

# Comments of the EPA Science Advisory Board on the Draft Report: Ethylene Oxide

(October 2, 2007)

## 1. Dr. Rogene Henderson:

a. Does the draft report adequately address the original charge questions asked by EPA?

The charge questions were given in the form of three issues, with sub-charge questions under each issue. In the Executive Summary, the replies to charge questions on Issues 1 and 2 were given, but not for Issue 3. The responses to the charge question related to Issue 3 should be included in the Executive Summary.

It was not clear that there was a response to the charge question under Issue 3 in the text of the report. This appears to be a major omission or not clearly marked.

Otherwise the report did a good job of addressing the charge questions for Issues 1 and 2.

b. Is the report clear and logical?

There are some problems here.

1. For the clarity of the report, the Introduction should include a description of the organization of the report, including the topics discussed in the Appendices.
2. In the Introduction, the charge questions are listed and in parenthesis, by the name of each issue, section numbers and appendices are listed. No explanation is given for what these mean. Presumably the parenthetical information refers to where the issue is addressed. It is obvious what the Appendix numbers mean but I have no idea what the section numbers mean. For example, supposedly one might find the answers to charge questions regarding Issue #3 in Sections 3 and 4, but where are they? Under the answers to charge question 2b, there are paragraphs numbered 1 through 7. Are those sections????? This is confusing.
3. There was a major point of disagreement in the review panel which should be mentioned as a part of the Introduction. This could be done by including a description of the content of the appendices in the Introduction. For this compound, a major question is whether a linear or a nonlinear extrapolation to zero is appropriate for estimating risk at low doses. Ethylene is present normally in the human body and enzymes can oxidize it to ethylene oxide. Exogenous exposures are in addition to an endogenous baseline that is already there. How to handle this in risk assessments is a highly debated issue and the group did not agree on this question. The report does a good job of presenting the two views on page 32 and references the fact that the arguments on either side are given in more detail in Appendices A (Hattis) and C (Swenberg). The recommendation was for the Agency to consider both linear and nonlinear functional forms in the final risk assessment. I think this major point of disagreement deserves to be mentioned not only in the text, but clearly in the Introduction.

c. Are the conclusions and recommendations supported by information in the draft SAB report?

Yes I think the text of the document is clear as to the conclusions and recommendations and how they came to those results. This is particularly true for pages 32-42.

d. Are there technical errors or omissions in the report?

I was surprised to not see a reference to the recent IARC review (June, 2007) of ethylene oxide carcinogenicity. Perhaps it was too recent a report to be included.

**2. Dr. Jana Milford**

I have completed my review of the Ethylene Oxide report and find it very satisfactory. I liked the way this panel handled differences of opinion among the members, by identifying clearly the strength of opinion on each side and objectively laying out each perspective when they couldn't be reconciled.

**3. Dr. Valerie Thomas**

The report is very clearly written. It was a pleasure to read. I have no comments, and I think the report should be approved.

There are also several appendices attached to the report. These do not appear to be part of the panel report, and they don't appear to be minority reports or statements of disagreement from panel members. Although the material may indeed be useful to the EPA, I suggest that they not be included in the report, or that they be rewritten as material from the entire panel if that is what they are. I didn't review the appendices.

**4. Dr. Rebecca Parkin:**

Overall, I found:

- a) the original charge questions to the SAB Panel adequately addressed in the draft report;
- b) the draft report clear and logical; and
- c) the conclusions drawn and recommendations made supported effectively by information in the body of the draft report.

I have the following additional comments.

- a) In both the letter to the Administrator and the Executive Summary there is the statement that “epidemiological data ... were not in and of themselves sufficient to prove a causal association ....” While this is technically correct, it is crucial to recognize that epidemiological studies can never PROVE causation; they can only disprove a null hypothesis. It is inappropriate to criticize a methodology for what it is not intended or designed to do. Language in the body of the report is more appropriate and should be used in the letter and summary in place of any statement using “prove causation.”
- b) EPA’s Supplemental Guidance (EPA, 2005b) is cited numerous times, but I didn’t find it in the references. Other sources cited but not found in the references include: EPA, 2005 a on p. 27, line 36; Steenland et al, 2004 on p. 28, line 31; Griefe et al, 1988 and Steenland et al, 1987 on p. 29, line 34; and Greenberg et al, 1990 and Teta et al 1993 and 1999, all on p. 31, lines 9-11. Maybe I just didn’t find the right list of references; in my

opinion, the numerous locations for references made searching for sources unnecessarily complicated.

- c) Which version of the Hill criteria is the committee referring to on p. 18, line 30? Several versions were published and present different lists of criteria. The committee needs to insert a specific reference here.
- d) Minor edit: “lose” on p. 33, line 9 should be “low.”

## **5. Dr. Agnes Kane**

The toxicity and carcinogenicity of ethylene oxide are complex issues. As pointed out by the members of the Review Panel, the EPA draft oversimplified some of these issues and omitted key published papers.

