

**Preliminary Comments to the SAB Dioxin Review Panel on  
EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments  
July 9, 2010**

**I. EPA HAS NOT FOLLOWED ITS OWN IRIS PROCESS GUIDELINES**

On May 21, 2010, EPA announced a 90-day public comment period for the draft *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Draft Report).<sup>1</sup> In the announcement, EPA stated:

This draft report is now considered to be under EPA's Integrated Risk Information System (IRIS) program, and thus, the new IRIS process announced in May 2009 [hyperlink omitted] is being followed. Per the May 2009 process, this draft report is beginning Step 4 – independent external peer review and public review and comment.<sup>2</sup>

Unfortunately, the process EPA has described for the Draft Report does **not** comport with its most recent IRIS process.<sup>3</sup> Consequently, the quality and integrity of the external peer review are at risk.

In particular, Step 4 of the IRIS process provides, in part, that –

- Public comments submitted before the close of the public comment period will be given to the peer reviewers at least ten working days before the peer review meeting; and
- Only those comments received by the close of the public comment period are **guaranteed** of being provided to the external peer review panel in advance of the peer review meeting.

Thus, Step 4 makes clear that the external peer review, in this case conducted by the SAB, will occur only after the public comment period has ended. This, of course, is entirely reasonable and, in fact, necessary to provide the public with sufficient time to review and comment on a draft report and provide comments to the SAB to review before it meets.

The June 24, 2010 conference call and the July 13-15 face-to-face meeting of the SAB, however, were all scheduled **during** the public comment period, not after it had closed. In fact, the June 24 conference call was scheduled only approximately a month after EPA publicly released its nearly 2,000-page Draft Report. Therefore, the public had little time to review this massive document, let alone prepare written and oral comments for submittal to assist the SAB prior to the June 24 conference call or the upcoming July 13-15 meeting. The SAB began its deliberations

---

<sup>1</sup> 75 Fed. Reg. 28610 (May 21, 2010), Docket ID No. EPA-HQ-ORD-2010-0395.

<sup>2</sup> 75 Fed. Reg. at 28610.

<sup>3</sup> See [http://www.epa.gov/iris/pdfs/IRIS\\_PROCESS\\_MEMO.5.21.09.PDF](http://www.epa.gov/iris/pdfs/IRIS_PROCESS_MEMO.5.21.09.PDF).

without a complete picture of the relevant science in hand, thus undermining the integrity of the peer-review process.

It may be true that the SAB meetings were scheduled in anticipation of EPA issuing the Draft Report in early 2010, not mid-year. However, EPA's failure to meet its self-imposed deadline for issuing the Draft Report does not justify circumventing the IRIS process, which is intended to provide the public with an adequate comment period. Nor does EPA's deadline slippage obviate the SAB's need to obtain a complete picture of the relevant science before expert deliberations begin.

To ensure consistency with the provisions of Step 4 of the IRIS process and to enable the SAB to meet its peer-review obligations, a number of entities urged the Chair of the SAB Dioxin Review Panel (Panel) to:

1. Reschedule the July face-to-face meeting until at least two weeks after the close of the public comment period to allow Panel members sufficient time to consider public comments and to review the Draft Report itself; and
2. Provide the public with ample time to present oral comments to the SAB, in excess of 5 minutes per speaker, especially given the wide-spread public interest in dioxin and the potentially far-reaching impacts of the final report.

We understand that the SAB Chair expects to schedule another face-to-face meeting after the close of the public comment period. This approach is alluded to by Dr. Vu in her letter to Cal Dooley, President and CEO of the American Chemistry Council.<sup>4</sup> If Dr. Vu's commitment is honored, the July meeting should serve as an opportunity for the SAB Panelists to initiate discussion, not to draw substantive conclusions.

We ask that the SAB proceed in accordance with the approach articulated by Dr. Vu in her letter.

## **II. EPA HAS NOT ADDRESSED IMPORTANT RECOMMENDATIONS AND COMMENTS FROM THE NATIONAL ACADEMY OF SCIENCES**

The Draft Report fails to adequately address a number important recommendations submitted by the National Academy of Sciences (NAS). Moreover, EPA provides no basis for its decision to respond to some recommendations but not others.

---

<sup>4</sup> "Given the complexity of the scientific issues, I expect that the SAB Panel will initiate discussion at the July meeting and that the SAB will need additional public meetings for follow up discussion and review of the panel's draft peer review report." Letter from Dr. Vanessa Vu to Cal Dooley, June 4, 2010, at p. 1.

