



June 8, 2015

Comments submitted to the Chartered SAB via email to Thomas Carpenter

Public statement from Bill Gullledge on behalf of the American Chemistry Council's Ethylene Oxide Panel to the Chartered Science Advisory Board regarding the Chemical Assessment Advisory Committee (CAAC) review of the Draft Ethylene Oxide (EO) IRIS Assessment.

Good Afternoon.

I am providing remarks today on behalf of the American Chemistry Council's Ethylene Oxide Panel (Panel). We have closely followed the CAAC review of the EO assessment and are pleased to have an opportunity to present these brief comments. The Panel previously commented on the 2013 draft IRIS assessment and provided comments at the November 2014 CAAC meeting.¹ These comments, including a summary of the Panel's technical comments on the 2013 IRIS draft, are available on the CAAC meeting webpage. We encourage the SAB members to review all of the public comments submitted for the CAAC review. Our understanding is that your role now is to comment on the quality of the report and determine whether it should be approved, returned for further work, rejected, or reconstituted in a completely new Panel.

After reviewing the CAAC draft report on the EO IRIS assessment and the 2013 draft of the assessment, it is clear that the CAAC has made many substantive and important recommendations to the EPA. While there was not significant discussion of the public comments during the CAAC review, the extensive public comments should be very helpful to EPA while addressing the CAAC concerns. Examples of major additions or revisions the CAAC recommends include:

- Addressing the existence and length of a latency period for breast and lymphoid cancers that includes a quantitative sensitivity analysis. Dr. Robert Sielken presented extensive comments on the impact of different latency periods in his comments on the 2013 IRIS draft and addressed this issue in his presentation during the November 2014 CAAC meeting. Dr. Chris Kirman et al discuss nine major uncertainty factors impacting the

¹<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/D7BBEC7186A4795785257D2300680D61?OpenDocument>

EPA's modeling of lymphoid cancer for workers exposed to EO in their 2015 presentation at the SOT Annual Meeting.²

- Providing more extensive documentation for the selection of the two-piece spline model for estimating breast cancer incidence. The use of alternative modeling approaches is provided in Dr. Kirman's and Dr. Sielken's comments on this issue.
- Conducting additional sensitivity analysis around regression models in the low exposure range that includes clarification of unit risks and excess risks.
- Articulating criteria for model selection. "Discarding a model because the fitted curve is too steep" and not providing justification for that decision is clearly inappropriate. Biologic plausibility should also be factored into model selection. Drs. Albertini and Irons addressed this issue in their comments on the IRIS assessment.
- Establishing regression models based on individual-level exposure data as the preferred approach. EPA should obtain and use available individual-level exposure data from all of the epidemiology data bases and consider a weight of evidence approach. The blinded, individual exposure data should be available to all reviewers of the IRIS draft.
- Discontinuing the use of categorical results to estimate lymphoid cancer and instead using individual level exposure data. As an alternative, the SAB is recommending the use of narrower exposure categories and/or category medians rather than means. Dr. Sielken also addressed this issue in his comments on the IRIS draft.
- Adding the Swedish sterilization workers study (Mikoczy et al, 2011) to the discussion of breast cancer. In a separate written statement, Dr. Gary Marsh, a biostatistician at the University of Pittsburgh Graduate School of Public Health, addresses the limitations of the Mikoczy study. Dr. Marsh concludes that the data in the Mikoczy study do not support a conclusion of a positive exposure/response relationship with EO and breast cancer. Dr. Jane Teta provided a similar conclusion in her comments to the CAAC on the study.
- Clarifying the discussion on mutagenic mode of action "within the context of more recent advances in the understanding of the biology of cancer". The information provided by Drs. Albertini and Irons on genotoxic mechanisms for EO and evidence-based medicine should be strongly considered in revising this section of the document.

All of the above extensive revisions together with other recommendations not mentioned in these comments due to time constraints, point towards the usefulness of a recommendation from the SAB on the need to ensure that the new analyses benefit from appropriate levels of public comment and peer review. The EO IRIS revision that comes from this SAB review should be released for public comment.

Thank you again for the time you have put into reviewing the CAAC report. I would be happy to answer any questions.

² Improving Transparency and Prioritization of Data Needs in Hazard Value Development; Chris Kirman, George Gray, Bette Meek; SOT 2015. <http://blog.americanchemistry.com/2015/04/what-you-may-have-missed-at-sot-how-show-and-tell-can-lead-to-a-greater-understanding-of-chemical-assessment-results/>