

**Comments Submitted by Lesa Aylward, Ph.D. on behalf of the American Chemistry
Council to the SAB Dioxin Review Panel on**

EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments

June 22, 2010

Introduction

On behalf of the Chlorine Chemistry Division of the American Chemistry Council, I offer the following comments and questions for your consideration as you begin the formidable task of peer-reviewing *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*.

An overriding theme in these questions and comments is whether or not EPA consistently and appropriately applied a weight of evidence approach to dioxin toxicity and risk. The questions set forth below both supplement and expand on the Charge to be addressed by the SAB Dioxin Review Panel.

Comments Related to General Charge Issues

1. In focusing on “three key NRC recommendations” I would encourage the Panel to recognize the emphasis that NAS has placed on the threshold basis for dioxin cancer risk assessment.¹
2. In the analysis of dose-response, did EPA take into account important *in vivo* and *in vitro* data that would have informed EPA's toxicodynamic and MOA factors relevant to the shape of the dose-response curve in the low dose-region or below the POD?²

Questions Related to Weight of Evidence in Derivation of the Non-Cancer RfD

1. ***Weight of evidence evaluation on endpoints selected for RfD derivation.***³ In the evaluation of epidemiological and animal studies, did the EPA conduct an appropriate weight-of-evidence evaluation using the best available scientific information for the endpoints considered prior to selecting key datasets and conducting a dose-response

¹ See Section Entitled “General Charge Questions” of EPA's Charge to the SAB (2010).

² See Section 3 of EPA's Charge to the SAB (2010). This was also the emphasis of EPA's dose-response workshop in February 2009, and was discussed in OMB's comments on the Reanalysis.

³ See Sections 2 and 4 of EPA's Charge to the SAB (2010).

assessment? Did EPA consider the weight of evidence in the quantitative as well as qualitative assessment?⁴

- a. Did the EPA carefully consider clinical and epidemiological aspects relevant to the interpretation of the Seveso thyroid and sperm parameter findings?
- b. Did the EPA provide sufficient background on the animal and human evidence linking TCDD to changes in TSH and sperm endpoints and the biology of these endpoints in support of its RfD derivations?

2. ***Inclusion of non-TCDD TEQ in human dose-response assessment.*** In the quantitative dose-response assessment of the identified key human studies, Baccarelli *et al.* (2008) and Mocarelli *et al.* (2008), did EPA account for the substantial non-TCDD TEQ present in these populations in their quantitative estimation of the POD and resulting RfD? Is the omission of non-TCDD TEQ in the quantitative exposure-response characterization appropriate or justifiable? Did EPA adequately discuss alternative approaches and present the uncertainties associated with each? Was an appropriate dose metric selected? In answering these questions, the SAB Dioxin Review Panel should note the following:

- a. Baccarelli *et al.* (2008): non-TCDD TEQ of approximately 25 to 50 ppt.⁵
- b. Mocarelli *et al.* (2008): non-TCDD TEQ of 80 to 100 ppt.
“If TCDD acts in concert with other dioxin-like chemicals in affecting sperm quality, the total dioxin toxic equivalency (TEQ) should be considered. In nine serum pools from females residing in the uncontaminated area in 1976, Eskenazi *et al.* (2004) found an average TEQ of 100 ppt.”⁶
- c. Note that in the U.S., the *upper bound* of current serum TEQ concentrations in persons of reproductive age is *less than* 20 ppt TEQ.⁷

⁴ See Goodman *et al.* (2010), (in press; attached) for a comprehensive, structured weight of evidence review of the available epidemiological literature which focused on reliability, relevance, and adequacy regarding thyroid hormone endpoints and measured dioxin concentrations.

See Bell *et al.* (2010) for a comprehensive, structured weight of evidence review which focused on reliability, relevance, and adequacy of the animal data regarding the effects of dioxin on developmental male reproductive system endpoints. See also Foster *et al.* (2010).

⁵ Baccarelli *et al.* (2008), Figures 2A and 2B; Table 5.

⁶ Mocarelli *et al.* (2008).

⁷ Patterson *et al.* (2009).

3. ***Selection of studies for candidate RfD development.*** The database on TCDD is robust and is replete with animal studies that employ subchronic or chronic administration using environmentally relevant modes of administration. Should EPA rely upon these studies, and exclude studies employing acute bolus dosing regimens or loading/maintenance dosing regimens, which result in peak exposures not relevant to human environmental exposure conditions, from the calculation of candidate RfDs?⁸

4. ***Pharmacokinetic model and enhanced elimination rates in infants and children.***⁹ Does the Emond *et al.* (2005) PBPK model include and account for the enhanced fecal clearance of TCDD observed in infants and children, which would substantially impact the external doses estimated in modeling for the Mocarelli *et al.* (2008) dataset? In addressing this question, the SAB Dioxin Review Panel should consider the following:
 - a. Enhanced fecal clearance of lipids in infants and children (as much as 7 times faster than in adults) results in far more rapid elimination of dioxins than in adults.¹⁰
 - b. Failure to consider this will significantly underestimate the daily dose rates associated with identified target body burdens, and thus underestimate the derived RfD.

