



October 20, 2010

VIA E-mail

Dr. Thomas Armitage

Designated Federal Officer, EPA Science Advisory Board Staff Office

armitage.thomas@epa.gov

Re: October 27-29, 2010 SAB Dioxin Review Panel

Dear Dr. Armitage:

The Chlorine Chemistry Division of the American Chemistry Council (ACC) appreciates this opportunity to provide comments to the SAB Dioxin Review Panel on the U.S. Environmental Protection Agency's (EPA's) draft *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Draft Reanalysis). These comments supplement ACC's July 9, 2010, Comments to the SAB Dioxin Review Panel and ACC's September 20, 2010, Comments to EPA.

The appended comments highlight a request for clarification from the SAB and EPA and the six most significant deficiencies in the Draft Reanalysis. These concerns parallel many of the comments raised by SAB members in both the October 1, 2010, Compilation of Individual Comments from Panel Members and the Summary of Discussion in Response to Charge Questions.

Clarification Requested:

1. What is the process being employed to account for and reconcile the tremendous amount of conflicting technical information developed by EPA, submitted by the NAS, other government agencies, and stakeholders throughout the entire IRIS assessment process for dioxin.

Draft Reanalysis Deficiencies:

2. EPA is non-responsive to four of the seven NAS findings.
3. In deriving the reference doses (RfDs) for cancer, EPA exaggerates dioxin potency and fails to employ a weight-of-evidence approach;
4. EPA presents results that are not reproducible;
5. EPA's epidemiology assessment and conclusions on TCDD carcinogenicity are not based on a "weight-of-evidence" approach;



6. EPA's evaluation of non-cancer risk ignores NAS recommendations and relies on observed effects with questionable relevance to human health; and
7. EPA's Draft Reanalysis does not represent "the best available science."

ACC urges the SAB to request EPA define the process for the development of the next iteration of the revised assessment, which fully responds to the NAS review (only a portion of which is addressed in the Draft Reanalysis) and employs the best science available in compliance with EPA's own risk assessment guidelines.

Please do not hesitate to contact me if we can provide additional information or technical support on these topics.

Best regards,

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Judith D. Nordgren
Managing Director, Chlorine Chemistry Division



COMMENTS FROM THE CHLORINE CHEMISTRY DIVISION OF THE AMERICAN CHEMISTRY COUNCIL TO THE US EPA SAB DIOXIN REVIEW PANEL ON EPA'S DRAFT REANALYSIS

The U.S. Environmental Protection Agency's (EPA's) draft *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Draft Reanalysis) is an important element of EPA's comprehensive reassessment of dioxin exposure and human health effects entitled, *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (Dioxin Reassessment). The Draft Reanalysis details EPA's technical response to some of the key comments and recommendations included in the 2006 National Academies of Science (NAS) review of EPA's reassessment, focusing on the NAS comments regarding TCDD dose-response assessment.

Enumerated below is a request for clarification and six significant deficiencies identified in the Draft Reanalysis. These concerns parallel many of the comments raised by SAB members in both the October 1, 2010, Compilation of Individual Comments from Panel Members and the Summary of Discussion in Response to Charge Questions.

- 1. What is the process being employed to account for and reconcile the tremendous amount of conflicting technical information developed by EPA, submitted by the NAS, other government agencies, and stakeholders throughout the entire IRIS assessment process for dioxin.**

EPA must define the next steps in the dioxin reassessment development process. The substantial and technically conflicting components contributing to what will become the final Dioxin IRIS Assessment are - the 2006 National Academies of Science (NAS) review of the Dioxin Reassessment, the more recent Draft Reanalysis, the ongoing SAB review of the Draft Reanalysis, and associated public comments. A defined process with appropriate peer review and quality controls for the preparation of the next iteration of the dioxin reassessment is paramount. With regard to public comments submitted to the SAB Dioxin Review Panel, it is unclear how the Panel plans to fully consider those comments in its deliberations. For example, was each SAB member asked to review the public comments on the Draft Reanalysis and to report to the Chairman the comments that merit discussion by the SAB?

- 2. EPA is non-responsive to four of the seven key NAS findings.**

The Draft Reanalysis fails to adequately address four key NAS comments intended to help EPA improve the scientific basis of its information on dioxin. The primary shortcoming is EPA's failure to evaluate the potential human cancer and non-cancer effects of dioxin using a weight-of-evidence analysis.

ACC urges EPA to revise the Draft Reanalysis to fully address the remaining NAS comments and accurately convey the best available science and weight-of-evidence in compliance with and all relevant EPA risk assessment guidelines.

3. In deriving the reference doses (RfDs) for cancer, EPA exaggerates dioxin potency and fails to employ a weight-of-evidence approach.

