

**COMMENTS FROM THE CHLORINE CHEMISTRY DIVISION OF THE  
AMERICAN CHEMISTRY COUNCIL TO THE US EPA SAB DIOXIN REVIEW  
PANEL**

The American Chemistry Council (ACC) appreciates the opportunity to provide written comments regarding the US EPA Science Advisory Board Dioxin Review Panel's February 9, 2011 draft report, *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (SAB draft report)*.

The SAB draft report identifies "major deficiencies" in *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Reanalysis)*. Specifically, the SAB's draft report criticizes:

- EPA's handling of the nonlinear (threshold) dose-response evaluation;
- EPA's mode-of-action approach by which threshold versus linearity decisions are made;
- EPA's uncertainty analysis of TCDD toxicity as requiring further attention; and
- The questions surrounding EPA's derivation of the RfD from the two Seveso studies (Mocarelli *et.al.* 2008; Baccarelli *et.al.* 2008) and for more fully evaluating the epidemiological data including the inclusion of negative studies and the use of MOA and corrected Hill Coefficients with respect to dose-response modeling.

The scientific shortcomings SAB identified are scientifically significant. The SAB clearly and concisely stated at the October 2010 public meeting that it was paramount EPA "get the science right." EPA must therefore fully address the deficiencies noted in the SAB report.

As set forth in these comments, ACC:

- Supports SAB and NAS recommendations related to the MOA-dependent threshold for dioxin carcinogenicity;
- Supports the draft recommendations to add additional alternative PODs which are consistent with recommendations of the 2005 EPA Cancer Guidelines;
- Supports SAB conclusion that the RfD derivation would be strengthened through inclusion of a comprehensive consideration of the body of literature available on the two endpoints selected for RfD derivation;
- Supports use of toxicokinetics in dose-response modeling for cancer and non-cancer endpoints;
- Supports the dissenting opinion offered by SAB member Dr. Rozman that there is no scientific basis for concluding dioxin would be carcinogenic to humans at background levels;
- Supports SAB's recommendation that the EPA more thoroughly address dose response modeling of the epidemiology data with the application of MOA information;
- Disagrees with the SAB's recommendation for modeling "All Cancer Mortality"; and
- Requests that the SAB instruct EPA to carefully review the scientific integrity of their quantitative assessment of cancer risk.

## **The MOA-dependent Threshold**

### **ACC supports the SAB and NAS recommendations related to the MOA-dependent threshold for dioxin carcinogenicity**

ACC strongly supports the SAB conclusion that the Reanalysis did not respond adequately to the NAS recommendation to adopt both linear and nonlinear methods of risk characterization (SAB Report pp. 7) and that the mode of action for TCDD toxicity should be reasonably well known rather than largely unknown (SAB Report pp. 6, 33).

The SAB's criticisms of EPA's rejection of a mode-of-action and related threshold nature, and EPA's willingness to go against the consensus of the scientific community, are similar to criticisms raised in reports issued by two prior EPA-convened SABs and the 2006 NAS panel. EPA's decision to apply a linear cancer slope factor is in opposition to the Agency's own 2005 Cancer Guidelines. The toxicology of dioxin, especially with respect to its carcinogenicity and tumor promotion capabilities, involves some of the most studied endpoints in science.

It is especially concerning that the SAB notes that in spite of recognized science to the contrary, EPA might be bound by policy to accept the linear option over the science supported non-linear, threshold approach (SAB Report p. 7). The SAB should clarify its guidance to EPA by stating that, regardless of Agency policy, the best available science supports adoption of a non-linear threshold approach.

### **ACC supports the draft recommendations to add additional alternative PODs which are consistent with recommendations of the 2005 EPA Cancer Guidelines**

Instead of following the recommendations of the NAS, and, in conflict, with EPA's own cancer risk guidelines, EPA's 2010 dioxin reassessment continues to rely 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.

Studies excluded by EPA<sup>1</sup> in the Reanalysis provide the key and associative events and modulatory factors that are essential to a proper dioxin MOA assessment. Exclusion of these studies runs contrary to EPA's own 2005 Cancer Guidelines and does not allow for the construction of a MOA-Key Event Analysis. EPA must take into account the entirety of the relevant MOA literature and conduct a thorough and competent MOA assessment. The SAB recommends that the Simon *et al*, (2010) paper, which was cited by EPA, be used to provide a number of alternative PODs for a nonlinear approach (SAB Report p.39). ACC supports the SAB's recommendations additional alternative PODs should be added.

