

FINAL MINUTES

MINUTES FROM THE EPA SCIENCE ADVISORY BOARD Ethylene Oxide Review Panel Public Meeting January 18-19, 2007

PURPOSE: The Ethylene Oxide Review Panel of the EPA Science Advisory Board (SAB) met on January 18-19, 2007. The purpose of this meeting was for panel members to deliberate on charge questions regarding the Agency's draft assessment entitled, *Evaluation of the Carcinogenicity of Ethylene Oxide*. There was an opportunity for panel members to ask questions regarding the assessment and to hear public commenters offering their opinions regarding the Agency's assessment. The SAB Ethylene Oxide Review Panel was asked to comment on the scientific soundness of this carcinogenicity assessment. Attachment A is the Federal Register notice announcing the meetings (71 FR 219, November 14, 2006). A meeting agenda is included as Attachment B.

LOCATION: Marriott at Metro Center 775 12th Street, NW, Washington, DC 20005

DATE AND TIME: January 18-19, 2007 from 9:00 AM – 4:00 PM Eastern Time.

PARTICIPANTS: The following individuals participated in this meeting: SAB Committee and Board Members - Drs. Stephen Roberts (Chair), Steven Belinsky, Timothy Buckley, Norman Drinkwater, Montserrat Fuentes, Dale Hattis, Steven Heeringa, James Kehrer, Ulrike Luderer, Mark Miller, Maria Morandi, A. Robert Schnatter, Ann Sweeney. James Klaunig was not able to attend. The Review Panel roster is included as Attachment C and a set of biographical sketches is included in Attachment D. SAB Staff - Dr. Sue Shallal, Designated Federal Officers (DFO); EPA Presenters – Henry Kahn, Jennifer Jinot, Paul White, David Bussard; Other Participants – Other EPA staff and members of the public listened in to the discussions. A sign-in sheet is attached (Attachment E).

MEETING SUMMARY: The meeting followed the agenda (Attachment B). A summary of the meeting follows.

Convene the Meeting and Introductory Remarks – Dr. Suhair Shallal, Designated Federal Officer (DFO), opened the meeting at 9:00 AM after allowing time for panel members to take their seats. She presented background information on the SAB panel formation process and informed the audience that the SAB operates under the rules and regulations of FACA where all meetings, during which discussions and deliberations take place, are held in public. She stated none of the panel members required waivers since there were no issues of a lack of impartiality or financial conflict of interest. She also reminded the members of the panel and the audience that the background materials including the charge questions (Attachments F) are located on tables in the lobby, as well as, the SAB website.

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Welcome - Dr. Roberts thanked the panel members for taking time from their busy schedules to devote to this review. He reviewed the agenda and explained the purpose of the meeting and then asked panel members to introduce themselves. He reminded panel members that he had assigned individuals as lead discussants for each of the charge questions. He stated that we will begin with presentations from the Agency and then panel members will be able to ask clarifying questions. This period will then be followed by several presentations from public commenters. The discussion of the charge questions would then ensue. Lead discussants would begin the discussion followed by an opportunity for other panel members to add further comments.

Presentations – Dr. Henry Kahn was unable to attend and Paul White of the EPA National Center for Environmental Assessment began the presentation with some of the background regarding the EtO assessment (Attachment G). He was followed by Jennifer Jinot who provided the details of how the Agency had conducted their analysis of the data. She further discussed the overall assessment and conclusions of the carcinogenic evaluation.

Panel members had the opportunity to ask clarifying questions through the presentation period and at the end of the entire presentation.

Panel members asked about the differences in the effects seen in males versus females. Panel members had questions regarding the use of models and the low dose extrapolation.

Mr. White then reviewed the charge questions and explained what the Agency was requesting of the Panel.

Dr. Roberts then introduced the public commenters. There were 9 individuals who had registered to present public oral comments. Dr. Shallal informed the participants that the oral comments would be made available on the SAB website.

Public comments

Public Comments were presented by Mr. Joe Hadley and followed by Mr. Bernie Leibler, Mr. William Gulledge, Dr. M. Jane Teta, Dr. Richard Albertini, Dr. Robert Sielken, Mr. Chris Kirman, Dr. William Snellings, and Mr. David Ludwig (Attachments H-P). After each presentation panel members had the opportunity to ask questions.

Questions regarding the actual exposure level of workers were addressed by Mr. Michael Shaw of Interscan Corporation and Mr. Steve Consiver of Honeywell Specialty Chemicals.

Dr. Roberts thanked all the commenters and adjourned for a one hour lunch break.

Discussion of the Charge

When the Panel reconvened after lunch, Dr. Roberts explained that several panel members were asked to respond to Charge Question 1 and 2. Charge Question 3 which focused on the issues of uncertainty would be addressed along with each of the first two questions. He told panel members that he would first ask those panelists that were assigned to the charge question to share

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their response and then others who may wish to add further comments would have the opportunity to do so.

He asked Dr. Drinkwater to start the discussion regarding Charge Question 1. He was then followed by other members assigned to address this question, Dr. Buckley and Dr. Walker. Other panel members also had an opportunity to make comments. The discussion focused on several issues, including:

The majority of panel members agreed with the Agency's conclusion of "strong but less than conclusive" epidemiologic data regarding the carcinogenicity of Ethylene Oxide. Panel members also agreed that the characterization of the risks associated with exposure to Ethylene Oxide should be better explained. Bringing the information contained in Appendix A of the Agency's assessment would be helpful.

