UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

August 7, 2015

EPA-SAB-15-012

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Science Advisory Board Review of the EPA's *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014)*

Dear Administrator McCarthy:

The U.S. Environmental Protection Agency's National Center for Environmental Assessment requested a peer review of the draft carcinogenicity assessment developed in support of the Integrated Risk Information System, *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014)*. An earlier version of the draft assessment was peer reviewed by the Science Advisory Board (SAB) in 2007. The draft assessment was revised in response to the SAB recommendations and, due primarily to additional modeling of the epidemiologic data, the agency requested an additional SAB peer review.

The SAB was asked to comment on how the agency responded to the 2007 SAB recommendations, including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and transparency of the revised draft assessment. The SAB was also asked to comment on other scientific issues related to the hazard identification and dose-response assessment associated with the inhalation carcinogenicity of ethylene oxide (EtO). In response to the EPA's request, the SAB augmented the Chemical Assessment Advisory Committee (CAAC) with additional experts to conduct the review. The enclosed report provides the SAB's consensus advice and recommendations. This letter briefly conveys the major findings.

Overall the SAB finds the agency has been highly responsive to the 2007 SAB recommendations. The SAB finds that the National Institute of Occupational Safety and Health (NIOSH) dataset is still the most appropriate dataset to use and concurs with the agency's decision to not use the Union Carbide Corporation cohort data. The statistical and epidemiological issues in this assessment are complex and the agency is to be commended for conducting the additional exposure-response modeling in response to the 2007 SAB recommendations. The SAB believes that the advice and recommendations in this report can be addressed relatively quickly and that the draft assessment should move forward to be finalized.

The draft assessment employed lagged exposure estimates in the derivation of cancer risk estimates. Although there is a scientific rationale for a period of latency between biologically important exposures and subsequent cancer incidence or mortality, the SAB did not find a strong biological or statistical argument supporting the particular selected latency periods applied for breast and lymphoid cancers. The EPA is encouraged to perform a sensitivity analysis of various latency periods to determine what effect this selection had on risk estimates.

A number of different statistical models were examined for estimating breast cancer incidence risk from low exposure to EtO. The draft assessment presents a number of considerations used in the selection of the preferred model. The SAB generally concurs with the selection of the two-piece spline model for estimating breast cancer incidence. However, the SAB has recommendations on improving the considerations used for model selection, including less reliance on the Akaike information criterion (AIC). However, if AIC is used for model selection, it should be used appropriately. There should be *a priori* considerations regarding the nature of the functional form being applied. Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low exposure range (e.g., spline models). The draft assessment also presents risk estimates from other "reasonable models." Although much of this approach is scientifically appropriate, the SAB finds that a clear definition of "reasonable models" is lacking and encourages some modifications and more transparency in the presentation. The SAB also provides recommendations on prioritizing statistical considerations in the selection of models. Any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.

For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO. The SAB prefers the use of continuous individual-level exposure data over the use of categorical results. The linear regression of categorical results should not be selected unless the individual exposure model results are biologically implausible. The SAB recommends presentation of multiple estimates of the unit risk in sensitivity analyses and an updated justification of model selection. The SAB suggests that the agency consider using the same model for both environmental and occupational exposures. The use of different models for environmental and occupational exposures should only be done with sufficient justification.

The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be improved and extended. Considerations about uncertainty directly pertaining to the analyses reported can be separated into uncertainty due to the data themselves (particularly from reliance on a single dataset), and uncertainty of the results given the data. The SAB recommends adding descriptive summaries of the characteristics of the NIOSH cohort, better quantification of the results from the various models (such as reporting unit risk estimates and comparisons in sensitivity analyses), and down-weighting epidemiologic results based on external standards that may be subject to bias due to the healthy worker effect.

The draft assessment presents an accurate, objective, and transparent summary of published studies on EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of action. The SAB finds that several areas of the draft assessment can be improved to enhance the clarity of presentation and to provide a more detailed interpretation of findings within the context of more recent advances in the understanding of the biology of cancer and has specific recommendations and suggestions for revision detailed in the report.

Appendix H of the draft assessment provides a summary of the 2007 SAB comments and the EPA's response to the comments. The responses are transparent, objective, and for the most part, accurate (exceptions are noted in the current report). In particular, the SAB supports the expanded discussion of endogenous EtO provided in the draft assessment and has suggestions for further improvement; agrees with the decision not to include a toxicity value for EtO based upon nonlinear extrapolation and recognizes and agrees with revisions to strengthen support for a classification of EtO as "carcinogenic to humans."