For example, with regard to exposure, the NAS suggested that to assess the total magnitude of emissions of dioxin-like compounds (DLCs), EPA should utilize a top-down approach to account for observed levels. EPA, however, has not addressed this recommendation. Likewise, the NAS recommended that EPA evaluate the impact of early emission inventory estimates of sources added in more recent assessments so that the overall percentage declines in environmental levels reflect all sources. An evaluation of this nature would help confirm the dramatic decreases in TEQs that appear to have occurred over time. In other words, accurate exposure information must be generated and incorporated to determine the relevant human exposures at human equivalent intakes. This recommendation also has been ignored by the Agency.

Moreover, the NAS made several recommendations regarding the use and application of toxic equivalency factors, or TEFs. Specifically, the NAS recommended that EPA adequately address the uncertainties and limitations inherent in the current TEF methodology. Nonetheless, the Agency failed to address these recommendations in its response to the NAS. Additionally, in the absence of EPA's response regarding these issues, it is unclear how the Agency's separate ongoing evaluation of TEFs, through the issuance of EPA's 2009 draft *TEF Guidance*, might impact the Dioxin Reassessment.

The foregoing recommendations, along with others, reflect the time, effort, commitment, and expertise of the NAS Panel. Its report was intended as a mandate for EPA to accurately characterize the health effects from dioxin exposure. Key to the deliberation of the Draft Report, then, is the NAS evaluation of the Dioxin Reassessment. Accordingly, in response to the NAS recommendations, EPA should have issued a side-by-side comparison "Response to Comments" table and posted to its website the 2006 NAS report, entitled *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, and made the document available for Panel review.

### **Suggested Charge Questions to the SAB Dioxin Review Panel**

In addition to drawing attention to the NAS recommendations that EPA failed to consider in the Draft Report, the charge questions should be amended as follows, to better focus the SAB's attention to EPA's inadequate responses to the NAS comments, thereby ensuring a thorough examination of the Draft Report.

1. With regard to EPA's Reference Dose (RfD), the Panel should be asked specifically to comment on the key limitations of the epidemiologic studies and any implications they may have for the utility of the RfD that EPA has derived using these studies.
2. Further, the Panel should be asked to offer recommendations on uncertainty factors applied to other potential studies that may be more appropriate for a RfD determination.
3. The Panel should be asked to comment on the implications of current exposures regarding the development of a point of departure for a RfD.

4. The Panel should be asked to comment on the use of peak blood concentration, and EPA's approach of averaging 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) blood concentrations over the entire dosing period.
5. The Panel should be asked to comment on the appropriateness of EPA's modification of the Emond *et al.* model, and whether such a modification should be peer reviewed prior to its application.

**III. EPA'S ASSUMED USE OF THE WHO TEFs FOR CONDUCTING HUMAN HEALTH RISK ASSESSMENTS OF OTHER DIOXINS, FURANS AND PCBs DOES NOT REPRESENT THE BEST AVAILABLE SCIENCE**

The Draft Report determines Cancer Slope Factors and non-cancer RfDs derived from human cohorts primarily exposed to TCDD, but does not respond to NAS recommendations that EPA address the uncertainties and limitations inherent in the current TEF methodology when applying its findings to other DLCs. Instead, EPA has chosen to conduct a separate evaluation of TEFs through the issuance of its 2009 draft *TEF Guidance*, and is expected to issue a guidance in final form in the near term. Given EPA's failure to address the NAS comments concerning the uncertainties and limitations of the TEF approach in the Draft Report, the public is left to assume that the 2005 WHO TEFs will be used in conjunction with the proposed TCDD-specific risk values for estimating the risk of DLCs, as outlined in EPA's draft *TEF Guidance*.

Although the TCDD-specific risk values were derived from human epidemiological assessments, the WHO TEFs were derived primarily from rodent studies. A National Research Council panel's evaluation of the 2003 draft Dioxin Reassessment emphasized that "if significant differences in the REPs (relative potencies) of DLCs are found between humans and other species, then adjustments should be made in the TEFs" (p. 87). EPA ignored the possible influence of species differences in DLC potency in both the Draft Report and the 2009 draft *TEF Guidance*, thus assuming that there are no species differences when applying the current TEF values.

