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**Comments to the Ethylene Oxide SAB CAAC**  
**September 30, 2014**

I am Bob Sielken. I am a statistician who has been working in the field of exposure-response modeling since the 1970s. I have been working with the American Chemistry Council (ACC) on ethylene oxide for more than 25 years including discussing several issues at the 2007 SAB and publishing a relevant paper in 2013 entitled "Misinterpretation of categorical rate ratios and inappropriate exposure–response model fitting can lead to biased estimates of risk: Ethylene oxide case study."

EPA asks in their Charge Question 3.a on Lymphoid Cancer - model selection. "Please comment on EPA's rationale for its use of the linear regression of the categorical results as the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer."

Despite the 2007 SAB's recommendation for EPA to focus on individual data, EPA's modeling continues to focus on a few categorical rate ratios. In ACC's comments on this charge question, I have suggested the following addition to question 3.a:

***"Please comment on EPA's method of implementing their linear regression of the categorical results and EPA's rejection (discussed in EPA's Appendix J.3.1) of the modeling recommendations in Valdez-Flores and Sielken (2013)."***

EPA's method results in a poor basis for model selection and, as we show in our 2013 paper, EPA's method is based on a misinterpretation of categorical rate ratios which leads to inappropriate exposure–response model fitting and biased estimates of risk.

We are also providing 3 attachments that relate to EPA's Appendix J.3.1 and include the Supplementary Material from our 2013 paper. Whereas the body of our 2013 paper provides specific modeling results for breast cancer mortality (the NIOSH breast cancer incidence data are not publicly available), the supplementary material provides specific modeling results for lymphohematopoietic cancers and lymphoid cancers. The supplementary material also provides more than just 4 categorical RRs for each endpoint (namely, 20 categorical RRs and also one categorical RR for each exposed individual with the cancer). These multiple categorical RRs as well as those in the body of the 2013 paper for breast cancer suggest that the underlying exposure-response relationship is not supralinear.

In ACC's comments, ACC has requested under charge questions 2.a and 2.c that the CAAC review EPA's breast cancer incidence modeling. My preceding comments

related to lymphoid cancers also apply to breast cancers. Namely, that EPA's visual impression of supralinearity is based on limited information and is inappropriate, and that EPA's selection of a two-piece linear spline model reflects EPA's misinterpretation of the categorical RR's and not a biological rationale. The spline model is not a peer-reviewed regulatory model. EPA's spline models are supra-linear for all endpoints including breast cancer incidence. Furthermore, EPA's spline models do not provide a statistically significant better fit to the data than the continuous log-linear models.

The best exposure-response model for all endpoints (including breast cancer) is a continuous log-linear Cox proportional hazards model fit to the individual data.

I feel that, with these explanations and the new published information, a better model selection can be made.

**Related Text not part of Oral Presentation:**

*In the supplemental material, for results for lymphohematopoietic cancers see pages 4 to 11 (Tables 3S through Figure 3S) especially page 8 (Table 6S), and for lymphoid cancers see pages 12 to 19 (Tables 7S through Figure 6S) especially page 16 (Table 10S).*

*In the supplemental material, for results for lymphoid cancers see pages 12 to 19 (Tables 7S through Figure 6S) especially pages 18 and 19 (Figures 5S and 6S).*