

Comments on the 5/4/11 Draft Science Advisory Report “SAB Review of EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments”

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I. Requests of the Chartered SAB

We are asking the Charter SAB to ensure that the following Dioxin Science Advisory Board (DSAB) recommendations are implemented by the EPA. We are also asking that the Chartered SAB require the DSAB to correct a number of errors and inconsistencies within certain recommendations.

1. Require EPA to develop a threshold cancer potency factor for dioxin using a weight-of-evidence approach according to their own 2005 Cancer Guidelines

The DSAB has correctly found EPA to be deficient in failing to address the 2006 NAS recommendation that a threshold approach be applied to dioxin cancer risk assessment. The NAS committee was clear and unequivocal with this recommendation. In correcting EPA’s position, the DSAB must require that the EPA adhere to their own 2005 Cancer Guidelines that spell out a detailed weight-of-evidence (WoE) approach for conducting mode of action (MOA) assessments. As explained below, EPA’s efforts to capture key literature and expert solicitation with public involvement around dose-response and critical toxicity endpoints never occurred and apparently, was never intended to address the critical issue of MOA. Consequently, this prevented EPA from addressing NAS’s strong recommendation for a threshold-established dioxin cancer risk value.

2. Recognize EPA’s contradictory use of mode of action

The DSAB must recognize and correct the fact that EPA endorses an MOA position for justifying the linear modeling of all cancer mortality reported in an epidemiology study of trichlorophenol production workers while at the same time rejecting a recognized MOA for allowing a threshold treatment of the animal cancer bioassay data. The Agency can’t have it both ways – a reasonable MOA can either be established or rejected but not both. According to the 2006 NAS panel, a known MOA exists for dioxin that supports a threshold approach in utilizing cancer incidence data for the purpose of developing a dioxin cancer potency value. The EPA is following an illogical and arbitrary line of reasoning with our current understanding of dioxin’s MOA for carcinogenicity.

3. Eliminate policy opinions from the DSAB report concerning EPA’s development of a cancer potency value(s)

The DSAB must adhere to the science around the NAS panel’s recommendation and eliminate comments concerning “mechanism” which is not required under EPA’s 2005 Cancer Guidelines for establishing MOA, or granting EPA, as a matter of policy, an excuse for rejecting NAS’ strong endorsement of a science-based threshold approach.

4. Correct the conclusion that EPA’s efforts at collecting and evaluating literature around the issue of dose-response and critical studies for establishing a reference dose has met the same obligation for MOA and threshold considerations for carcinogenicity.

The DSAB frequently compliments EPA for a robust collection and examination of the scientific literature that is not true, nor deserved for the critical issue of linearity versus a threshold approach and the MOA. The DSAB does not understand that the EPA’s February 2009 Dose-Response Workshop was never intended to address the issue of linearity versus threshold or the MOA. In fact, it was stated to the effect, that “weight of evidence” and “mode of action” were not to be covered in the Dose Response workshop effort (explained in the footnote of Appendix C of the EPA’s January 2010 Dioxin Workshop Report). This single, February 2009 Dose-Response workshop was the only transparent effort conducted by the Agency for engaging the larger scientific community in responding to the multiple recommendations of the NAS.

II. Background Summary

To fulfill the recommendations of the 2006 NAS panel, EPA’s DSAB is responsible for holding EPA accountable for implementing a threshold approach for dioxin as a matter of science. The NAS report from 2006 commented that:

The committee concludes that EPA did not support its decision adequately to rely solely on this default linear model and recommends that EPA add a scientifically rigorous evaluation of a nonlinear model, that is consistent with receptor-mediated responses and the recent NTP cancer bioassay studies. ...the available data support the use of a nonlinear model, which is consistent with receptor-mediated responses and a potential threshold, with subsequent calculations and interpretation of MOEs. [pg. 24 – 2006 NAS Report]

The committee unanimously agrees that the current weight of evidence on TCDD, other dioxins, and DLCs carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data. To the extent that EPA favors using default assumptions for regulating dioxin as though it were a linear carcinogen, such a conclusion should be made as part of risk management. EPA should strictly adhere to the distinction between risk assessment, which is a scientific activity, and risk management, which takes into account other factors. [pg. 190 – 2006 NAS Report]

The criticism expressed in the 2006 NAS panel’s review of the 2003 assessment was not new to EPA staff. The need to conduct a threshold approach had been previously stated by two prior SAB panels in 1995 and 2001 but continues to be ignored by the EPA. In the 20 plus years of peer review by noted scientists around the world, the EPA has failed to address this repeated criticism on how EPA models dioxin’s cancer risk potential. Indeed, the current Dioxin SAB has concluded that EPA’s response to NAS is still deficient as noted in the following comment.

