

Comments of the American Chemistry Council, Chlorine Chemistry Division to the US EPA Chartered SAB on the *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* by the SAB Dioxin Review Panel

The American Chemistry Council appreciates the opportunity to provide comments to the Environmental Protection Agency's (EPA's) Chartered Scientific Advisory Board (CSAB) on the SAB Dioxin Review Panel (Panel) report entitled: *Science Advisory Board Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Dioxin Report)*.

ACC commends the work of the Panel, but urges the CSAB to ensure that the Panel's report is augmented so that it represents the highest quality peer review to EPA. In particular, and as discussed in more detail below, ACC believes it critical that the Dioxin Report be amended to recommend to EPA that it revise aspects of its draft *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Draft Reanalysis) so that the Draft Reanalysis (i) responds in a scientifically robust and defensible way to certain recommendations of the National Research Council (NRC) National Academy of Sciences review which EPA has not yet adequately addressed, and (ii) otherwise reflects a technically sound weight-of-evidence analysis applying all best available science.

The Dioxin Report provides a critically important peer review of EPA's Draft Reanalysis, which is a key element of EPA's comprehensive reassessment of dioxin exposure and human health effects. This EPA review of dioxin has been underway for 20 years and subject to an exceptional level of scrutiny and interest from the scientific community and other stakeholders. Given the investment to date by EPA and numerous peer review committees, the dioxin reassessment should be a model of how to correctly conduct and draft a risk assessment. Instead, the SAB Panel report before you today points to significant scientific deficiencies. In particular, the Dioxin Report highlights EPA's failure to adequately address a non-linear cancer risk model for dioxin and to conduct a quantitative uncertainty analysis.

Unfortunately, these and other deficiencies are symptomatic of what the NRC recently described as "the persistence of problems encountered with IRIS assessments over the years." As discussed further below, the longstanding and systemic methodological flaws in the IRIS process identified by NRC, and the specific recommendations NRC made last month for improving that process to ensure the scientific integrity of IRIS assessments, warrant that the CSAB evaluate both the Draft Reanalysis and the Dioxin Report with a particularly careful and critical eye.

The Dioxin Report provides important guidance to EPA to address key deficiencies in the Draft Reanalysis. However, as you will hear in detail from speakers on June 6, 2011, there are additional serious scientific shortcomings related to epidemiology, RfD derivation, Mode of Action and the preparation of an uncertainty analysis that necessitate active engagement by the full CSAB and revisions to both the Dioxin Report and the Draft Reanalysis if the objectives of peer review and sound science are to be fulfilled.

Accordingly, ACC urges the CSAB to send the Dioxin Report back to the Panel for additional work. Specifically, the CSAB should ask the Panel to:

- Revisit EPA's analysis of epidemiology data and provide clear recommendations for EPA to conduct a full weight-of-evidence analysis of that data.

- Strengthen the Dioxin Report’s recommendations on cancer dose-response modeling to ensure nonlinear approaches are fully presented and given at least equal weight as linear models, as recommended by NRC.
 - Consistent with additional NRC recommendations, evaluate EPA’s adoption of Toxic Equivalency Factors (TEFs) for assessing and regulating dioxin-like compounds, and recommend that EPA formally address the TEFs through an uncertainty analysis rather than simply adopt the 2005 WHO TEF values.
 - Revise its recommendations regarding quantitative uncertainty analysis to specifically reference relevant EPA guidance that should be applied in conducting that analysis.
 - Review the recent NRC recommendations for improving the IRIS process, and assess where specific recommendations should be applied to improve EPA’s assessment of dioxin. The following comments are aimed at strengthening the Dioxin Report so as to (i) address current gaps in the report, and (ii) provide clearer guidance to EPA as to what EPA needs to do to ensure the scientific soundness of its dioxin reassessment.
1. The Dioxin Report does not adequately address problems with EPA’s analysis of epidemiology data and clearly recommend that EPA conduct the weight-of-evidence evaluation required by its own Cancer Assessment Guidelines for evaluating whether a substance is properly classified as a carcinogen.

a. Recommendation to CSAB

The SAB Dioxin Panel failed to describe significant deficiencies in EPA’s analysis of epidemiology data in the Draft Reanalysis. In selecting the Cheng et al study as the sole model to be employed for evaluation of all cancer mortality, EPA failed to account for and weigh other credible, recent studies of significant TCDD exposure which demonstrated no excess cancer mortality (e.g., Mundt et al. (2011), Cole et al. (2004), and Buffler et al (2011)). In doing so, EPA failed to conduct the weight-of-evidence evaluation required by its own Cancer Assessment Guidelines and Information Quality Act guidelines for evaluating whether a substance is properly classified as a carcinogen. In order to conform to scientific standards that it has set for itself, EPA must adopt a weight of evidence approach to assessing epidemiological data. The weight-of-evidence approach should include a meta-analysis to objectively assess consistency across studies, as well as EPA’s conclusion that there is strong evidence of an association between TCDD exposure and human cancer, despite the absence of any consistency in site-specific cancers, which suggests the opposite. In addition, EPA should discard its inappropriate use of the principle of “additivity to background” and population heterogeneity to support low dose linearity, and address the “best available science” by reviewing the biological relevance of reported effects in view of NRC’s observation that available studies have not yet shown clear associations among TCDD exposures and the risks of individual, clinically significant non-cancer endpoints. Moreover, EPA’s premise for modeling a linear cancer slope factor in the first place is based on a non-validated assumption that TCDD can promote any cancer type in humans, a premise that is biologically implausible. These concerns were raised by public commenters, but not addressed in the Dioxin Report. To ensure a high quality peer review and dioxin Reanalysis, the final Dioxin Report should incorporate recommendations designed to remedy these basic methodological flaws.

