February 20, 2015

Comments submitted to the SAB CAAC via email to Aaron Yeow

Public statement from Bill Gulledge, on behalf of the American Chemistry Council's Ethylene Oxide Panel, to the Scientific Advisory Board Chemical Assessment Advisory Committee (CAAC) for the review of the Draft IRIS Ethylene Oxide (EO) Assessment.

Good Afternoon.

I am providing remarks today on behalf of the American Chemistry Council's Ethylene Oxide Panel (Panel). The Panel and its experts reviewed the draft report on the IRIS Ethylene Oxide Assessment and we recognize the time and effort that has been put into conducting this review.

There are many recommendations in the draft report but due to the time constraints I will not address them all. Here are the key points.

1) **Clarifying the Cover Letter and Executive Summary**. While the report covers many topics in depth, the cover letter and executive summary mention only a few of the report's findings and, appropriately, the depth of discussion is much more limited. Since not every topic area from the charge is addressed, it is unclear why certain topics are the focus of the cover letter and executive summary and others are not mentioned. It may be helpful to clarify which recommendations are most important to the CAAC. For example, the cover letter categorically rejects the use of the Union Carbide Corporation (UCC) cohort data, while the executive summary and the body of the report recommend that the UCC data and the Swedish cohort be included to corroborate or distinguish from the NIOSH data. A thorough review of how the cover letter and executive summary relate to the full final report may be helpful.

2) **Use of the Swedish Cohort (Mikoczy, 2011).** Adding the use of the Mikoczy study while excluding the UCC data and other data provides a bias in the study selection. If the Swedish data are added to the review, then the Swan (2009) and the UCC data should also be added. The CAAC should clearly document the criteria they are using to judge certain studies acceptable and other studies unacceptable. Acceptance of the study should not be judged solely by the results of the study. As EPA's Science Advisor, Dr. Thomas Burke has stated[1]: "EPA should consider all relevant well-conducted and peer-reviewed studies, regardless of whether they are positive or negative, and include clear criteria for inclusion and exclusion of

[1] See Thomas Burkes Questions for the Record from the December 17, 2013 Hearing in front of the Committee on Environment and Public Works, US Senate.

studies." We recommend that the CAAC clarify their own criteria and then use these clear criteria to benchmark each study. This will make the CAAC report far more objective and useful to EPA. While not discussed in the draft CAAC report, one or two CAAC members, during the November meeting, suggested that data should not be considered if it were funded by industry. As Dr. Ramos, a CAAC member, and former Society of Toxicology (SOT) President, can explain, the SOT states that "Research should be judged on the basis of scientific merit, without regard for the funding source or where the studies are conducted (e.g., academia, government, or industry)."[2] The Panel believes that EPA concurs with Dr. Ramos's view, but that bias against industry data was clearly expressed by one or more CAAC members during the November meeting. Presenting clear criteria and benchmarking each study against these criteria will go a long way towards ensuring the objectivity of the CAAC's s report and the thought processes behind its recommendations.

The Panel recently submitted a review of the Mikoczy study to the CAAC.[3] The review notes that several CAAC members attributed the different results between the external and internal analyses to the "healthy worker effect" (HWE). Extreme differences in the results of external and internal statistical analyses indicate that confounding but not the HWE occurred in the Mikoczy study. The Panel recommends that a new, independent review be conducted of the Mikoczy data and conclusions.

3) **Uncertainties in the NIOSH Data.** Obtaining the NIOSH data and detailing the exposure data uncertainty was a key issue mentioned by several CAAC members during the November 2014 meeting. However, the uncertainty issue is not mentioned as a major point in the cover letter or executive summary. The Panel recommends that the uncertainties in the NIOSH data be outlined in the cover letter, summarized in the executive summary, and detailed in the body of the report. Similarly, the CAAC recommended that continuous individual-level exposure data be used over categorical results. The Panel concurs with this recommendation.

4) **Impact of the Dose Response Curve.** What is the reasonableness in the steep slope of the dose response curve in the low dose range? Significant discussion of this issue occurred during the November meeting, yet the issue remains. The Panel provided extensive comments on this issue in advance of the November 2014 meeting, and the CAAC should recommend that EPA use the abundant epidemiology and toxicology data to determine the reasonableness of the dose response curve. The NIOSH and UCC data do not support the steep slope at low doses.

5) **Advances in Understanding the Biology of Cancer.** During the November meeting, both Dr. Albertini and Dr. Irons presented to the CAAC members current biological mechanistic information on ethylene oxide. This information supports the belief that genotoxic compounds can have thresholds. The Panel recommends that the presentations by Dr. Irons and Dr. Albertini be further reviewed in light of the CAAC recommendation to provide a more detailed interpretation of the findings within the context of more recent advances in the

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[2] See SOT position statement available at: http://toxicology.org/pr/PrinResearch.asp

[3] See http://yosemite.epa.gov/sab/sabproduct.nsf/55005852EF5FB56785257DB1007430E1/$File/EO-+comments+on+Mikoczy+study-+Dec+2014.pdf

understanding of the biology of cancer and that only linear modeling is presented in the IRIS assessment.

The Panel appreciates the time and energy you have put into this important review. I would be happy to answer any questions.