EPA’s Report did not respond adequately to the NAS recommendations to adopt both linear and nonlinear methods of risk characterization to account for the uncertainty of dose-response relationships below the ED01... The choice not to include both linear and

nonlinear risk assessment approaches for TCDD was inconsistent with the EPA (2005) Cancer Guidelines (pages 3 23/24) (pg 39) It is, in fact, the fundamentally nonlinear nature of the dose-response for receptor mediated processes. (pg 35) EPA should provide the receptor mediated nonlinear mode of action for dioxin (citing some studies) ..as well as evidence regarding the fundamentally nonlinear nature of receptor mediated cellular responses (citing more studies). (pg 36)

If this Dioxin SAB's recommendations are left unaddressed by the EPA, EPA's tradition of being non responsive to multiple peer review panels will carry forward yet again.

Additionally, the current Dioxin SAB's conclusions present mixed messages and errors. Unless corrected, this may obscure the extensive revisions required to make EPA's risk assessment compliant with the NAS recommendations and previous SABs. We summarize these concerns as follows.

General Weight of Evidence

The current Dioxin SAB noted deficiencies in the weight-of-evidence (WoE) assessment but still concluded: "During the course of its discussion, the Panel did not identify any additional studies that would make a significant impact on the conclusions of the hazard characterization and dose-response assessment" (pg 2). This conclusion makes no sense since the additional and critically important inclusion of negative studies required for a thorough and balanced WoE evaluation which will impact the hazard and dose-response assessment were excluded. It should be noted that the American Chemistry Council has provided detailed technical comments to the SAB but it is not known if these comments were considered in the DSAB's deliberations.

Recommendation:

The SAB must correct this conflicting statement, i.e., a complete WoE will very likely change the hazard and dose response characterization in the EPA's dioxin reassessment.

Linear Modeling of All Cancer Mortality

The EPA argued for the existence of an MOA for justifying human cancer classification and linear modeling of "all cancer mortality". At the same time, the EPA rejects the existence of a MOA and a threshold approach, for modeling the animal tumor data. Placed side by side, the Chartered SAB is being asked to endorse an illogical argument put forth by the EPA. The current Dioxin SAB's failed to note this discrepancy and to rightly criticize it. Instead, the Dioxin SAB endorsed EPA's MOA argument as justification for human cancer classification and linear modeling of all cancer mortality. Because the Dioxin SAB strongly endorsed a threshold MOA for modeling the animal tumor data, logic would likewise reject EPA's decision to use MOA as an excuse for modeling "all cancer mortality" in a linear fashion. The current Dioxin SAB also opined that extensive dose-response information justifies acceptance of all cancer mortality as a legitimate response endpoint.. However, it is the MOA and the biological plausibility information for dioxin that would justify whether "all cancers" should be combined, as if in a biologically based meta-analysis. There is no MOA proof that sustained AH receptor activation is operating in any and all human tissues/cells allowing dioxin to act as a tumor promoter for any tumor type, i.e., "all cancer mortality.". In fact, to the contrary, it is well known that the AHR receptor contributes to different responses depending on cell type, i.e., Thymic atrophy versus hepatic hypertrophy and hyperplasia.

Recommendation:

The Dioxin SAB must correct the conflicting endorsements over MOA which bear upon the important modeling of the epidemiological and animal tumor data. and require equal application of a threshold to both the epidemiological and animal tumor data. (please see Note 1 for supplemental information).

Failure to Conduct A Weight of Evidence Assessment of Mode Of Action

The Dioxin SAB's report suggests that the EPA conducted a thorough Weight-of-Evidence (WoE) examination of the MOA. However, at the same time, the Dioxin SAB is also requiring EPA complete A WoE evaluation on the MOA issue which indicates that EPA's effort was not thorough. In addition, the facts concerning how EPA compiled information on key studies for dose-response assessment never intended, and in fact plainly stated, that the EPA's one effort (the February 2009 Dose-Response workshop) would not address MOA. For example, in Appendix C of EPA's Dioxin Workshop Report, EPA stated their criteria for inclusion of "key in-vivo mammalian studies" but also noted: "These criteria are not designed for hazard identification of weight-of-evidence determinations. Studies addressing data other than direct TCDD dose-response in mammals (including toxicokinetics data on absorption, distribution, metabolism, or elimination; information on physiologically –based pharmacokinetic [PBPK] modeling, and **mode of action data**) will be evaluated separately." EPA never followed this up with subsequent workshops to address the scientific literature on MOA. The current Dioxin SAB was apparently unaware that the EPA's February 2009 dose response workshop did not intend to address MOA (see following comment from the DSAB draft report). In fact the workshop's agenda' precluded the use of key scientific studies around the question of MOA.