2. The SAB Dioxin Panel neglected to address at all Toxic Equivalency Factors, a key topic of the 2006 NRC review and recommendations, and a critical component of EPA's overall dioxin assessment

a. Recommendation to CSAB

In strictly adhering to EPA's charge questions, the SAB Dioxin Panel missed an opportunity to address TEFs, a key topic of the 2006 NRC review and a critical component of EPA's overall dioxin assessment. Moreover, since EPA has adopted the TEF approach for assessing the risks of, and regulating, dioxin and dioxin-like compounds, it is not logical for the SAB to consider only TCDD. The SAB is not, and should not have been, constrained by the scope of the charge questions and should address other important and relevant issues in its Dioxin Report, especially to the extent such issues were a focus of the NRC review and recommendations. As the SAB has noted in its draft letter to EPA Administrator Jackson summarizing the SAB peer review report, the dioxin Panel was asked to comment on the scientific soundness of EPA's responses to the NRC recommendations, and those recommendations addressed EPA's use of TEFs. In fact, the SAB Dioxin Panel's report contains many comments reflecting concern that EPA did not account for other dioxin-like compounds in derivation of the cancer and non-cancer toxicity values and in the overall weight-of-evidence assessment. If EPA had addressed the TEF issue, as requested by NRC, the Agency would presumably have included these important dioxin-like compounds in the overall risk characterization. The SAB should recommend that EPA formally address TEFs through an uncertainty analysis rather than simply adopt the 2005 WHO TEF values without further examination or explanation. In addition, the SAB should recommend that EPA establish a mechanism for ongoing evaluation of TEFs as they evolve, as well as a task force to review probability density functions EPA needs to conduct a quantitative uncertainty analysis using a balanced methodological approach.

3. The Dioxin Report does not specify that in the Reanalysis, EPA did not adhere to the NRC EPA 2003 Dioxin Review or its own comprehensive guidance documents and stated science policies regarding characterization of uncertainty and weight of evidence.

a. Recommendation to CSAB

The Dioxin Report should identify the following EPA guidance addressing these topics and request it be followed:

1. 2000 Risk Characterization Handbook
 2. 2002 Information Quality Guidelines
 3. 2003 Assessment Factors Handbook
 4. 2004 Risk Assessment Principles and Practices documentation
 5. 2005 Guidelines for Carcinogen Risk Assessment
4. The Dioxin Report includes several inappropriate comments related to EPA policy and other considerations unrelated to science. Most significantly, while strongly stating that EPA should "formalize and extend" a nonlinear risk assessment approach, the report notes that the Agency "might still conclude that, in the absence of a definitive nonlinear mode of action, policy dictates that the linear option is preferred to assure protection of public health." By speculating on a policy decision that EPA *might* make in response to its Report, the Panel undermines its own scientific findings. Similarly, the draft report muddles its strong recommendation to conduct a

quantitative uncertainty analysis by suggesting that EPA might justify not doing one based on “other grounds of practicality or timeliness.” The CSAB should not inject such non-scientific considerations into its report.

a. Recommendation to the CSAB

Inappropriate references to EPA policy and other non-scientific considerations should be deleted from the final Dioxin Report”

5. In conducting its review and preparing its report, the SAB should ensure not only that the draft Reanalysis provides a scientifically sound response to NRC’s 2006 recommendations regarding the dioxin reassessment, but that it also address the IRIS methodological flaws and recommendations identified by NRC in April 2011.

a. Recommendation to the CSAB

In conducting its review of the Dioxin Report, ACC urges the CSAB to review and be mindful of certain comments and recommendations in the report by the NRC on EPA’s draft IRIS assessment for formaldehyde. That report underscores significant methodological flaws that have repeatedly plagued EPA IRIS assessments and are evident in the Draft Reanalysis. As the NRC noted there,

“[t]he committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them, and encourages EPA to address problems with development of the draft assessments that have been identified [M]odels for conducting IRIS assessments more effectively and efficiently are available If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted here.”

Among other concerns, the NRC report cites the lack of “sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RFC and unit risk estimates.” NRC’s report notes, in particular, EPA’s failure to clearly articulate the criteria used to include and exclude studies for consideration, to describe the outcome of the application of those criteria, to weigh both negative and positive study results comprehensively, to address more thoroughly, systematically, and transparently weight of evidence approaches and determinants, and to pursue scientifically rigorous approaches to hazard identification and dose-response assessment [See “Review of the Environmental Protection Agency’s Draft IRIS Assessment of Formaldehyde,” NRC, April 2011 (pre-publication copy), Chapters 1 and 7].

NRC was sufficiently concerned with these persistent deficiencies that it provided EPA in its formaldehyde report a “roadmap” for correcting them. Notably, NAS concluded that it considered its recommendations “critical for the development of a scientifically sound IRIS assessment.”

As explained by several commenters during the public sessions regarding the SAB Dioxin Panel’s consideration of the Draft Reanalysis, these same deficiencies noted by the NRC are evident in Draft Reanalysis. It would ill-serve the purpose of high quality peer review - and the SAB’s overall charge to

ensure the scientific soundness of EPA's response to NRC recommendations - if the SAB report to EPA addressed only the 2006 NAS recommendations on the draft dioxin reassessment and neglected to address very recent NAS concerns and recommendations regarding significant scientific flaws in the underlying IRIS methodological approach for conducting assessments such as the Draft Reanalysis. At a minimum, therefore, the CSAB should instruct the Dioxin Panel to revisit the Draft Reanalysis, make a determination as to whether it suffers from the same deficiencies the NAS has concluded persistently plague IRIS assessments, and recommend to EPA what it needs to do to address all such deficiencies.