

**Summary Minutes of the
U.S. Environmental Protection Agency (EPA)
Chemical Assessment Advisory Committee (CAAC)
Augmented for the Ethylene Oxide (EtO) Review
Public Meeting
November 18-20, 2014**

Date and Time: Tuesday, November 18, 2014, 9:00 AM – 5:15 PM ET; Wednesday, November 19, 2014, 8:30 AM – 5:30 PM ET; Thursday, November 20, 2014, 8:30 AM – 12:30 PM ET.

Location: Hyatt Regency Crystal City Hotel, 2799 Jefferson David Highway, Arlington, VA 22202

Purpose: To peer review the EPA's *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014)*¹

Participants: Augmented CAAC for EtO

Dr. Peter S. Thorne, Chair (for full Augmented CAAC for EtO, see roster²)

Dr. Henry Anderson

Dr. James Bruckner

Dr. William Michael Foster

Dr. Gary Ginsberg

Dr. Steve Herringa

Dr. Peter Infante

Dr. Lawrence Lash

Dr. Maria Morandi

Dr. Victoria Persky

Dr. Kenneth Ramos

Dr. Stephen Roberts

Dr. Elizabeth (Lianne) Sheppard

Dr. Daniel Zelterman

Mr. Aaron Yeow, Designated Federal Office (DFO), EPA SAB Staff Office

Mr. Christopher Zarba, EPA SAB Staff Office

Mr. Thomas Brennan, EPA SAB Staff Office

Dr. Vincent Cogliano, EPA, Office of Research and Development (ORD)

Ms. Jennifer Jinot, EPA, ORD

Other Attendees (See Attachment A)

Tuesday, November 18, 2014

Opening Remarks

Mr. Aaron Yeow, DFO, opened the meeting. He noted that as required under the Federal Advisory Committee Act (FACA), the SAB's deliberations are held in public with advanced notice given in the

Federal Register, and the meeting minutes will be made publicly available after the meeting. He noted that there were ten members of the public who registered in advance with the SAB Staff Office to present oral comments. He noted that the Augmented CAAC for EtO received written public comments, which were also posted on the meeting webpage. He stated that the SAB Staff Office determined that there were no issues with conflict-of-interest nor any issues with an appearance of a lack of impartiality for any of the Augmented CAAC for EtO members. He then turned it over to Mr. Christopher Zarba, Director of the SAB Staff Office. Mr. Zarba welcomed everyone and thanked them for their service. He noted the importance of the Augmented CAAC's role in reviewing the Agency's document. He then turned the meeting over to Dr. Peter S. Thorne, Chair of the Augmented CAAC for EtO. Dr. Thorne welcomed everyone, had the Augmented CAAC for EtO members introduce themselves, and provided an overview of the Agenda.³

EPA Presentations

Dr. Vincent Cogliano, Acting IRIS Program Director of EPA's National Center Environmental Assessment (NCEA), provided welcoming remarks, noting that the assessment was reviewed by the SAB in 2007 and revised based on the SAB's advice. He stated that because this assessment was already underway when the National Research Council (NRC) made recommendations for the IRIS process, it does not fully incorporate all of the NRC recommendations. However, many of the short-term recommendations have been incorporated.

Ms. Jennifer Jinot, Assessment Manager in NCEA, provided an overview of the Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. Her presentation⁴ covered background information from the September presentation, the hazard characterization conclusion, the mode of action (MOA) conclusion, and the modeling of the exposure-response data from the NIOSH epidemiology study.

Public Comments

Registered public speakers made oral statements in the order provided in the List of Public Speakers.⁵

Mr. Dave Ludwig, Balchem Corporation, presented his oral statement,⁶ which emphasized the importance of EtO for sterilizing medical equipment, that the IRIS draft overstates the potential risks of EtO, that the conclusions in the draft IRIS assessment are erroneous, and if the values in the draft assessment are not revised to reflect the available science and data, many Americans will face significant adverse public health consequences.

Mr. Bill Gullledge, American Chemistry Council (ACC), stated that ACC has an EtO panel composed of manufacturers of EtO and major users of EtO. One of the major uses of EtO is as a chemical intermediary in the manufacture of ethylene glycol. One of the smaller users of EtO is as a sterilizing agent. He indicated that the next six speakers were speaking on behalf of the American Chemistry Council.