*The SAB commends EPA for the comprehensive and rigorous process that was used to identify, review and evaluate the TCDD literature. (Letter to Administrator Jackson). The Panel was particularly impressed with the process that EPA used for identifying, reviewing, and evaluating the relevant literature. (pg 11) The Panel found that EPA's study criteria and considerations were scientifically justified and clear...(pg 15) The EPA's collaboration with Argonne National Laboratory and invitation to the public to engage in updating the literature search to identify all appropriate studies for evaluation, as well as the conduct of the dioxin workshop in February of 2009, were instrumental in enhancing the transparency and clarity regarding the process of selection of studies for the dose-response analysis. (pg 14) **The panel complements (sic) the Agency for providing an up-to-data dioxin cancer mode of action section... A large amount of data related to the mode of action for the carcinogenicity is described in the Report....but the focus appears to be on presenting evidence that supports the use of a default linear approach rather than providing a balanced evaluation of alternative mode of action hypotheses. (pg 35 Dioxin SAB Report)***

..the Panel did not identify any additional studies that would make a significant impact on the conclusions of the hazard characterization and dose-response assessment (pg. 2).

Recommendation:

The current Dioxin SAB must correct their report to reflect the fact that EPA's evaluation of MOA is incomplete and deviates from the known biological understanding of the AH receptor.

Complimenting the work completed by the EPA regarding the MOA literature and weight of evidence related to the MOA is without merit. (please see note 2 Supplemental information)

III. Supplemental Information

Note 1

The Dioxin SAB could strengthen the following comment concerning EPA's use of the MOA:

EPA should expand the discussion in the Report to consider the possibility that mode of action considerations could help to inform whether linear extrapolation of the Cheng data to obtain risk estimates in this range of exposures is appropriate. (pg. 38)

However, as noted by others, the “all cancer mortality” basis and its insignificant relative risk of 1.3 preclude the Agency from modeling these epidemiological data in the first place, even with a threshold approach (Cole et al., 2004; written comments of Dr. Ken Mundt). Furthermore, the Dioxin SAB should re-state the NAS' position on linearity that it is a matter of policy and risk management, but not science, that linearity can be adopted by the Agency. Maybe this was the intent of the statement on page 8 of the DSAB's draft report but the statement requires clarification.

In the absence of a definitive nonlinear mode of action, the linear option results can serve as the baseline for comparison with these other estimates. (pg 8)

Note 2

In 2008 and into 2009 EPA appeared interested in convening a number of workshops on how to respond to the key NAS issues, e.g., MOA, linearity/Threshold, TEFs, RfD development. After the February 2009 Dose-Response workshop, however, EPA shut down its stakeholder and technical outreach efforts and proceeded with preparing their draft report with no further stakeholder input. One technical contractor for EPA, Dr. Jack Vanden Heuvel of Penn State, was hired to look at the biology of the AHR but apparently was not asked to provide input on MOA or how this would impact the choice of dose-response modeling (Dr. Vanden Heuvel's statement during the July 2010 SAB meeting in Washington, D.C.). Thus, MOA was never specifically addressed by EPA in the fashion suggested in the Dioxin SAB's compliments.

The Dioxin SAB must be informed about the true intent of the EPA's Dose-Response Workshop, conducted under FACA, in February of 2009. The workshop focused on identifying TCDD-only key dose-response studies and ignored the other dioxin and furan congeners. As a result, the workshop failed to recognize many published studies that bear on the question of MOA.

The Dioxin SAB should retract it's statement about the apparent completeness of EPA's efforts on MOA because the facts speak otherwise. The compliment only extends to EPA's efforts to identify key dose-response studies for TCDD For setting forth the RfD and the cancer potency estimate but does not include MOA and the larger question of a threshold.

Extensive technical comments were submitted on behalf of the ACC with numerous citations that never made it into EPA's discussion on MOA and yet are pivotal papers on the MOA, its Key Events, and dose-response characteristics. The Dioxin SAB should note these technical comments as examples of where the Agency fell short of addressing the NAS panel on MOA.