In some instances, the current TEFs have been shown to predict the toxicities of dioxins and DLCs in rodents, both *in vivo* and for cells cultured *in vitro*. However, in actual experimental testing procedures, it has been demonstrated that not all rodent-derived TEFs are conserved between rodents and humans. This is true for the most potent PCB congener, PCB 126, which was tested in several human cell types. In these experiments, human relative potencies were consistently found to be about 50 times lower than the TEFs derived from rodents. In addition, many of the relatively less potent mono-ortho PCBs in rodents have been found to have little or no activity in human cells.

Based upon actual human responses observed using numerous *in vitro* assays, the TEFs are not universally transferrable between rodents and humans. Additionally, a multitude of other questions remain unanswered concerning use of the TEF scheme in human health risk assessment for PCBs. These issues include, but are not limited to, the invalid assumptions of

additivity and equal efficacy for all DLCs, and the lack of a validated method for determining concentrations of dioxin-like PCB congeners in soil, water, and other media.

Thus, in order for this newly-anticipated dioxin risk assessment scheme to accurately predict the risk of real-world mixtures of dioxins and DLCs, EPA must, at the very least, attempt to reduce some of the inherent uncertainty by addressing the clear species differences in TEFs. In that respect, we encourage the Panel to consider whether it is scientifically appropriate to use the TEQ approach absent, at minimum, implementation of the NAS recommendations. Moreover, the Panel should consider whether it is scientifically appropriate to treat PCB mixtures as if they represent mixtures of dioxins. The Panel should examine the scientific basis on which EPA has concluded that it is justifiable to treat PCB exposures as if they represent exposures to DLCs. The Panel should also inquire as to the basis of EPA's opinion that TEFs are necessary or scientifically valid for use in PCB risk assessments and clean-up efforts.

#### **IV. EPA HAS NOT FOLLOWED ITS OWN RISK ASSESSMENT GUIDELINES AND PRINCIPLES IN EVALUATING DIOXIN TOXICITY AND RISK**

In conducting its peer review of the Draft Report, the SAB Panel should evaluate whether EPA consistently and appropriately followed its own guidelines and principles and applied a weight of evidence approach, using best available scientific information, in its evaluation of dioxin toxicity and risk.<sup>5,6</sup> The need for a weight of evidence evaluation using best available science is at the heart of the recommendations made by the NAS and is fundamental to all of the other specific comments made by the NAS reviewers. EPA's guidance and principles that address the use of best available scientific information are embodied in a variety of Agency documents, but the following are most relevant to risk assessment principles and weight of evidence.

- *Risk Characterization Handbook* was created as a single, centralized body of risk characterization implementation guidance (EPA 100-B-00-002, December, 2000). EPA states in the *Handbook* that "A risk characterization should be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency." The Agency further states that the principles of transparency, clarity, consistency, and reasonableness (TCCR) must be fully applied throughout every aspect of the risk assessment process. This standard also must be applied in the SAB's review of the Draft Report. For example, on pp. 5-60 to 5-61, beginning at line 27, the Draft Report introduces the theory of "interacting background" as a basis to argue against the development and use of a nonlinear cancer

---

<sup>5</sup> See National Center for Environmental Assessment's, "Guidelines for Carcinogen Risk Assessment" (2005), at p. 2-40.

<sup>6</sup> See Administrator Jackson's May 9, 2009 memorandum "Scientific Integrity: Our Compass for Environmental Protection," at p. 1.

dose-response, and further cites an NAS (2009) report as support, appearing to carry the authority of guidance.

The Panel should evaluate whether the adoption of the “interacting background” concept comports with these principles, absent the formal process of public notice, peer review and public comment that is typically given to guidance documents. Otherwise, EPA’s acceptance of this theory and consequent dismissal of the NAS recommendation to employ a nonlinear cancer model appears to be contrary to the principles outlined in the *Handbook*.

- *An Examination of Risk Assessment Principles and Practices* was published in March, 2004 (EPA/100/B-04/001) and was initiated as an internal investigation of EPA’s approach to risk assessment. In this document, EPA makes a commitment to assessing all available scientific information using a weight of the evidence process that is consistent, comprehensive, balanced, and reproducible. The Panel is urged to evaluate whether the Draft Report fulfills that commitment.
- *Guidelines for Carcinogen Risk Assessment* (EPA/630/P-03/001F), published in 2005, embraces a weight of evidence approach as a key feature. In conducting the dose-response assessment, the *Guidelines* recommend starting with a critical analysis of all available data, rather than assuming a linear mode of action (MOA). This analysis should include a complete evaluation of all existing data on tumor incidence rates and potential MOAs for tumor formation. The *Guidelines* are written to provide latitude and opportunity to use the published literature, to re-analyze previous data in light of new scientific understandings, or to conduct original research. Default assumptions must be employed only in the absence of critical information, or if the available data do not support a convincing alternative approach.

