primary considerations in much current practice, they are not *sufficient* criteria to confidently

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<sup>2</sup> EPA (2000) Risk Characterization Handbook. EPA 100-B-00-002. Science Policy Council, Washington, DC

<sup>3</sup> EPA (2002) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008. Office of Environmental Information, Washington, DC

<sup>4</sup> EPA (2003) A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information. EPA 100/B-03/001. Science Policy Council, Washington, DC

<sup>5</sup> EPA (2004) Risk Assessment Principles and Practices. EPA/100/B-04/001. Office of the Science Advisor, Washington, DC

<sup>6</sup> EPA (2005) Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Risk Assessment Forum, Washington, DC

<sup>7</sup> Goodman JE, Kerper LE, Petito Boyce C, Prueitt RL, Rhomberg LR. 2010. Weight-of-evidence analysis of human exposures to dioxins and dioxin-like compounds and associations with thyroid hormone levels during early development. *Regulatory Toxicology and Pharmacology* 58(1):79-99.

establish an RfD. When a study is chosen, its results are taken to represent a valid and reliable endpoint, and the study's results are taken as the best representation of the dose-response for that endpoint. That is, even if the study is one of many on an endpoint, its selection as the RfD basis puts it in the place of embodying the general understanding of the endpoint as a whole, in that study and in others, especially with regard to dose-response patterns. It is therefore critical to provide transparent evaluation of (1) whether the endpoint in question is to be deemed a reliable causative consequence of the exposure, in view of all of the studies that bear on this question, and (2) whether the particular observed dose-response pattern *in the selected study* serves well or poorly as the epitomization of the dose-response patterns observed *across all of the relevant studies*. Any one "high quality" and readily modeled study could fail on either of these criteria. For instance, it could represent an effect that is not generally seen in other studies or is implausible on mode-of-action grounds, or it could be a poor quantitative surrogate for the patterns of dose-response and the necessary dose levels for effect as seen in the larger body of evidence on that endpoint.

I urge the SAB to call attention to this issue, to recognize the interconnection of weight-of-evidence when applied to the existence and reliability of hazard determinations with when it is applied to the question of whether a study constitutes a good and generalizable quantitative characterization of those causal processes. This kind of weight of evidence analysis should consistently be applied in choosing studies on which to base an RfD.

#### 4. The Baccarelli Study to Characterize Thyroid Effects Should be Questioned

**In particular, in view of the above comment, the choice of the Baccarelli study to characterize thyroid effects should be questioned, since different human studies disagree among one another in how, whether, and in what direction dioxin exposure can affect the thyroid hormone system.**

As noted in the previous comment, my colleagues and I have reviewed the human studies on dioxin exposure during early development and perturbation of thyroid hormones (Goodman *et al.*, 2010). Our finding was that these studies are not consistent among one another as to whether any components of the thyroid hormone system are altered, which components (if any) are altered, or even the direction in which they are altered by early developmental exposure to dioxins. The patterns of alterations when they are seen are not consistent with any single means by which dioxins might be effecting alterations. There is the further challenge that different studies have measured different dioxin congeners, and the mix of congeners varies to some degree among studies. All of these considerations call into question whether any single study, the Baccarelli study or any other, can serve as the quantitative measure of dioxins' expected effects on the thyroid system. Since the changes, even when detected, occur in different directions from study to study and are not of clear clinical significance, the choice of the Baccarelli study imposes on the RfD determination the properties of *that* study's outcomes, in contradiction to what was seen elsewhere. In view of the much higher dioxin levels needed to reliably alter thyroid hormone patterns in rodent studies, our conclusion in the review was that human studies are not actually measuring real causal effects of dioxins, and so no study is reliable. But even if one concluded that there were some effect, which among the contradictory findings is to be chosen to serve as the sole quantitative representation of that effect?

#### 5. The Use of the Cheng Study On All-Cancer Mortality Is Questionable

**Similarly, the use of the Cheng study results on all-cancer mortality is questionable on mode-of-action grounds, and use of such data imply a much more general causation pattern than is warranted.**

A similar consideration to the above applies to the assessment of carcinogenicity. The SAB looked favorably on the EPA's decision to use all-cancer mortality in the Cheng study as a basis for quantitative analysis. This may have good dose-response properties, and alternatives based on particular cancers may be problematic, but to accept an all-cancers dataset as a basis for quantification of risk logically necessitates that the mode-of-action proposition of such broad activity is reliably established. It is usual for chemical carcinogens to be much more specific in their effects, a fact on which most quantitative risk assessment for carcinogenicity is predicated. To deviate from this requires a strong mode-of-action justification, and the implications for causal processes raised by using an all-cancers dataset need to be examined for plausibility and consistency with mode-of-action understanding. Again, the main point is that simple amenability to quantitative analysis does not justify ignoring the link between quantitative manifestations of causation and the biological understanding and consistency of observation of those causal processes at the qualitative, hazard identification level.

## Conclusion

The dioxin SAB has identified deficiencies in EPA's report with respect to the completeness of its consideration of two critical elements of the assessment: (1) nonlinear dose-response for TCDD carcinogenicity, and (2) uncertainty analysis of TCDD toxicity. It is critically important that the EPA undertake the necessary actions to remedy an incomplete and inadequate response to the NAS recommendations and to revise the assessment by using appropriate weight of evidence methodology to do so.

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