June 3, 2015

Comments submitted to the Chartered SAB via email to Thomas Carpenter

Public statement from Nancy Beck, PhD, DABT, on behalf of the American Chemistry Council, 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 (ACC). We have closely followed the CAAC review of the EO assessment and are pleased to have an opportunity to present brief comments to inform your review. Our understanding is that your role is to comment on the quality of the CAAC report and determine whether it should be approved, returned for further work, rejected, or reconstituted in a completely new Panel.

Although the CAAC panel found the agency to be "highly responsive" to the 2007 SAB recommendations, much more work remains to be done by the IRIS program before the EO assessment can be completed. For instance sensitivity analyses are needed, a new approach to linear modeling is suggested (using individual data over categorical), the uncertainty discussion needs improvement and extension, and the clarity and interpretation of findings relating to genotoxicity need revision as per the many detailed suggestions. In light of these recommendations, it would be helpful for the SAB to ensure that EPA does not make these new analyses simply a "box-check" exercise but instead uses this work to ensure that the overall findings and quantitative values make sense, are plausible and realistic. A recommendation from the SAB on this aspect, and on the need for new analyses to benefit from appropriate levels of public comment and peer review, would be helpful.

I would like to raise two particular areas where the CAAC report could be improved.

1) **The rationale for supporting only linear extrapolation should be further clarified and expanded.** The report notes, at page 4 "The SAB finds that the empirical data on EtO and EtO's MOA are consistent with a linear low-dose extrapolation and the database does not provide the type of evidence that the Cancer Guidelines would find sufficient to support a nonlinear MOA, which precludes the need for the presentation of nonlinear modeling approaches." No further elaboration is provided in the CAAC report. The EPA Cancer

Guidelines state, at page 3-23, "Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework." The EPA Cancer Guidelines do not require understanding of the full mode of action, yet the type of information the CAAC believes is missing to support nonlinear modeling is not clear.

In 2007, the SAB suggested that both linear and nonlinear modeling be presented.[1] Despite a lack of panel consensus in this area, the 2007 SAB report provided significant scientific details supporting a nonlinear mode of action. As these data still exist today, even more information on genotoxicity was presented to the panel in 2014 by Dr. Albertini, and in light of the 2007 report, the current CAAC report should provide a scientific argument why nonlinear modeling should not be presented. Unfortunately, the current report falls short and instead of discussing the EO science, it vaguely cites the guidance (which is non-binding), without providing any further scientific elaboration.

In addition, for the report to be useful in resolving stakeholder concerns, the CAAC should discuss what information they believe is missing to support a nonlinear approach. Without further elaboration, major uncertainties will remain regarding the presentation of only the linear cancer modeling approach and public confidence in the IRIS assessment will be diminished.

ACC concurs with the 2007 SAB report that the data support, at a minimum, the presentation of a nonlinear approach in addition to the linear approach. If the CAAC disagrees, the final report should clearly explain why.

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[1] See 2007 SAB Report available at: http://yosemite.epa.gov/sab%5Csabproduct.nsf/5D661BC118B527A3852573B80068C97B/$File/EPA-SAB-08-004-unsigned.pdf. Discussion of interest begins on page 23 where the report states: "The Non-linear Low Dose Response Model Argument: Linear extrapolation of risk below the chosen point of departure (POD) to a zero baseline is a conservative assumption, given EtO's reactivity (which will diminish the amount reaching the nucleus), mutagenic mode of action, and that it is generated endogenously. Some repair seems likely and some threshold probably exists. Thus, the human risk estimates at the lower end of the observable range are likely to be exaggerated under a linear extrapolation. Furthermore, a linear model through zero (linear model per se at low doses is acceptable) assumes that other effects of EtO on the development of cancer are insignificant. This seems unlikely given the reactive nature of this compound and thus its ability to affect signaling pathways that may positively and negatively influence the development of cancer. Measuring such effects is problematic, but they must exist and impact the incidence of cancer. Linear regression is for "extra" risk; but this still seems problematic given the endogenous level of EtO and base levels of damage and repair. In other words, is it justified to assume linear above baseline levels? At low doses, a reactive compound like EtO will react with cellular constituents before it ever gets to DNA. Linear defaults are not supported when a framework analysis is done of genotoxicity and this is even more strongly so for clastogenic agents, which are quadratic in dose response (Preston, 1999). Swenberg (2007, Appendix C) provides a framework analysis of Genotoxicity and Risk Assessment in support of an argument for a nonlinear low dose response mechanism for EtO."

2) **The CAAC reasoning for concurring with EPA's decision to not use the Union Carbide Corporation (UCC) data for the unit risk derivation needs further elaboration.** Page 34 of the report provides the CAAC reasoning for rejecting the UCC data: "The EPA response is concise and clear. This issue is discussed in detail in the draft assessment and was supported by the SAB (2007) report. The NIOSH study meets the criteria of being a high-quality study much more strongly than the UCC data. This response is well-supported and appropriate. The SAB concurs with the EPA decision to not combine UCC EtO exposure data with those from the NIOSH study." No other rationale is provided.

   The use of the NIOSH cohort over the UCC data is a very important issue and one that stakeholders asked (at the very first teleconference) be addressed directly by the CAAC. While the chair stated that all the recommended charge questions would be addressed, it appears that this one has been given very short shrift. This is particularly troubling since the CAAC panel noted significant concerns about the NIOSH individual data being unavailable for analysis, while the UCC data are fully available. At the public meetings, despite repeated public comments, there was never any significant discussion of using the UCC study by the CAAC.[2] In response to public concerns, to help respond to question 7 of their charge, and in light of the significant shortcomings in the availability of the NIOSH dataset, the CAAC panel should review the UCC study and provide detailed scientific comments on the use of the study, rather than simply deferring to the previous EPA interpretation.

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

[2] We note that the most substantive comment was from one CAAC member who suggested that the UCC study should not be used because it was industry funded. This approach is not consistent with judging science on its merits.