In fact, the *Guidelines* do not discuss specific criteria for conducting the MOA evaluation. When the *Guidelines* were being peer-reviewed before adoption, EPA disagreed with comments calling for the development of specific criteria, stating that “with the multitude of types of data, analyses, and risk assessments, as well as the diversity of needs of decision makers, it is neither possible nor desirable to specify step-by-step criteria for decisions to invoke a default option.”

In light of the foregoing, the SAB Panel should determine whether a significant inconsistency exists between a straightforward reading of the *Guidelines* and the way in which EPA has interpreted them in order to justify its use of a linear, no-threshold cancer model in the Draft Report. For example, the statement made on p. 5-61 lines 27-28 of the Draft Report is illuminating because it illustrates how far EPA has strayed from the *Guidelines* in its interpretation of the MOA assessment: “The linear approach is used if there is sufficient evidence supporting linearity or if the mode of action is not understood (U.S. EPA, 2005).” The Panel should evaluate whether EPA, at the very least, should have presented two dose-response assessments because the *Guidelines* do

not require a full understanding of the MOA to support a nonlinear approach. In light of the NAS's unequivocal recommendation that a nonlinear approach is scientifically justified, the Panel should consider why EPA has not presented such an approach and the significance and import of such an omission.

V. **EPA HAS NOT APPLIED A WEIGHT OF EVIDENCE APPROACH AND HAS NOT USED BEST AVAILABLE SCIENCE IN DEVELOPING BOTH NON-CANCER AND CANCER TOXICITY FACTORS FOR DIOXIN**

Emhart Industries, Inc. (Emhart) is providing technical comments directed towards correcting critical shortcoming in EPA's non-cancer and cancer risk characterization. It is the intent of these comments to assist the Panel in examining the scientific validity of EPA's approach and conclusions, and to frame questions for the Panel to help examine the many scientific limitations associated with EPA's derivation of the RfD and the cancer slope factor. However, the Draft Report is almost 2,000 pages in length and had taken EPA nearly four years to complete. It is unrealistic for interested members of the public, including Emhart, to provide detailed comprehensive comments on such highly technical and complex issues by July 9, 2010, in order for the Panel to consider such comments at its July meeting. Therefore, the following comments are preliminary in nature, and are framed as questions for the Panel to consider as it begins to query and examine the scientific basis of the Draft Report.

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

- a. *Weight of evidence evaluation on endpoints selected for RfD derivation.*<sup>7</sup> In the evaluation of epidemiological and animal studies, did EPA conduct an appropriate weight-of-evidence evaluation using the best available scientific information for the endpoints considered prior to selecting key datasets which were subsequently used in EPA's dose-response assessment?
  - b. Did EPA carefully consider clinical and epidemiological aspects relevant to the interpretation of the Seveso thyroid and sperm parameter findings?
  - c. Did 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 its quantitative estimation of the point of departure (POD) and resulting RfD? Is the omission of non-TCDD TEQ in the quantitative exposure-response

---

<sup>7</sup> See Sections 2 and 4 of EPA's Charge to the SAB (2010).

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 Panel should note the following:

- a. Baccarelli *et al.* (2008): non-TCDD TEQ of approximately 25 to 50 ppt.<sup>8</sup>
  - 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.”<sup>9</sup>
  - 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.<sup>10</sup>
3. ***Selection of studies for candidate RfD development.*** The database on TCDD is robust and 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?<sup>11</sup>
4. ***Pharmacokinetic model and enhanced elimination rates in infants and children.***<sup>12</sup> 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 Panel should consider the following:

---

<sup>8</sup> Baccarelli *et al.* (2008), Figures 2A and 2B; Table 5.

<sup>9</sup> Mocarelli *et al.* (2008).

<sup>10</sup> Patterson *et al.* (2009).

<sup>11</sup> 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 TCDD 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 that occurred in 1976 in Seveso, however, constitutes a semi-bolus dose relative to the slow accumulation of dioxin from the diet.