In general, the literature review of new studies presented in Appendix J appears complete. The logic and progression of the review is clearly supported. The clarity can be improved by distinguishing between statements made by study authors and statements made by the EPA. The SAB concurs that inclusion of the new studies would not substantially alter the findings of the assessment, with the exception of the Mikoczy et al. study of Swedish sterilization workers, which can strengthen support for the hazard characterization of EtO and provide support for the modeling of the NIOSH data.

Appendix L presents public comments on the July 2013 draft of the assessment and EPA responses to the public comments. The SAB finds that overall, the EPA has been very responsive to the public comments. The responses are thorough, clear, and appropriate.

The SAB appreciates the opportunity to provide the EPA with advice on the EtO assessment and looks forward to the agency's response.

Sincerely,

/S/

Peter S. Thorne, Chair
Science Advisory Board

Enclosure

NOTICE

U.S. Environmental Protection Agency
Science Advisory Board
Chemical Assessment Advisory Committee Augmented for the Ethylene Oxide Review

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Acronyms and Abbreviations

ADAF	age-dependent adjustment factor
AIC	Akaike information criterion
CAAC	Chemical Assessment Advisory Committee
EC	effective concentration
EPA	U.S. Environmental Protection Agency
EtO	ethylene oxide
HERO	Health and Environmental Research Online
IRIS	Integrated Risk Information System
IRR	incidence rate ratio
LH	lymphohematopoietic
MOA	mode of action
MSPE	mean-square prediction error
NCEA	National Center for Environmental Assessment
NIOSH	National Institute for Occupational Safety and Health
ORD	Office of Research and Development
POD	point of departure
ppm	parts per million
RfC	reference concentration
RfD	reference dose
SAB	Science Advisory Board
UCC	Union Carbide Corporation

1. EXECUTIVE SUMMARY

The Environmental Protection Agency's (EPA) National Center for Environmental Assessment (NCEA) requested the Science Advisory Board to conduct a peer review of the draft *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft – August 2014)* developed by the Integrated Risk Information System (IRIS) program, hereafter referred to as the draft assessment. An earlier version of the draft assessment was peer reviewed by the SAB in 2007. The draft assessment was revised in response to the SAB recommendations and, due primarily to additional modeling of the epidemiologic data, the agency requested an additional SAB peer review.

The EPA requested comments on how the agency responded to the SAB (2007) recommendations, including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and transparency of the revised draft assessment. The EPA also requested comments on other scientific issues related to the hazard identification and dose-response assessment associated with the inhalation carcinogenicity of ethylene oxide (EtO). In response to this request, the SAB augmented the Chemical Assessment Advisory Committee (CAAC) with additional experts to conduct the review.

Exposure Lagging

The draft assessment employed lagged exposure estimates in the derivation of cancer risk estimates and they are clearly described. There is a scientific rationale for a period of latency between biologically important exposures and subsequent cancer incidence or mortality. However, the National Institute for Occupational Safety and Health (NIOSH) epidemiological data (Steenland et al., 2003, 2004) do not provide a strong biological argument in support of or against the 15-year latency periods for breast and lymphoid cancers that are adopted in the statistical modeling of relative risks and estimates of unit risks in the draft assessment. Thus, the existence and length of a latency period for the cancers in question remain a scientific uncertainty in the risk assessment and the EPA is encouraged to continue to address it as such in the assessment. The SAB encourages the EPA to conduct a sensitivity analysis of unit risks over the plausible range of latency periods (i.e., 0-20 years). This should be detailed in an appendix. The body of the draft assessment should include a short summary of the quantitative results of the sensitivity analysis accompanied by a qualitative discussion of how the results should factor into an overall assessment of the biological and statistical uncertainty of the unit risk estimates derived under the alternative models of exposure risk.

Breast Cancer Incidence – Model Selection

A number of different statistical models were examined for estimating breast cancer incidence risk from low exposure to EtO. Following extensive discussion, the SAB generally concurs with the selection of the two-piece spline model for estimating breast cancer incidence, but the model selection could be described more clearly and transparently. The SAB requests that the EPA provide better documentation of the NIOSH study data, particularly with respect to exposure.

The SAB has recommendations on improving the considerations used for model selection, including less reliance on the Akaike information criterion (AIC). However, if AIC is used for model selection, it should be used appropriately. There should be *a priori* considerations regarding the nature of the functional form being applied. Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low exposure range (e.g., spline models). Sensitivity analyses should be reported for a range of results and should include the target quantity of interest (unit risk, excess risk). Although not all models are equally reasonable from a risk assessment perspective, full and transparent reporting of the target parameters of interest provides valuable context. Any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.