- a) Review of the epidemiological evidence: The EPA draft concentrated on one study; however, multiple studies have been reviewed previously by Shore et al., 1993 and LaMontagne and Kelsey, 1998. The women in the NIOSH cohort most likely had lower exposures that resulted in their lower risk of NHL (LaMontagne and Kelsey, 1998). Since the epidemiologic evidence for carcinogenicity of ethylene oxide is mixed, the EPA draft should include a more complete discussion of biological mechanisms and evidence from other animal and human studies using intermediate biomarkers as endpoints (for example, Schulte et al., 1992; Mayer et al., 1991; Schulte et al., 1995). These papers also compare these biomarkers in ethylene oxide – exposed workers as well as controls and may provide insight about exposure to endogenous ethylene oxide which is a metabolite of ethylene.
- b) Ethylene oxide is a highly-reactive, flammable, and explosive chemical. Accidental release resulting in transient, high-level exposures should be a serious concern for EPA. Accidental exposures have been documented in hospital workers (LaMontagne and Kelsey, 1998). In the past, ethylene oxide was intentionally vented to the urban environment in Providence by industries involved in sterilizing hospital supplies (RI Department of Health, personal communication). The EPA draft should mention the potential for accidental and environmental exposures.
- c) The EPA draft focuses on carcinogenicity as an endpoint. However, ethylene oxide has multiple toxic effects on mucous membranes, skin, and the nervous system. It also crosses the testis and placental blood barriers and can cause adverse reproductive effects in males and females in both animals and humans. Ethylene oxide can also cause allergic sensitization in animals and humans leading to skin rashes, eosinophilia, and asthma (reviewed in LaMontagne and Kelsey, 1998).
- d) The target cell involved in ethylene oxide – induced leukemias and lymphomas has not been identified. In primates, a subpopulation of peripheral blood lymphocytes were shown to have elevated frequency of sister chromatid exchanges that persisted up to six years after exposures (Kelsey et al., 1988). This observation raises questions about the repair of ethylene oxide – induced DNA alkylation and DNA strand breaks in some hematopoietic cell populations. In the absence of a substantial research base on ethylene oxide – induced DNA damage and repair in potential target cell populations, it is premature to speculate about the shape of the dose-response curve at low doses or the possibility of a threshold dose level.

## 6. Dr. Kristin Shrader-Frechette

9-23-07 Comments by Kristin Shrader-Frechette on EPA Ethylene Oxide Peer Review

This peer-review document is superb.

Especially good is the peer-review's emphasis on using the full NIOSH data set to estimate the cancer-slope coefficients (p. 35), and on reconsidering the scientific justification for a men-only model for assessing the risk of lymphohematopoietic cancer (p. 40).

Two particularly important sections of the peer-review report, which reinforce the correctness of the original EPA conclusions, are the pp. 36-37 discussion of the strengths of animal, over human epidemiological, data, and the Appendix A (pp. 46-65) discussion of the flaws in presupposing hormetic effects and risk thresholds for ethylene oxide. These two superb discussions clarify why the majority of the panel is right to support the descriptor of "Carcinogenic to Humans."

One minor way of improving the report would be to ensure grammatical agreement in number throughout the report. Two of the many places where there is disagreement are on p. 9 ("EPA...their...") and p. 14 ("EPA's Office...their..." and "ORD...they..."). To catch all the instances of this grammatical error, it would be possible to do search commands for "their" and "they" throughout the document.

## 7. Dr. Meryl Karol:

This is an excellent review that addresses the EPA request. The Panel was successful in addressing Charge 3 in the context of the Charges 1 and 2. The response to Charge 2b is organized and presented very clearly and effectively.

### a) **Does the draft document address the charge questions?**

The Panel's decision to address the third charge in the context of Charges 1 and 2 is reasonable.

### b) **Is report clear and logical?**

The *Cover Letter* is written very clearly and carefully. It identifies when Panel members expressed differing viewpoints, and the rationale for each viewpoint, with one exception (paragraph #7 of the letter). The Panel's recommendation for low dose extrapolation of cancer risk is unclear.

*Summary*, Charge 1a. The final sentence in response to this charge is unclear (ie, "Subsequent recommendations in our report MAY address the apparent inconsistency"). The recommendations either do, or do not, address the inconsistency.

*Summary*, Charge 2a. The Summary is unclear as to whether the Panel considers the NIOSH cohort to be the best data set for cancer incidence as well as for cancer mortality.

"Unit risk estimate" should be defined (by words and by formula) either in the

*Summary or in the Introduction.*

*P. 28 lines 43-45, please clarify “cancer outcomes”. Is this more than cancer mortality?*

c) **Are conclusions and recommendations supported**

It is stated that the literature search for the EPA assessment was current through June 2004. It is helpful that the SAB document includes more recent citations. Perhaps the Albertini and Sweeney reference, currently 2006, in press, can be updated.

d) **Technical errors/omissions**

None

**8. Dr. Granger Morgan**

The report is clear and well written and is responsive to the charge questions.

To my reading the discussion of the diversity of opinion on whether to label ethylene oxide "carcinogenic to humans" or "likely to be carcinogenic to humans" point up again the problem of using qualitative language that is not tied to any quantitative probabilities. But, at least for the moment we seem to be stuck with this approach and under the circumstances the committee has handled things well.

The argument to work directly with the NIOSH data makes good sense.

I found the Appendices by Dale Hattis and James Swenberg to be interesting and to make a valuable contribution. I would like the letter to include a sentence that mentions them.