OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Ethylene Oxide (EO) and draft IRIS Summary (dated July 2011)

Nov 2, 2011

In these comments, OMB focused on EPA's response to the external SAB peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary. Page numbers referred to in the tox review refer to the redline version (unless otherwise noted).

General Science Comments:

- Issue 1 Carcinogenic Hazard:
  1A: Qualitative Characterization of Epidemiology Data
  - In responding to reviewer comments, EPA notes, on page H-3, that they agree with the majority of the panel regarding the weight of evidence. As per recent interagency discussions, EPA should clearly articulate, using a scientific justification, why they agree with the majority of reviewers and why they do not agree with the minority opinion regarding using a "likely to be carcinogenic" description. Page 3-15 of the tox review describes the cancer guidelines criteria for a "carcinogenic to humans" listing; however, it does not discuss whether or not EPA is applying this criteria based on convincing epidemiological evidence or if there is a lesser weight of evidence strengthened by other lines of evidence, as described in the cancer guidelines. Based on the SAB report, the majority of panel members supported an approach that used the combined weight of evidence. The minority of panel members, did not think the combined weight of evidence was sufficient to support a "carcinogenic to humans' listing. In the tox review and Appendix H, EPA should clearly articulate the specific justification for the chosen descriptor.

  - In responding to SAB comments regarding the recommendation for a "clear articulation of the criteria by which epidemiological studies were judged", EPA has added some general language to page 3-1 of the tox review. This language mentions study design, exposure assessment and data analysis. However, it does not appear to describe the criteria at the level of detail the SAB panel recommended. Page 21 of the SAB report states: "While the advantages of the Steenland data set are described, the Draft Assessment contains no list of the criteria that were utilized to select studies for inclusion in the risk assessment process. For example, a description of what constituted adequate sample size, exposure assessment, minimum length of employment, length of follow-up, lag time for selected outcomes, etc., would be helpful. It is certainly appropriate to critique all available datasets and provide justification for excluding those who did not meet these criteria." As recommended by SAB, it would be helpful to have these specific criteria discussed for each study, perhaps in the revised table (A-4) that EPA has provided. SAB also recommended (at page 10 of the SAB report) that the tables provide information regarding cancer type within the broad category of lymphohematopoietic cancers. In looking at table A-4, we could not determine if this comment was addressed.

1B: Relevant Additional Key Studies

- Page H-4 acknowledges the SAB comments regarding the need for an expanded discussion on endogenous metabolic production. EPA states that the breadth and depth of the discussion has been expanded. However, in reviewing the toxicological review, there appears to be only a few paragraphs discussing endogenous production. There is some new language on page 3-23 through 3-24 and a mention on page 4-74. SAB stated on page 11 of their report "Because the levels of background 7-HEG are fairly substantial, and there are no chemical differences in DNA damage by endogenous versus exogenous EtO, the Draft Assessment requires a section considering the potential impact of endogenous versus exogenous EtO exposure that carefully lays out (i) why the current evidence of background levels of 2-hydroxyethylation of DNA does not constitute a threshold and (ii) whether the magnitude and variability in endogenous EtO-induced damage may overwhelm any contribution from exogenous EtO exposure (other than some acute high-dose exposure). Second, a more comprehensive discussion of the production of DNA adducts by EtO exposure would be appropriate." It was not clear that EPA has fully addressed the SAB concerns.

- On page H-4 EPA states "EPA agrees with the majority of the Panel that data on ethylene are not directly relevant and their contribution to the assessment of the carcinogenicity of EtO may be minor." We could not find any statements in the SAB report suggesting that the majority of panel members found that the data on ethylene were not directly relevant and would have only a minor contribution.

- SAB report at pages 13-15 lists a number of studies (34) that the reviewers considered relevant but not included in the draft. It would be helpful for EPA to describe how these studies were incorporated into the revised tox assessment, if they in fact have been incorporated.

- <u>Issue 2 Dose Response Analysis:</u>

2B: Methods of Analysis

- EPA acknowledges on page H-11, that "The Panel was unanimous in its recommendation that the EPA develop its risk models based on direct analysis of the individual exposure and cancer outcome data for the NIOSH cohort rather than the approach based on published grouped data that is presently used." SAB also referred to this as an 'important shortcoming'. On Page H-12, EPA states that additional extensive analyses were conducted but they 'proved problematic in one or more ways'. Thus EPA has retained the approach that was presented in the draft. Considering that this was identified as an important shortcoming, it would be helpful for EPA to go back to SAB, or a subset of the panel, to seek their input on the analyses EPA conducted and to see if, in light of these analyses, the SAB can now support the original approach. Without further external review of the new analyses it is hard to see how EPA can justify using an approach that was identified as being a major concern of the SAB panel.