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<sup>1</sup> ACC comments to SAB and Docket (October 2010 and September 2010)

## **The RfD Derivation**

**ACC supports the SAB conclusion that the RfD derivation would be strengthened by a comprehensive consideration of available literature on the two endpoints selected for RfD derivation.**

The SAB report would be strengthened by discussing papers by Goodman *et al.* (2010) and Bell *et al.* (2010) that review the endpoints selected for RfD derivation. Goodman *et al.* (2010) provides a comprehensive review of the available human data providing a dose-response assessment for alterations in thyroid hormone levels in association with biomonitored concentrations of dioxins and related compounds. As suggested in the SAB report, EPA's reliance on the Baccarelli *et al.* (2008) dataset, and the selection of a point of departure for the dataset and appropriate uncertainty factors, should be placed into proper context by a fuller consideration of this body of literature. The SAB report should emphasize that review across the available body of evidence could support the quantitative observation by Baccarelli *et al.* (2008) that no statistically significant relationship between maternal dioxin or TEQ concentrations was observable at maternal serum concentrations below 75 ppt TEQ (50 ppt TCDD). This consistent finding across many studies would support reconsideration of the selection of a point of departure based on this study.

This is also supported by consideration of the likely mode of action of thyroid hormone alterations, enzyme induction leading to altered thyroid homeostasis. As noted by the SAB:

...because of the wealth of data on P450s and their importance in disease development, normal development and chemical response to exogenous agents, EPA should discuss biochemical endpoints, particularly P450s, relevant to establishing and strengthening the proposed reference dose. (SAB Report p. 29)

Substantial data demonstrate that enzyme induction in humans occurs only at substantially higher exposure levels (serum levels in excess of 300 ppt TEQ; Lambert *et al.* 2006; Aylward *et al.* 2008). While consistent with a potential response in the highest exposed portion of the Baccarelli *et al.* study population, this suggests that EPA's RfD, which corresponds to a serum concentration approximately 2 orders of magnitude lower, is likely to be overly conservative.

Bell *et al.* (2010) provides a comprehensive review of available literature on rodent studies that address potential impacts of in utero and lactational exposures to dioxins on sperm parameters. This review is referenced in the SAB report, and we support the SAB in recommending that EPA consider the role of acute vs. subchronic exposure regimens in producing effects on these parameters. The dose-response assessment for the Mocarelli *et al.* (2008) study of sperm outcomes in men exposed as children at Seveso requires use of the pharmacokinetic model to assess intakes leading to observed serum concentrations in children over a dynamic period of acute exposure and rapid growth, as well as extrapolation of that exposure to an environmentally relevant regimen. The SAB report should recommend that EPA assess the performance of the Emond *et al.* pharmacokinetic model in reproducing observed elimination rates in children from

Seveso. We also suggest that SAB strengthen its recommendation that EPA more carefully assess the role of peak vs. average exposure levels in influencing sperm parameters.

### **Epidemiology Interpretation and Modeling**

#### **ACC Supports the Use of toxicokinetics in dose-response modeling for cancer and non-cancer endpoints**

ACC fully endorses SAB's recommendations that EPA assess the sensitivity of the human Emond model calculations to the Hill coefficient value and rely upon the robust data from Walker et al. (1999) to select a value for this coefficient. ACC supports the recommendation that a more quantitative uncertainty analysis be conducted for the PBPK model using Monte Carlo techniques in the dose range where the model is used by EPA. ACC strongly supports these two recommendations and believes that they are essential to ensuring that the Agency is in fact using best science in developing toxicity benchmarks for TCDD.

The SAB also recommended that the newly developed Emond mouse model be subject to external peer-review, a recommendation that fully comports with current EPA guidance and practice.

#### **ACC strongly endorses the dissenting opinion offered by SAB member Dr. Rozman that there is no scientific basis for concluding dioxin would be carcinogenic to humans at background levels**

ACC endorses Dr. Rozman's comments that there is insubstantial scientific basis for concluding that TCDD is carcinogenic to humans at background levels. If TCDD truly was as potent as the Agency believes, then there would be clear evidence of carcinogenicity in the many occupational cohorts where workers were exposed to very high levels for long periods of time. The fact that there is insubstantial evidence, despite extremely high exposures, further supports a threshold, and that the cancer risk at current background levels is in fact negligible. As stated so eloquently and accurately by Dr. Rozman, "*any other conclusion is incompatible with sound science.*"

#### **ACC supports the SAB's recommendation that the EPA more thoroughly address dose response modeling of the epidemiology data with the application of MOA information**

In a series of comments, the SAB panel expressed concern that the EPA did not adequately respond to the NAS recommendation to adopt both linear and non-linear methods. As a result, the SAB panel recommended that EPA provide more balanced discussions of the evidence of possible modes of action, including using mode of action information to determine whether linear extrapolation of the Cheng *et al* (2006) data is appropriate to obtain risk estimates associated with background exposure levels. ACC agrees with this recommendation and believes that doing so is essential to ensuring that the EPA assessment is in fact based on sound science.