Dr. Jane Teta, Exponent, presented her oral statement,⁷ which focused on uncertainties in the NIOSH exposure assessment, the value of using the Union Carbide data to increase the study power for males, the potential selection bias in the breast cancer study was not adequately considered, and inconsistencies in the breast cancer study exposure-response trends were not adequately addressed. She recommended that the IRIS assessment incorporate the Union Carbide data and consider dropping breast cancer as a target endpoint.

Dr. Richard Irons, Cinpathogen, presented his oral statement,⁸ first pointing out that his correct affiliation is Fudan University. His statement focused on charge question 3 and the lymphoid cancer model. He indicated that the consensus evidence-based medicine does not support grouping all lymphohematopoietic or all lymphoid cancers in a single category and recommended evaluation of each hematopoietic and lymphoid cancer separately, rather than combining them.

Dr. Richard Albertini, Genetic Toxicology Consultants, presented his oral statement,⁹ which focused on outlining the rationale for considering, in addition to the default non-threshold extrapolation now employed, a non-linear extrapolation for determining the cancer risk for EtO.

Dr. Robert Sielken, Sielken & Associates Consulting, presented his oral statement,¹⁰ which focused on charge questions 2 and 3, EPA's approach to exposure-response modeling, especially model evaluation and selection. He referred to his written comments,¹¹ which develop several points including: despite the 2007 SAB recommendation for EPA to model individual data, the EPA is still modeling categorical data; NIOSH's breast cancer data is not publicly available and therefore cannot be verified; the NIOSH cancer exposure-response data for breast and lymphoid cancers are not supralinear and only show up when using four categorical rate ratios; the method of evaluating different models is not correct; the best exposure-response model for all endpoints is a continuous log-linear Cox proportional hazards model based on cumulative exposure (not log cumulative exposure) and fit to the individual data. There was some discussion between the members and Dr. Sielken regarding pre-1978 data.

Dr. Chris Kirman, Summit Toxicology, presented his oral statement,¹² which focused on Charge Question 5 - Transparency and Charge Question 7 - EPA's response to previous comments. He stated that ten decisions are embedded in the EtO unit risk calculation and they are not transparent. Regarding risk comparisons, he concluded that the potency estimate is not consistent with the relative toxic and mutagenic potencies.

Dr. William Snellings, Snellings Toxicology Consulting, presented his oral statement,¹³ which focused on summarizing the key points the previous five speakers made on behalf of ACC. He stated that EtO is a weak rodent carcinogen, weak mutagen, and outcomes from plausibility checks are not reasonable.

Dr. Nancy Beck, American Chemistry Council, referred to her written comments,¹⁴ and highlighted three main points: thanking Dr. Thorne for confirming on the September teleconference that all the public comments and recommendations on the charge questions would be considered; highlighting the SAB initiatives to improve public engagement with all stakeholders; and recommending that the Augmented CAAC not to be concerned with how difficult it would be for the Agency to implement its recommendations.

Ms Kathleen Hoffman, Sterigenics, presented her oral statement,¹⁵ which focused on the EtO sterilization industry, the EtO sterilization customers, and potential impacts to public health. She indicated that Sterigenics has significant concerns regarding the cancer risk estimates and the draft IRIS assessment as a whole.

Review of Charge Questions and Discussion of Response to Charge Questions

After the lunch break, Dr. Thorne reviewed the charge questions and the Augmented CAAC proceeded with their discussion of the response to the charge questions.

For Charge Question 1 – Exposure Lagging, the members generally found that there was little statistical evidence to choose one lag period over another. They stated that the choice of a lag period should be based on biological considerations as opposed to statistical considerations and that it would be helpful to have unit risk estimates for a range of lag periods to understand how sensitive the estimates are to the choice of lag periods.

For Charge Question 2 – Breast Cancer Incidence – Model selection, the members had discussion about the use of the two-piece spline model. There was discussion on challenges of models fitting data, model selection, local versus global fit, and responsiveness of the document to the previous SAB review. There was discussion about the appropriate use of Akaike information criterion (AIC).

For Charge Question 3 – Lymphoid Cancer – Model selection, the members recommended that the EPA provide better justification and rationale for their model selection. There was discussion about the use of categorical data versus individual data. There was also the recommendation that unit risk estimates for the other models should be presented. There was some discussion on animal studies, potency, and dose-response.