5. ***Non-cancer risk characterization.*** In regards to comments and recommendations made by OMB in its review of EPA's Reanalysis, should EPA develop margin of exposure (MOE) and margin of safety (MOS) information reflecting NOAEL and RfD estimates? The importance of the MOE concept was emphasized in the 2006 NAS Report of the draft dioxin reassessment.

⁸ See Section 4 of EPA's Charge to the SAB (2010). Section 4.2 in particular notes that "In the Seveso cohort, the pattern of exposure to TDCC is different from the average daily exposure experienced by the general population." The high level exposure incurred by young Seveso males was reported to show lower sperm counts almost twenty years later. The high level inhalation, dermal, and ingestion exposures taking place in 1976 in Seveso, however, constitutes a semi-bolus dose relative to the slow accumulation of dioxin from the diet.

⁹ See Section 3 of EPA's Charge to the SAB (2010).

¹⁰ Reviewed by Milbrath *et al.* (2009); See Leung *et al.* (2006) and Kerger *et al.* (2007).

Questions Related to Weight of Evidence in the Cancer Risk Assessment

1. ***Non-linear cancer risk assessment.*** Has EPA appropriately characterized and responded to the unequivocal NAS recommendation that a non-linear cancer dose-response assessment is the scientifically justified approach for dioxin? In responding to this question, the SAB Dioxin Review Panel should consider the following:
 - a. NAS emphasizes the scientific justification for a non-linear approach in numerous places in the report.¹¹
 - b. NAS notes that, rather than being a scientifically justified approach, the linear approach is a policy default and the choice to rely upon this approach should be part of risk management rather than risk assessment.¹²
 - c. OMB comments identify the ability for EPA to develop both a linear and non-linear cancer slope factor: “In light of the NAS evaluation and their recommendations for a nonlinear approach, it would seem that in this case, the nonlinear approach has significant biological support and thus it may make sense to present results using both approaches.”¹³ OMB’s comments further elucidate EPA’s guidance on cancer risk assessment and perspective on what EPA could have done but failed to do.

2. ***Mode of Action and Human Relevance Framework.*** Have the EPA Cancer Risk Assessment Guidelines, which include the mode of action human relevance framework, been appropriately used in the evaluation of the cancer mode of action and dose-response? Is EPA’s conclusion that no MOA has been established for TCDD-induced tumors, especially liver tumors, consistent with these cancer guidelines?¹⁴ Related questions include the following:
 - a. Has EPA adequately investigated the biology of tumor promotion and used this information to examine the published studies on dioxins within a framework for a tumor promotion MOA? Has EPA

¹¹ See National Academy of Sciences, “Health Risks From Dioxin and Related Compounds: Evaluation of the EPA Reassessment,” pp. 122-128 (2006).

¹² See *Id.* at 142.

¹³ See Office of Management and Budget, “OMB Staff Working Comments on EPA’s Response to ‘Health Risks from Dioxin and Related Compounds Evaluation of the EPA Reassessment,’” p. 3 (2010).

¹⁴ See Question 5.8 of EPA’s Charge to the SAB (2010).

adequately included toxicodynamic information in informing the derivation of cancer potency estimates below the point of departure?

- b. Has EPA adequately considered the evidence of TCDD's role as a tumor promoter in rejecting nonlinear TCDD cancer dose-response modeling?¹⁵
- c. Did EPA conduct a structured evaluation of the entire body of available cancer epidemiologic data (not only those reporting a positive exposure-response association) employing the Hill criteria, including consistency, biological gradient, and biologic plausibility, in supporting EPA's opinion of an epidemiological relationship suitable for dose-response modeling of all cancer mortality?¹⁶

In responding to these questions, the SAB Dioxin Review Panel should consider the following:

- a. Key events *can* be identified and corresponding reference doses derived.¹⁷
- b. Uncertainty factors can be evaluated appropriately considering interspecies sensitivities and, in particular, the weight-of-evidence indicating that humans are less sensitive to dioxin toxicity than rodents or non-human primates.¹⁸

3. ***Assumptions inherent in use of human occupational epidemiology studies for quantitative dose-response assessment.*** Has EPA appropriately acknowledged the many assumptions inherent in relying on the human cancer epidemiology for quantitative dose-response assessment? These include:

- a. Assumption that human data weight of evidence supports a positive dose-response for cancer, despite more current studies with long follow-up showing no increased mortality in highly exposed populations?¹⁹ OMB commented on EPA's decision to ignore non-

¹⁵ See Question 5.3 of EPA's Charge to the SAB (2010).