<sup>12</sup> See Section 3 of EPA’s Charge to the SAB (2010).

- 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.<sup>13</sup>
  - b. Failure to consider the foregoing data 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 the Draft Report, should EPA develop margin of exposure (MOE) and margin of safety (MOS) information reflecting the no-observed-adverse-effect level (NOAEL) and RfD estimates? The importance of the MOE concept was emphasized in the 2006 NAS Report concerning the draft Dioxin Reassessment.

#### 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 Panel should consider the following:
  - a. NAS emphasizes the scientific justification for a non-linear approach in numerous places in the report.<sup>14</sup>
  - b. NAS notes that, rather than being a scientifically justified approach, the linear approach is a policy default; the choice to rely upon this approach should be part of risk management rather than risk assessment.<sup>15</sup>
  - c. OMB comments identify EPA's ability 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."<sup>16</sup> OMB's comments further elucidate EPA's guidance on cancer risk assessment and our views concerning the nature and extent of the

---

<sup>13</sup> Reviewed by Milbrath *et al.* (2009); See Leung *et al.* (2006) and Kerger *et al.* (2007).

<sup>14</sup> See National Academy of Sciences, "Health Risks From Dioxin and Related Compounds: Evaluation of the EPA Reassessment" (2006), at pp. 122-28.

<sup>15</sup> See *id.* at p. 142.

<sup>16</sup> 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'" (2010) at p. 3.

evaluation that EPA could have undertaken in the Draft Report, but failed to do, as described in our comment above.

2. ***Mode of Action and Human Relevance Framework.*** Have the EPA Cancer Risk Assessment Guidelines, which include the MOA human relevance framework, been appropriately used in the evaluation of the cancer MOA 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?<sup>17</sup> 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 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?<sup>18</sup>
  - 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?<sup>19</sup>

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

- a. Key events *can* be identified and corresponding reference doses derived.<sup>20</sup>
- 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.<sup>21</sup>

---

<sup>17</sup> See Question 5.8 of EPA's Charge to the SAB (2010).

<sup>18</sup> See Question 5.3 of EPA's Charge to the SAB (2010).

<sup>19</sup> See Questions 5.1 and 5.2b of EPA's Charge to the SAB (2010).

<sup>20</sup> See Simon *et al.* (2009) for a discussion of hepatic tumorigenicity. See also Chapter 6, Part II, of the 2003 draft Dioxin Reassessment.

<sup>21</sup> See Connor and Aylward (2006); See also Silkworth *et al.* (2005); See generally Question 4.3 of EPA's Charge to the SAB (2010).

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?<sup>22</sup> OMB commented on EPA's decision to ignore non-positive studies in deriving their cancer potency estimates as a weight-of-the-evidence deficiency.<sup>23</sup>
  - 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 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 assumptions?
  - 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

---

<sup>22</sup> See Collins *et al.* (2009), Appendix B; See Generally Question 5.3 of EPA's Charge to the SAB (2010).

<sup>23</sup> See OMB Comments (2010), at p. 2.

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 also has an error in Table 5-2, in which the lagged, untrimmed coefficient is designated as statistically significant – it is not.<sup>24</sup>] The SAB should consider whether it is appropriate for EPA 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 a 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?<sup>25</sup>

In summary, the NAS 2006 review of the EPA Dioxin Reassessment was unequivocal in recommending a non-linear dose-response assessment for assessing TCDD cancer risks. NAS emphasized the scientific justification for a non-linear approach in numerous places in the report. NAS noted that, rather than being a scientifically-justified approach, the linear approach is a policy default and if the choice is made to rely upon this approach, then it should be part of risk management rather than risk assessment. We urge the SAB Panel to examine the preceding questions in light of the NAS Report and the voluminous recommendations made by that group of experts.

---

<sup>24</sup> See Cheng *et al.* (2006), Table III.

<sup>25</sup> See Question 5.4 of EPA’s Charge to the SAB (2010).

\* \* \*

Emhart appreciates the opportunity to submit these preliminary comments for the Panel's consideration at its July meeting. We will submit more comprehensive comments by the end of the public comment period.

