



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
National Center for Environmental Assessment  
Washington, DC 20460

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OFFICE OF  
RESEARCH AND DEVELOPMENT

**MEMORANDUM**

**SUBJECT:** Request for Clarifications in the SAB Draft Report (1-07-15) on Ethylene Oxide  
**FROM:** Jennifer Jinot, Chemical Assessment Manager for Ethylene Oxide, NCEA  
**THRU:** David Bussard, Director, Washington Division, NCEA  
**TO:** Aaron Yeow, EPA Science Advisory Board

This memorandum provides clarifications about EPA's draft carcinogenicity assessment of ethylene oxide of relevance to the SAB draft report as well as a list of clarifications requested by EPA pertaining to the SAB draft report. The citations are to the main text of the draft SAB report; however, some of the clarifications might then affect the summary statements in the Executive Summary or transmittal letter in parallel.

**Clarifications about EPA's Draft Assessment:**

1. *page 11, beginning on line 25, of the draft SAB report, regarding what EPA considered to be the set of "reasonable" breast cancer incidence models referred to in charge question 2b.*  
EPA intended the question to refer to only the 4 models for which unit risk estimates were presented (i.e., the linear and log-linear two-piece spline models, the linear regression of the categorical results, and the continuous exposure linear model, but not the log-linear Cox regression models with cumulative and log cumulative exposure), not all the models in Table 4-13.
2. *page 30, lines 11-14, of the draft SAB report, regarding the public comments discussed in Appendix L.* EPA would like to suggest that the report say that "16 sets of comments were received by EPA, and from these sets of comments, EPA extracted 14 major substantive science comments and provided responses to those major comments." The complete collection of all 16 sets of public comments received can be found in the docket referenced

on lines 20-21 on page L-1 of Appendix L. [EPA will clarify the text in the Appendix L to avoid the confusion in the future.]

**Clarifications Requested of the SAB:**

1. *page 13, lines 4-18, of the draft SAB report, regarding the AIC.* As discussed on page 4-4 of the draft assessment, EPA did not use the AIC to evaluate goodness of model fit. Rather, the AIC was used to help select a breast cancer incidence model from among some of the models listed in Table 4-12 (p. 4-39 of the draft assessment) that EPA had determined fit the data.

The draft SAB report seems to suggest that the AIC should only be used to compare nested models (page 13, lines 5-6; also page 15, lines 29-30). Authoritative sources ((Claeskens and Hjort, 2008); (Burnham and Anderson, 2002)) demonstrate the use of the AIC for model selection for both nested and non-nested models, provided these models use the same likelihood formulation and the same data. While the draft panel report notes some instances in which it might be inappropriate to compare models using AIC, if the SAB panel is specifically recommending that the AIC should not be used to compare the non-nested models evaluated by EPA in Table 4-12 of the draft assessment, it would be helpful to EPA if the panel could elaborate on this recommendation and include citations that go into greater length as to why AICs should not be used to compare models that use the same likelihood formulation and the same data (assuming the AICs are calculated in ways that are comparable and unaffected by the concern raised by the panel about software tools differing in whether or not they remove constants [page 13, lines 9-11]). EPA believes the models it is comparing do not use different transformations of the outcome variable.

In addition, the draft SAB report states that challenges in comparing the AICs can come from the software tools being used (page 13, lines 9-11) and how the calculations were done (page 13, lines 15-18). With respect to the models considered in Table 4-12 of EPA's draft assessment, the log-linear Cox regression and spline models were fitted using SAS PHREG and the linear models were fitted using SAS NPL (Langholz and Richardson, 2010). If the SAB panel thinks that these specific software applications present problems for comparing AICs, it would be helpful if the report could clarify which specific AICs should not be compared or what specific information would be required to determine this (lines 16-18 on page 13 of the draft SAB report). It would also be useful to EPA if the SAB panel could elaborate on which software programs implement the AIC calculation incorrectly and what software programs would calculate it correctly (or, alternatively, which programs remove constants and which do not). Citations for each of the particular clarifications would help EPA better understand this issue and be able to address the SAB comments.