EPA's Draft Reanalysis states that there is "insufficient evidence" to support the use of a nonlinear cancer dose-response model, defaulting to a low-dose linear model instead. EPA does not provide a balanced weight-of-evidence analysis of the science supporting linearity versus nonlinearity. Its conclusion is in conflict with the unanimous conclusions of the NAS review panel, with EPA's own guidance and procedures, and with virtually every other scientific and regulatory government organization that has reviewed dioxin.

EPA relies on a linear model for TCDD, adding some nonlinear calculations only as "illustrative examples." There is no balanced weight-of-evidence analysis of the science supporting linearity versus nonlinearity. The omission of a nonlinear approach is contrary to the requirement that EPA present "potential error sources" in the information disseminated and "complete, accurate, and unbiased" information (as a matter of presentation) and "accurate, reliable, and unbiased" information (as a matter of substance). In particular:

- EPA failed to conduct a meaningful mode-of-action (MOA) examination on how sustained AhR activation leads to a tumor promotion outcome. EPA presented a limited effort to identify "key events" related to the tumor promotion of sustained AhR activation; however, the information in Chapter 5 falls far short of a Human Relevance Framework basis for concluding that there is no known MOA and that linearity is the preferred dose-response model. EPA should have conducted a more complete key event review in accordance with the 2005 Guidelines for Carcinogen Risk Assessment Guidelines
- EPA's use of the Emond toxicokinetic model exaggerates dioxin potency estimates. EPA chose to ignore reported TCDD concentrations in adipose and liver tissue which should have been used as the dosimetry endpoints for extrapolation to human equivalent dosages. Instead, EPA applied the Emond model in deriving estimates of whole-weight rat blood TCDD concentrations. The model significantly underestimates liver and adipose tissue concentrations in the NTP (2006) bioassays. Using modeled concentrations while reporting measured concentrations introduces unnecessary inaccuracies in the derivation of the illustrative RfDs.

- EPA assumed, without data justification, a partition factor of 100 for TCDD in human fat compared to blood. Available human data demonstrate that the actual partition factor, however, is between 150 and 200. The failure to incorporate the available human data results in underestimation of the human-equivalent doses at the BMDLs and the resulting calculated RfD values in Table 5-21.
- EPA applied an unsupported 3x uncertainty factor to account for animal to human extrapolation in deriving the candidate human RfD values for the MOA analyses. Because it has been demonstrated that humans are less sensitive by 3-fold or more to TCDD than rats for the specific early biological responses that are modeled by EPA, application of a much lower uncertainty factor (i.e., 1.0 or 0.1) is warranted.

As a result of the failures identified above, the Draft Reanalysis is not transparent. Risk managers and the public, therefore, are unable to fully assess its utility.

4. EPA presents results that are not reproducible

EPA's presentation of RfD calculations (Table 5-21) contains numerous errors, raising troubling questions regarding the reliability of the reported results throughout the entire Draft Reanalysis. These errors include transcription errors in data and annotations of statistical significance or identification of LOAEL and NOAEL values from the original studies. In addition, EPA failed to update the PBPK model results that had been revised or discarded in other sections of the document. As a result, a significant number of values used to derive RfDs cannot be reproduced.

The lack of reproducibility of the values in Table 5-21 has been confirmed by EPA staff. ACC has not evaluated other quantitative results presented in the Draft Reanalysis. Moreover, ACC is not aware that SAB has attempted to reproduce the many quantitative data presented in the Draft Reanalysis. Many would require replicating runs of the PBPK model and BMD software. In addition, some of the analyses presented in the document are not described in sufficient detail to allow them to be reproduced, even by a qualified expert. Such information must be corrected.

5. EPA's epidemiology assessment and conclusions on TCDD carcinogenicity are not based on a "weight-of-evidence" approach

- EPA concludes that there are "consistent" elevations in all cancers combined across studies; however, the Agency did not conduct a meta-analysis that is needed to objectively evaluate consistency across study results. EPA's bias in this conclusion is evident in its exclusion of studies that do not demonstrate

excess cancers from its selection of studies for dose response analysis. Lacking the support of any formal analysis, EPA's conclusion fails to employ and present "the best available science and supporting studies conducted in accordance with sound and objective practices."

- A "weight-of-evidence approach" is also lacking in EPA's conclusion that its epidemiology review provides "strong evidence of an association between TCDD exposure and human cancer...." The lack of a specific cancer site or sites consistently related to dioxin exposure across epidemiology studies argues against such an association. In fact, a causal relationship for all cancers combined without a consistent elevation of a specific cancer site would be unique in occupational epidemiology. EPA must conduct a weight-of-evidence approach entailing a more formal examination of these issues, possibly by the pooling of data.