## References

- Aylward, L. L., Brunet, R. C., Starr, T. B., Carrier, G., Delzell, E., Cheng, H., Beall, C., 2005. Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. *Risk Anal.* 25, 945-56.
- Baccarelli, A., Giacomini, S. M., Corbetta, C., Landi, M. T., Bonzini, M., Consonni, D., Grillo, P., Patterson, D. G., Pesatori, A. C., Bertazzi, P. A., 2008. Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. *PLoS Med.* 5, 1133-1142.
- Bell, D. R., Clode, S., Fan, M. Q., Fernandes, A., Foster, P. M., Jiang, T., Loizou, G., MacNicoll, A., Miller, B. G., Rose, M., Tran, L., White, S., Interpretation of studies on the developmental reproductive toxicology of 2,3,7,8-tetrachlorodibenzo-p-dioxin in male offspring. *Food Chem Toxicol.* 48, 1439-47.
- Cheng, H., Aylward, L., Beall, C., Starr, T. B., Brunet, R. C., Carrier, G., Delzell, E., 2006. TCDD exposure-response analysis and risk assessment. *Risk Anal.* 26, 1059-71.
- Collins, J. J., Bodner, K., Aylward, L. L., Wilken, M., Bodnar, C. M., 2009. Mortality rates among trichlorophenol workers with exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Am J Epidemiol.* 170, 501-6.
- Connor, K. T., Aylward, L. L., 2006. Human response to dioxin: aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. *J Toxicol Environ Health B Crit Rev.* 9, 147-71.
- Emond, C., Michalek, J. E., Birnbaum, L. S., DeVito, M. J., 2005. Comparison of the use of a physiologically based pharmacokinetic model and a classical pharmacokinetic model for dioxin exposure assessments. *Environ Health Perspect.* 113, 1666-8.
- Foster, W. G., Maharaj-Briceno, S., Cyr, D. G., Dioxin-induced changes in epididymal sperm count and spermatogenesis. *Environ Health Perspect.* 118, 458-64.
- Goodman, J. E., Kerper, L. E., Boyce, C. P., Prueitt, R. L., Rhomberg, L. R., 2010. Weight-of-evidence analysis of human exposures to dioxins and dioxin-like compounds and associations with thyroid hormone levels during early development. *Regul Toxicol Pharmacol.*
- Kerger, B. D., Leung, H. W., Scott, P., Paustenbach, D. J., Needham, L. L., Patterson, D. G., Jr., Gerthoux, P. M., Mocarelli, P., 2006. Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. *Environ Health Perspect.* 114, 1596-602.
- Leung, H. W., Kerger, B. D., Paustenbach, D. J., 2006. Elimination half-lives of selected polychlorinated dibenzodioxins and dibenzofurans in breast-fed human infants. *J Toxicol Environ Health A.* 69, 437-43.
- Milbrath, M. O., Wenger, Y., Chang, C. W., Emond, C., Garabrant, D., Gillespie, B. W., Jolliet, O., 2009. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function

- of age, body fat, smoking status, and breast-feeding. *Environ Health Perspect.* 117, 417-25.
- Mocarelli, P., Gerthoux, P. M., Patterson, D. G., Jr., Milani, S., Limonta, G., Bertona, M., Signorini, S., Tramacere, P., Colombo, L., Crespi, C., Brambilla, P., Sarto, C., Carreri, V., Sampson, E. J., Turner, W. E., Needham, L. L., 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. *Environ Health Perspect.* 116, 70-7.
- Patterson, D. G., Jr., Wong, L. Y., Turner, W. E., Caudill, S. P., Dipietro, E. S., McClure, P. C., Cash, T. P., Osterloh, J. D., Pirkle, J. L., Sampson, E. J., Needham, L. L., 2009. Levels in the U.S. population of those persistent organic pollutants (2003-2004) included in the Stockholm Convention or in other long range transboundary air pollution agreements. *Environ Sci Technol.* 43, 1211-8.
- Silkworth, J. B., Koganti, A., Illouz, K., Possolo, A., Zhao, M., Hamilton, S. B., 2005. Comparison of TCDD and PCB CYP1A induction sensitivities in fresh hepatocytes from human donors, sprague-dawley rats, and rhesus monkeys and HepG2 cells. *Toxicol Sci.* 87, 508-19.
- Simon, T., Aylward, L. L., Kirman, C. R., Rowlands, J. C., Budinsky, R. A., 2009. Estimates of cancer potency of 2,3,7,8-tetrachlorodibenzo(p)dioxin using linear and nonlinear dose-response modeling and toxicokinetics. *Toxicol Sci.* 112, 490-506.