- The SAB report, at page 24 states: "At the conclusion of its discussion, the Panel was not in agreement on the linearity vs. non-linearity of the cancer response to EtO exposure levels in: 1) the occupational exposure data used to estimate the point of departure for the low dose extrapolation; and 2) in the form of the model used to extrapolate cancer risk below the POD to a zero or baseline exposure level. With appropriate discussion of the statistical and biological uncertainties, several Panel members advocated the consideration of both linear and nonlinear functional forms in the final EtO Risk Assessment. These Panel members pointed out that such an approach was consistent with the latest guidance in the EPA Guidelines for Cancer Risk Assessment. Quoting Section 1.3 p. 1-9, "*Significant risk management decisions will often benefit from a more comprehensive assessment, including alternative risk models having significant biological support.*" The executive summary of the SAB report notes that the panel was divided, and does not refer to a majority or minority opinion. In light of the SAB recommendation, we recommend that EPA present a non-linear dose response assessment. EPA should also clarify why it believes non-linear modeling is "not warranted" (page H-19) in light of the SAB comments. It would appear to be more consistent with SAB recommendations to provide both analyses. This would also be consistent with the language the SAB refers to in the EPA Cancer Guidelines.

- Page H-15 states "As recommend by the Panel, the primary risk estimates are now based on the lymphoid cancers. Analysis based on total lymphohematopoietic (LH) cancers is also included for completeness and comparison." When we review the SAB report, we do not see an SAB recommendation to base the primary risk estimate on lymphoid cancers. SAB does state, at page 4, "The Panel recommends that data be analyzed by subtype of LH cancers (e.g. lymphoid, myeloid) and strong consideration be given to these more biologically justified groupings as primary disease endpoints." In addition, page 28 of the SAB report recommended that "data be analyzed by subtype of LH cancers with biological rationale for any groupings that are formed." We could not determine if EPA addressed this comment. It would be helpful to clarify how EPA responded to this concern and where in the assessment changes can be seen.

- Page H-16, EPA discusses and responds to the SAB concerns and recommendation that "discourages the use of the BEIR IV algorithm." EPA in their response noted that SAB provided no alternative approaches and that EPA has retained the application using the BEIR approach. Considering that this is not what SAB recommended, we suggest that EPA go back to SAB, or a subset of SAB, to seek specific comment and feedback on alternatives before finalizing an approach that SAB did not endorse.

- On page H-16 EPA states: "Lower bound confidence estimates on potency have not been developed for EPA IRIS assessments, and EPA decided not to seek to initiate development of such an approach in this assessment." This is not a compelling rationale for not following an SAB recommendation. The cancer guidelines (at page 1-9) clearly state: "To the extent practicable, such assessments should provide central estimates of potential risks in conjunction with lower and upper bounds (e.g.,

confidence limits) and a clear statement of the uncertainty associated with these estimates." At page 1-14 the Cancer Guidelines also note the SAB opinion on this stating "However, the consensus of the SAB (1997) was that, "both point estimates and statistical bounds can be useful in different circumstances, and recommended that the Agency routinely calculate and present the point estimate of the ED_{10} [or central estimate] and the corresponding upper and lower 95% statistical bounds."

- Page H-23, describes some of the new analyses that Professor Steenland has provided. In particular, EPA states "Working with Professor Steenland, alternative models based on direct analysis of all individual data using (1) linear relative risk models (Langholz, B., and Richardson, D.B., Am J Epidemiol 2010) and (2) two piece linear and log-linear spline models (e.g., Rothman et al. Modern Epidemiology, 3rd Edition, 2008) were developed and evaluated. In the final assessment, linear low dose risk estimates based on the two-piece linear spline model (using the Langholz-Richardson linear relative risk approach) were used for breast cancer incidence risk estimates." As these results are critical for the recommended unit risk value, has EPA considered having these new analyses peer reviewed before adopting them in a final IRIS file? We also note that it is not typical for EPA to rely on a two-piece linear spline model (which is not necessarily a biologically based model) and we question if this is consistent with the Cancer Guidelines recommendations. If this is a new modeling approach for an IRIS assessment, shouldn't its use for this purpose be peer reviewed first? Even if this information is in a journal, it is not clear that a new modeling approach would automatically be considered acceptable for IRIS use without further review.

- In certain cases, it is not clear how EPA addressed some important peer review comments in preparing Appendix H. It would be helpful if EPA addressed these comments. Two examples are provided below:
  - SAB report page 22: "The Panel did not believe that it was necessary to use only one study to arrive at a single potency estimate or to limit the assessment to a single modeling approach. Panel members emphasized that the EPA's own cancer risk assessment guidelines support the consideration of the full range of available data as well as alternatives to the default exposure models. Quoting from the EPA's Guidelines for Cancer Risk Assessment, Section 1.3, p. 1-8, *"[T]hese cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information".*"

  - Page 26-28 of the SAB report discusses the SAB concerns regarding the EPA exclusion of high exposure groups in the NIOSH cohort, noting that "the Agency's current analysis does not yet take into account some important differences between animal and human carcinogenic dose response data. These differences need to be factored in for designing a modern set of analytical procedures for human data to achieve more comparable types of risk inferences and a better analysis of uncertainties." Further details are provided by SAB in the report.

Specific Comments on Appendix A:

- Page H-5, line 2, it would be helpful for EPA to identify the specific sections of the document that contain the expanded discussion.
- Page H-5, line 16-18, it would be helpful for EPA to describe a few examples of the types of changes that have made to provide a more 'complete and balanced' discussion.
- Page H-16, line 29-31, EPA states that a central estimate has been provided. It would be helpful to clarify where in the toxicological review this information can be found. We see table 4-10 which provides upper bounds, but could not find a table showing similar central estimates. To be responsive to SAB concerns, such a table should be added.
- Page H 19-H26, it is unclear why these comments and responses are not provided in the section which addresses charge question 2B.