6. EPA's evaluation of non-cancer risk ignores NAS recommendations and relies on observed effects with questionable relevance to human health

The Draft Reanalysis ignores recommendations of the NAS review panel and EPA's own guidance by failing to evaluate the clinical relevance of the effects considered for RfD derivation. Furthermore, since the NAS concluded that there is no convincing evidence of adverse non-cancer effects, EPA's RfDs for these effects cannot be considered to be based on the best available science.

- The NAS committee that reviewed EPA's 2003 dioxin risk assessment recommended that EPA evaluate the biological relevance of reported effects.

Attention should also be directed to addressing the potential biological significance of very small statistically significant physiological or biochemical changes that remain well within the normal range of variation and adaptation. [p. 163]

- In addition, EPA's 2004 Risk Assessment Principles and Practices document indicates the need to determine the biological relevance of an effect.

As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events. [p. 53]

- Overall, the NAS committee concluded that the evidence for dioxin exposure as a cause of reproductive and hormonal abnormalities is not strong.

Although the spectrum of reported human reproductive and hormonal abnormalities following dioxin exposure is generally similar to that found in animals, the strengths of the individual associations in studies thus far, are

weak, and confidence in the causal nature of these associations while suggestive is not compelling. [p. 162]

- In fact, the NAS committee stated that there is no convincing evidence of adverse, non-cancer effects as a result of dioxin exposure.

In humans, the association of TCDD exposure with other reported, detrimental non-cancer effects has not been convincingly demonstrated. The available studies have not yet shown clear associations among TCDD exposures and the risks of individual, clinically significant, non-cancer end points. [p. 173].

7. EPA’s Draft Reanalysis does not represent “the best available science”

- The Draft Reanalysis inappropriately invokes the principles of “additivity-to-background” and population heterogeneity to support low-dose linearity. As discussed in comments prepared by Dr. Gail Charnley of Health Risk Strategies and Lorenz Rhomberg and Robyn Prueitt of Gradient (Appendix A), EPA’s decision to apply these new science policy principles runs counter to a weight-of-evidence perspective, as well as the spirit and intent of EPA’s Risk Characterization Handbook. Furthermore, using such methods will produce misleading and unreliable estimates – most likely radical overestimates – of the actual effect, even if the presumptions of the additivity- to- background effect are true.

The additivity-to-background argument presumes *without evidence* that any amount of change in the degree of AhR occupancy increases the magnitude of the downstream subsequent processes involved in tumorigenesis without a threshold. However, the linearity of one component early in a complex receptor-mediated process gives little information about the larger behavior of the system. The argument does not itself provide any basis for estimating the size of any low-dose linear component, for determining the range of doses over which additivity produces linearity, or whether the effect (even if it exists) substantially alters the dose-response relationship.

Use of those arguments as the basis for determining appropriate dose-response analyses has not been widely accepted nor even widely discussed in the scientific community,¹ and therefore does not reflect “the best available science.” The Dioxin Reanalysis fails to present the significant uncertainties associated with those concepts. This should not be done without thorough discussion and peer review.

¹ Rhomberg, L.R. (2009). Linear low-dose extrapolation for noncancer responses is not generally appropriate. *Environmental Health Perspectives*, 117:141A.

- EPA fails to address the significant uncertainties associated with key studies used to develop non-cancer RfDs. Both the Baccarelli et al. (2008) and Moccarelli et al. (2008) studies describe outcome measures that are useful clinical markers to guide further investigation but are not indicative of adverse effects in and of themselves. EPA does not accompany the use of the data from these studies for dose-response modeling and RfD derivation with a discussion of the clinical significance of the effects or the levels of change that represent an adverse effect for each of the endpoints.
- EPA's study inclusion criteria for both cancer and non-cancer data specifically preclude a weight-of-evidence analysis. The criteria select solely epidemiologic studies that demonstrate "an association between TCDD and an adverse health effect" [p. 2-7] or for which the "magnitude of animal responses is outside the range of normal variability exhibited by control animals" [p. 2-8]. The criteria specifically exclude studies that demonstrate no effect, effectively preventing a balanced consideration of available evidence supporting or refuting the biological plausibility and likelihood of effects. The analysis cannot be considered comprehensive.
- EPA's justification for choosing linearity is that TCDD's carcinogenic mode of action is unknown. However, while TCDD's exact *mechanism* of action may not be entirely clear, its *mode* of action is known.

In sum, ACC urges the SAB to request EPA define the process for the development of the next iteration of the revised assessment, which fully responds to the NAS review and employs the best science available in compliance with EPA's own risk assessment guidelines.