Discussion of the use of the studies conducted on Ethylene then followed. Dr. Walker advocated for the inclusion of this data in the Agency's EtO assessment. Others did not agree citing the fact that EtO already has a large database and bringing in new data on a different compound would add to the complexity of the assessment instead of adding clarity.

Dr. Walker then added that the available data strongly support the action of EtO as a genotoxic agent producing DNA adducts as well as cytogenetic and mutagenic effects. However, there is little information on the sequence of events that are presumed to lead to EtO-induced clastogenic and mutagenic events. Dr. Swenberg agreed and cited a review paper written by Dr. Julian Preston.

Dr. Miller noted that there is no pre-requisite for having target organ concurrence between animal studies and human effects in order to conclude that a compound is a carcinogen. It was agreed that the key events leading to tumorigenesis were still undetermined. However, there was enough epidemiologic data available that leads to a conclusion of carcinogenic to humans. The caveats need to be captured in a narrative that states the data, while abundant is not strong.

The discussion of Question 2 then followed.

Dr. Hattis stated that he agreed with the EPA's conclusion that the epidemiological evidence alone was strong but less than completely conclusive and the use of epidemiological data, in particular the Steenland et al. (2003, 2004) data set, was the most appropriate for estimating the magnitude of the carcinogenic risk to humans from environmental EtO exposures.

Dr. Swenberg pointed to Dr. Teta's presentation and the Union Carbide (UC) data as additional data that could also be used in the analysis.

Dr. Heeringa noted that there were gender differences in the effects. He also stated that the data should only be separated if there is exposure model bias or biological rationale for the separation. The Union Carbide should be looked at as a second dataset and a comparison of the results from each analysis should be conducted. The limitation is the UC data only looks at males.

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The Steenland data is best; however the UC data can be used for an uncertainty analysis. The data may possibly be combined and a Bayesian analysis conducted.

The first day of deliberations ended and the meeting was adjourned until 8:30 AM the next morning.

Friday January 19, 2007

The meeting convened at approximately 8:30 AM.

The UC data studies were provided to the panel members. A discussion regarding how to best incorporate this data with the Steenland data occurred. It was noted that the raw data from the studies could be combined after the exposure information is re-estimated, however, exposure estimates may be difficult to do.

The best use of the UC data, concluded most panel members, was to inform the dose-response assessment by Steenland. Combining the data and doing a Bayesian analysis is difficult and should not be done added Dr. Fuentes. It may be possible to use the modeling methods from the UC studies for analyzing the Steenland data.

Question 2b

When analyzing the Steenland data Dr. Hattis suggested that excluding the high dose data should not be done. Saturation is not likely under the exposure conditions for humans as compared to those in the case of animal studies. A multi-phase model is preferable to a fixed model. Dr. Hattis stated that he agrees with the use of a quadratic model.

Others on the panel also commented that the full data set should be used. A discussion of the advantages and disadvantages of combining the lymphohematopoietic (LH) cancers ensued. Use of the World Health Organization categories (WHO) for LH cancer was suggested. It was also noted that such information may not be included in some of the older studies since the WHO classifications were not available in the 1970s or earlier.

A discussion of whether to aggregate or separate the male and female data also occurred. Some suggested that separating the data should only occur when there is a strong biological or mechanistic rationale. Others however noted that there are often differences in the male and female biological environment and pathways.

Dr. Heeringa suggested that modeling the data using a point of departure (POD) approach may be appropriate. Multiple models should be explored and the uncertainties associated with them should be discussed.

Some panel members objected to the separation of the male and female data, others however noted that this was standard practice for animal studies.

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The next subject discussed was low dose extrapolation. Panel members had differing opinions on whether there should be a linear or non-linear extrapolation. It was suggested that both linear and non-linear analyses be conducted with a discussion of the uncertainties associated with each.

Question 3 dealing with uncertainty was responded to within the responses for the other charge questions. The panel suggested a more balanced handling of the data and models. A sensitivity analysis should be conducted. Alternatives should be more fully explored and advantages and disadvantages of each should be discussed. There should be a better explanation of the uncertainties associated with models that were rejected. A more quantitative measure of the uncertainties should be presented.

The discussion of the charge questions concluded and panel members were asked to submit their revised responses by January 29, 2007.

Dr. Shallal reminded panel member to include her as a recipient on any correspondence with other panel members. All preliminary comments are to be sent to both Dr. Roberts and Dr. Shallal.

The meeting adjourned at approximately 4:00 PM.

Respectfully Submitted:

_____/s/_____
Dr. Suhair Shallal
Designated Federal Officer,
EPA SAB PFOA Review Panel

I certify that these minutes are accurate to the best of my knowledge:

_____/s/_____
Dr. Stephen Roberts
Chair,
EPA SAB EtO Review Panel

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All attachments available in hardcopy upon request

<u>Attachment A</u>	Federal Register notice (71 FR 219, November 14, 2006).
<u>Attachment B</u>	Meeting agenda- January 18-19, 2007
<u>Attachment C</u>	EtO Panel roster
<u>Attachment D</u>	Biographical sketches
<u>Attachment E</u>	List of participants
<u>Attachment F</u>	Charge Questions
<u>Attachment G</u>	powerpoint presentation by Henry Kahn and Jennifer Jinot
<u>Attachment H</u>	Oral presentations by Public Commenters