¹⁶ See Questions 5.1 and 5.2b of EPA's Charge to the SAB (2010).

¹⁷ See Simon *et al.* (2009) for a discussion of hepatic tumorigenicity. See also Chapter 6, Part II, of the 2003 draft Dioxin Reassessment.

¹⁸ See Connor and Aylward (2006); See also Silkworth *et al.* (2005); See Generally Question 4.3 of EPA's Charge to the SAB (2010).

¹⁹ See Collins *et al.* (2009), Appendix B; See Generally Question 5.3 of EPA's Charge to the SAB (2010).

positive studies in deriving their cancer potency estimates as a weight-of-the-evidence deficiency.²⁰

- b. Assumption that all cancer mortality is a biologically plausible endpoint, despite lack of any site-specific concordance across human studies or with animal datasets. For example, has the EPA established scientific support for the presumption that AHR receptor presence and function is adequate to result in tumor promotion in any and all tissues and cell types consistent with an all cancer mortality causality assumption?
 - c. Assumption that human dose reconstructions can accurately be made over decades, based on a single serum measurement made in a small, non-random, non-representative subset of the surviving population decades after last exposure.
 - d. Assumption that the pharmacokinetic model accurately predicts the relationships between intake dose and tissue concentrations even at dose levels far below current and historical body concentrations (i.e., in an exposure range in which the model is untested and unvalidated).
 - e. Assumption that sufficient MOA information exists to support classifying TCDD as a known human carcinogen that is capable of promoting any tumor type in humans while at the same time assuming that insufficient MOA information exists to support a non-linear (threshold) cancer potency derivation.
4. ***Quantitative analysis of cancer slope factor based on human data.*** EPA relies upon the regression results from the Cheng *et al.* (2006) analysis of the NIOSH cohort data employing the pharmacokinetic modeling and exposure reconstruction of Aylward *et al.* (2005). EPA derives a series of potential slope factors that vary over more than an order of magnitude from this data set and analysis, and emphasizes the upper end of this range as their preferred cancer slope factors. Two issues should be addressed in evaluation of this choice:
- a. EPA selects results based on the statistical upper bound of the regression coefficient derived from an analysis of the lagged dataset with the most highly exposed individuals omitted (“trimmed”). This analysis is, in itself, already an “upper bound” of the regression coefficient that can be considered to be consistent with the NIOSH dataset, and is two orders of magnitude steeper than the non-significant regression coefficient that results when the dataset is *not* trimmed. Note that the draft EPA document has an error in Table 5-2, in which the lagged, untrimmed coefficient is designated as

²⁰ See OMB Comments, Page 2 (2010).

statistically significant – it is not.²¹ Is it appropriate to focus on the statistical upper bound of this upper bound regression coefficient?

- b. Because the pharmacokinetic model used by EPA is concentration-dependent, estimation of incremental risk-specific doses (RSDs) (and therefore slope factors) at the lowest incremental risk levels without accounting for existing background tissue concentrations of TEQ results in unrealistically low RSDs. Because cancer risk assessment is always conducted as an incremental exercise by risk managers, the focus should be on estimating RSDs (and corresponding slope factors) incremental to current background concentrations. Has EPA applied the concentration-dependent pharmacokinetic modeling to derive slope factor estimates consistent with the application in risk management context?
5. **Modeling of animal data.** Is EPA's proposed counting of different tumors in the same animal validly based on independence of tumor type when the different tumors are presumably due to a shared AHR activation MOA? Is EPA's approach adequately supported in light of the weight-of-evidence of pathology examinations for TCDD and other compounds?²²

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²¹ See Cheng *et al.* (2006), Table III.

²² See Question 5.4 of EPA's Charge to the SAB (2010).

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The paper, Weight-of-evidence analysis of human exposures to dioxins and dioxin-like compounds and associations with thyroid hormone levels during early development (Goodman et al., in press) referenced in Dr. Lesa Aylward's public comments is available at the following URL:

http://www.sciencedirect.com/science?_ob=MImg&_imagekey=B6WPT-4YX0015-1-1&_cdi=6999&_user=14684&_pii=S0273230010000681&_orig=browse&_coverDate=04%2F21%2F2010&_sk=999999999&_view=c&_wchp=dGLbVlb-zSkzV&_md5=0e4b44cdc35f8ed205691c5c3681f8d1&_ie=/sdarticle.pdf