The SAB should comment on whether the Agency's determination regarding the mode of action data, which in turn drives their selection of a dose-response modeling approach, was consistent

with the Cancer Risk Assessment Guidelines. ACC believes that EPA's cancer assessment is in fact fatally flawed because EPA failed to follow their own guidance and develop a mode of action framework to evaluate the extensive data available for dioxin on animal tumor promotion evidence. Only after careful MOA evaluation can the EPA correctly model the epidemiological data. The ACC believes that doing so is essential for evaluating the extensive body of data in a scientifically rigorous and sound manner for purposes of assessing the mode of action and determining the appropriate dose-response modeling approach for their cancer assessment.

### **ACC disagrees with the SAB's recommendation for modeling "All Cancer Mortality"**

The SAB endorsed EPA's use of "*all-cancer mortality data*" from the Cheng *et al* (2006) study "*because of the extensive dose-response information.*" This endorsement is perplexing for several reasons. First, EPA has taken the position that one must know the mode of action for each specific cancer endpoint, when in fact all cancer mortality precludes this evaluation. In fact, the increase is marginal at best (and not even statistically significant) even when all cancers are combined. Why must one know the mode of action for each specific cancer type if the Agency cannot even model individual cancers due to a complete lack of response in the workers relative to non-exposed individuals? For instance, no biological evidence exists that any and all human cell types, tissues, or organs have AHR responsivity that would act in a tumor promotion mode provided sufficient, sustained AHR activation. Therefore, the "all cancer mortality" approach is hypothetical at best and lacks the scientific acceptance as an endpoint for quantitative dose-response modeling for a sustained AHR activation MOA.

Second, the exposure information is actually very limited and, therefore, the dose-response information can in no way be characterized as "*extensive*". The exposure information in the Cheng *et al* (2006) paper is based on serum measurements from only 170 workers at a single plant that were then extrapolated to all of the other individuals in the subcohort (a total of 3,538 in the subcohort), including those at other plants, using a job exposure matrix (JEM) that is based on qualitative parameters that incorporates subjective judgment. As such, the resulting exposure estimates are not quantitative and thus have limited application in the mathematical models used by the EPA to derive an OSF. This major limitation is acknowledged by original authors in the peer-reviewed literature but was not recognized by the EPA.

ACC requests that the SAB panel instruct EPA to carefully examine these issues and modify their quantitative assessment of cancer risk accordingly.

### **ACC requests that the SAB instruct EPA to carefully review the scientific integrity of their quantitative assessment of cancer risk**

The SAB endorsed EPA's use of the Cheng *et al* (2006) study for quantitative cancer risk assessment but did not note concerns about the potential for co-exposures to other carcinogenic chemicals. There is in fact a substantial amount of environmental data collected on plant sites that were included in the NIOSH study indicating the presence of numerous carcinogenic compounds in soil and groundwater (e.g., benzene, ethylene oxide, acetaldehyde, etc). If these chemicals are present in the soil and groundwater at the plants, then presumably there were

releases to the environment and exposures to workers. This information was included in comments submitted to the docket by ToxStrategies, Inc. on behalf of Tierra Solutions for consideration by the SAB. One of the NIOSH cohort investigators, Dr. Kyle Steenland, in his oral comments to the SAB (October 2010), summarily dismissed co-exposures in the NIOSH cohort (the basis of the Cheng *et al* (2006) as “not relevant”. However, we believe that this was inappropriate as co-exposures must be considered.

EPA excluded data from the Ranch Hand study due to confounding exposures to 2,4-D, yet failed to address the confounding exposures in the NIOSH cohort. Given the marginal at best increase in cancer in the NIOSH cohort, it is essential that EPA closely examine potential exposures to other carcinogens. As such, the ACC requests that the SAB recommend EPA investigate environmental data for the plants to determine the likelihood of exposure to other carcinogens, and consider the findings in Cheng study in light of these co-exposures.

ACC strongly endorses the SAB’s concern over EPA’s rejection of using negative epidemiological results in deriving their cancer potency values.

## **References**

American Chemistry Council Comments to the Dioxin SAB (October 2010) and EPA Docket (September 2010).

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US EPA Dioxin Review Panel, SAB Review of EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, February 9, 2011.