The Augmented CAAC was ahead of schedule and decided to begin discussing the response to Charge Question 4 – Uncertainty in Cancer Estimates. There was discussion of documenting uncertainty that could be quantified, presenting unit risk estimates for all the reasonable models, and increasing the number of categories.

The Augmented CAAC recessed for the day.

Wednesday, November 19, 2014

Discussion of Response to Charge Questions (cont'd.)

The Augmented CAAC reconvened and began with some clarification and further discussion of the appropriate use of AIC.

For the discussion of the response to Charge Question 5a – Genotoxicity, members found that the document appropriately captured the recent literature on genotoxicity, particularly for mutagenic mechanisms. They agreed that the weight of the evidence supports the conclusion that the carcinogenicity of EtO is mediated through a mutagenic mode of action (MOA). They noted several areas where the assessment could be improved to enhance the clarity of presentation and to provide a more detailed interpretation of findings within the context of recent advances in the understanding of the biology of cancer.

For Charge Question 5b – Appendix H, the members found that the Agency did a good job responding to the 2007 SAB comments. An overview of the 2007 SAB review was provided, particularly the viewpoints of the 2007 SAB panel members regarding linear versus non-linear extrapolation. The Augmented CAAC members discussed the availability of the NIOSH cohort data, appropriate use of the Union Carbide data, and linear versus non-linear modeling approaches.

The members discussed the new studies in Appendix J of the assessment in response to Charge Question 6. The studies were discussed in detail, including their strengths and weaknesses. The members found that the EPA generally did a good job in discussing the new studies, but that the Swedish sterilization

worker study should be highlighted more because it has high quality exposure assessment data and supports the importance of the low-dose relationship.

For Charge Question 7 – EPA Response to Public Comments, the members found that the EPA was very responsive to public comments. They went through the summary of the public comments and EPA responses presented in Appendix L. They found that the responses were thorough, clear, and appropriate.

Opportunity for Brief Clarifying Comments

Dr. Cogliano, EPA, asked the members to give thought to the wording of the recommendations and to strive for consensus. He asked that they distinguish between strong recommendations versus advice for consideration.

Dr. Jane Teta, Exponent, stated that the data used for the first UCC study was collected by NIOSH. She agreed that the Mikoczy study has a great exposure assessment, but had low breast cancer rates and did not have a strong dose-response, as indicated in her presentation.¹⁶ She also discussed breast cancer standard mortality rates by cumulative exposure for the Steenland study.

Dr. Richard Albertini, Genetic Toxicology Consultants, provided clarifying remarks that focused on mode of action and genotoxicity.

Dr. William Snellings, Snellings Toxicology Consulting, made a presentation¹⁷ which focused on tumor incidence in a rat study of EtO exposure.

Dr. Robert Sielken, Sielken & Associates Consulting, presented clarifying remarks,¹⁸ which focused on supralinearity, lymphoid cancer mortality, breast cancer mortality, and risk assessment and excess risk characterization.

Mr. Dave Ludwig, Balchem Corporation, stated that if the assessment went forward as is, 95% of surgeries would not happen because the medical devices could not be sterilized by EtO. He stated that there are no alternatives to EtO for medical device sterilization.

Discussion of Response to Charge Questions (cont'd.)

The Augmented CAAC had further discussion on the responses to charge questions, focusing on lag periods, minimum latency periods, the two-piece spline model, dose metrics, and modeling continuous exposure data versus categorical data.

The Augmented CAAC recessed for the day.

Thursday, November 20, 2014

The Augmented CAAC reconvened and began their writing session in subgroups.

Summary of Major Findings and Recommendations

The Augmented CAAC members reported out the summary of their major findings and recommendations.¹⁹

Summary and Next Steps

Dr. Thorne and Mr. Yeow discussed the next steps in drafting the report and scheduling a follow-up teleconference.

The meeting was adjourned by Mr. Yeow at 12:05 pm.

Respectfully Submitted:

Certified as Accurate:

/SIGNED/

/SIGNED/

Mr. Aaron Yeow
Designated Federal Officer
EPA SAB Staff Office

Dr. Peter S. Thorne
Chair
Chemical Assessment Advisory Committee
Augmented for the Ethylene Oxide Review

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Panel members during the course of deliberations within the meeting. Such ideas, suggestions and deliberations do not necessarily reflect consensus advice from the Panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters or reports prepared and transmitted to the EPA Administrator following the public meetings.