2. *page 14, lines 3-7, of the draft SAB report, regarding recommended tables.* Please clarify what is meant by "Marginal summaries of workers' ages, exposures, and years of entry to employment" and "Cumulative exposure to EtO in each of the risk categories". It could be that in asking for "marginal summaries" the panel is asking to see a histogram or data table of the number of workers in the cohort as a whole for categorical ranges of the variables mentioned (e.g., for "year of entry into employment in this industry", the number of workers in the cohort by year or by five-year intervals). If the panel's request for marginal

summaries is something else, it would be useful to have greater specificity. Similarly, can the panel specify what it is seeking when it asks for exposures by “risk category”?

3. *page 14, lines 28-29, of the draft SAB report, regarding biological implausibility as a reason to reject the individual exposure model results.* EPA anticipates doing further investigation into possible statistical or other reasons that the best-fitting two-piece spline model fit to the lymphoid cancer data shows such a steep slope for very low exposures and then quite little additional risk for large increases in exposure above that region. EPA may investigate if there is some complex behavior occurring with the “knot” in the spline being close to a constraint or if the model is sensitive to lag periods or variability (“noise”) in the data due to small numbers of cases in the low-exposure regions. The SAB suggested there might be biological reasons to reject a model. Would the SAB consider whether there might also be statistical or mathematical reasons that could provide an alternative rationale for rejecting the individual exposure model results?

While the panel made a recommendation (page 16, lines 12-14) that estimates of expected extra cases in the cohort assuming one or more of the fitted models would allow one to illustrate the consistency of the models with the cohort data, such analysis may not increase confidence in the plausibility of different model forms. Are there other ways to assess how much confidence EPA should have in the low-exposure slope of the two-piece spline or other models fit to the lymphoid cancer data?

4. *page 14, lines 41-43, of the draft SAB report, regarding using categorical medians rather than means as the basis for a linear regression.* In a memo dated 4 December 2014 (and posted on the SAB website), EPA provided rationales as to why the mean could be a better representation of exposure for the purposes of reflecting risk for an exposure category when the relative risk, or rate ratio, is a linear function of cumulative exposure. Further, EPA’s use of the categorical data was focused on estimating the exposure-response relationship in the low-exposure range and EPA’s implementation of that approach involved excluding the highest exposure category. In the draft panel report, the SAB recommends use of the median exposure for each category if EPA does a linear regression of categorical data. Can the SAB please provide an enhanced explanation of the panel’s preference for medians in light of this supplemental material, especially if EPA is not using the highest exposure category in the linear regression (in reference to line 43)?
5. *pages 15-16 of the draft SAB report, regarding model selection for lymphoid cancer.* There was a “local maximum” to the overall likelihood function for the two-piece spline model fit to the lymphoid cancer data for a knot of 1600 ppm × days (see Figures D-3a on p. D-45 and 4-1 on p. 4-9 of the draft assessment). Does the panel see merit in EPA considering that model as plausible?
6. *page 20, lines 11-15, of the draft SAB report, regarding MOA considerations.* The draft report states, “The rationale for decisions made regarding model selection for calculations of unit risk should be presented in this section, and elsewhere, within the context of MOA considerations and the initial key biological events involved in mutagenesis and carcinogenesis. The evidence for [a] mutagenic MOA can be used to explain the behavior of

the data in low dose regions and the subsequent extrapolation for risk assessment.” EPA’s draft assessment concluded that a mutagenic MOA is operative in EtO carcinogenicity and that such an MOA supports using a linear extrapolation to lower exposures to estimate risk at exposures below the point of departure. If the panel means that the MOA explains some additional aspect of the behavior in the low-dose region or in the dose-response relationship generally, especially something that would inform model selection, it would be very useful if the panel can explain that further.

Burnham, KP; Anderson, DR. (2002). Model selection and multimodel inference: a practical information-theoretic approach (2nd ed.). New York: Springer.

<http://www.springer.com/statistics/statistical+theory+and+methods/book/978-0-387-95364-9>

Claeskens, G; Hjort, NL. (2008). Model selection and model averaging. Cambridge, England: Cambridge University Press.

Langholz, B; Richardson, DB. (2010). Fitting general relative risk models for survival time and matched case-control analysis. Am J Epidemiol 171: 377-383.

<http://dx.doi.org/10.1093/aje/kwp403>