Materials Cited

The following meeting materials are available on the SAB website: <http://www.epa.gov/sab>, at the [November 18-20, 2014 SAB Meeting page](#):

¹ Agency Review Document – *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft – August 2014)*

² Roster

³ Agenda

⁴ EPA Presentation – Overview of the Draft Carcinogenicity Assessment of Ethylene Oxide

⁵ List of Public Speakers

⁶ Presentation by Mr. Dave Ludwig, Balchem Corporation

⁷ Presentation by Dr. Jane Teta, Exponent-2

⁸ Presentation by Dr. Richard Irons, Cinpathogen

⁹ Presentation by Dr. Richard Albertini, Genetic Toxicology Consultants, LLC

¹⁰ Presentation by Dr. Robert Sielken, Sielken & Associates Consulting, Inc. – Updated Slides

¹¹ Comments from Dr. Robert Sielken, Sielken & Associates Consulting, Inc.

¹² Presentation by Dr. Chris Kirman, Summit Toxicology

¹³ Presentation by Dr. William Snellings, Snellings Toxicology Consulting

¹⁴ Comments from the American Chemistry Council

¹⁵ Presentation by Ms. Kathleen Hoffman, Sterigenics

¹⁶ Presentation by Dr. Jane Teta, Exponent – 11/19/14 Clarifying Comments

¹⁷ Presentation by Dr. William Snellings, Snellings Toxicology Consulting - 11/19/14 Clarifying Comments

¹⁸ Presentation by Dr. Robert Sielken, Sielken & Associates Consulting, Inc. - 11/19/14 Clarifying Comments

¹⁹ Compilation of Slides the Augmented CAAC for EtO Discussed in Developing Responses to the Charge Questions November 20, 2014

**ATTACHMENT A – Other Attendees
CAAC EtO Public Meeting**

Name	Affiliation	11/18/14	11/19/14	11/20/14
Albertini, Richard	University of Vermont	x	x	x
Bartow, Susan	USEPA	x	x	x
Beck, Nancy	American Chemistry Council	x		
Berner, Ted	USEPA	x	x	
Brennan, Tom	USEPA		x	
Britton, Cathryn	USEPA	x		
Bussard, David	USEPA	x		
Carpenter, Thomas	USEPA	x		
Cashin, Joanne*	Balchem	x	x	x
Choi, Haylee*	RegNet Environmental Services	x	x	x
Deneux, Christopher	Becton Dickenson	x	x	
Fensterheim, Bob*	RegNet Environmental Services	x	x	x
Flowers, Lynn	USEPA	x		
Gulledge, Bill	American Chemistry Council	x	x	x
Guz, Jackie	USEPA	x	x	x
Gwinn, Maureen	USEPA	x		
Hegstad, Maria	Inside EPA	x		x
Hoffman, Kathleen	Sterigenics	x	x	
Hsu, John	Raymond James			x
Irons, Richard	University of Colorado	x		x
Jones, Samantha	USEPA	x		
Kent, Ray	USEPA	x		
Kirman, Chris	Summit Toxicology	x	x	x
Koch, Kristen	USEPA		x	x
Ludwig, David	Balchem	x	x	x
Maguire, Megan*	USEPA	x	x	x
Miller, David	USEPA	x		x
Morris, John	Louisiana Tech University			x
Nguyen, James	USEPA	x	x	x
Olsen, Geary	3M	x	x	x
Plunkett, Laura	Integrative Biostrategies	x	x	x
Putzrath, Resha*	Navy and Marine Corps Public Health Center	x	x	x
Reed, Konner*	Northcoast Research	x	x	x
Reitman, Fred	Shell	x		x
Rizzuto, Pat	Bloomberg BNA	x		x
Ross, Christine*	USEPA	x	x	x
Sarkar, Bayazid	USEPA	x	x	x
Shallal, Sue	USEPA	x	x	x
Shams, Dahnish	USEPA	x		
Sielken, R. L. Jr.	Sielken and Associates	x	x	x

Snellings, William	American Chemistry Council	x	x	
Strother, Dale*	ToxSolve LLC	x	x	x
Subramaniam, Ravi	USEPA	x	x	x
Teta, Jane	Exponent	x	x	x
Timmerman, Chris	Boston Scientific Corporation	x		
Vandevort, Jake	Ethylene Oxide Sterilization Association	x		x
Wong, Diana	USEPA	x	x	x

* participated by teleconference