The draft assessment also presents risk estimates from other "reasonable models." Although much of this approach is scientifically appropriate, the SAB finds that a clear definition of "reasonable models" is lacking and encourages some modifications and more transparency in the presentation. Discarding a model because the fitted curve is "too steep" needs scientific justification. Furthermore, the EPA should clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible." The SAB recommends assigning weight to certain types of models based on a modified combination of biologic plausibility and statistical considerations, and using somewhat different considerations for comparing AICs than those currently employed in the draft assessment.

Regarding statistical considerations about various models, the SAB recommends a different set of priorities for establishing the most reasonable models and gives guidance on the preference for their ordering. First, prioritization should be given to regression models that directly use individual-level exposure data. Second, among models fit to individual-level exposure data, models that are more tuned to local behavior in the data should be relied on more heavily. Third, the principle of parsimony should be considered.

Lymphoid Cancer – Model Selection

For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO. The SAB does not concur with this choice and prefers the use of continuous individual-level exposure data over the use of categorical results. The SAB recommends that the linear regression of categorical results not be selected as the preferred model unless the individual exposure model results are biologically implausible. If a linear regression of categorical results is used, then the SAB recommends the use of category medians rather than the means, as they provide a better representation of exposure to individuals in each category. The SAB recommends presentation of multiple estimates of the unit risk in sensitivity analyses and an updated justification of model selection.

Overall, the SAB finds the rationale for the selection of the preferred exposure-response model for lymphoid cancer to be lacking and not transparently communicated. The SAB suggests that the EPA consider using the same model for both environmental and occupational exposures. The use of different models is acceptable only with sufficient justification.
The approach used for deriving risk estimates for lymphoid cancer incidence and the rationale for using the approach is transparently explained and scientifically appropriate. The SAB suggests that the EPA consider including a simplified example of deriving unit risk and excess risk estimates to improve the readers' understanding of these risk measures. The SAB suggests that extra lifetime risk could be presented in terms of the number of lymphoid cancers that are due to the exposure to EtO in the cohort and that scientific notation be used to present risk estimates.

Uncertainty in the Cancer Risk Estimates

The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be improved and extended. Considerations about uncertainty directly pertaining to the analyses reported can be separated into uncertainty due to the data themselves (particularly from reliance on a single dataset), and uncertainty of the results given the data. The SAB recommends that the EPA consolidate the current discussion of exposure uncertainty and include a qualitative discussion of uncertainty associated with model-based predictions of annual exposures. In order to provide a deeper understanding of the data source, the EPA should obtain and archive the NIOSH data and include several tables or figures with descriptive summaries of the characteristics of the NIOSH cohort. The uncertainty arising from the use of a single data source can be reduced by highlighting how the Swedish sterilization workers data (Mikoczy et al., 2011) help support the conclusions reached from the NIOSH data.

The qualitative discussion of uncertainty can be improved by better quantification of the results from the various models (such as more extensive reporting of unit risk estimates and comparisons in sensitivity analyses). The SAB recommends down-weighting epidemiologic results based on external standards (e.g., standardized mortality ratio, standardized incidence ratio) that may be subject to bias due to the healthy worker effect.

Accuracy, Objectivity, and Transparency of the Revised Draft Assessment

Genotoxicity

The draft assessment presents an accurate, objective, and transparent summary of published studies on EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of action (MOA). The SAB finds that several areas of the draft assessment can be improved to enhance the clarity of presentation and to provide a more detailed interpretation of findings within the context of more recent advances in the understanding of the biology of cancer. Specific recommendations include revisions to Table 3.6 to specify the sites involved and the weight assigned to each of the studies; presenting the rationale for decisions made for model selection within the context of MOA considerations; and presenting the synthesis of information supporting a mutagenic MOA in a more systematic and complete manner.

Response to the 2007 SAB Comments

Appendix H of the draft assessment provides a summary of the 2007 SAB comments and the EPA's response to the comments. Overall the SAB finds that the EPA was highly responsive to the comments and recommendations. The responses are transparent, objective, and for the most part, accurate (exceptions are noted in the current report). There are four main comments and recommendations from the 2007 SAB report that are not implemented in the current draft assessment:

1. using a non-linear modeling approach for deriving a toxicity value;
2. using the Union Carbide cohort data (Greenberg et al., 1990; Teta et al., 1993; Benson and Teta, 1993) for unit risk derivation;
3. using a single model to fit the occupational and environmental exposure-relevant regions of the dose response curve; and
4. moving the contents of Appendix A to the main body of the assessment.

The SAB generally agrees with the EPA's decisions not to include these in the draft assessment (with the exception to point 3 noted below). In particular, the SAB:

1. finds that EtO likely acts via a mutagenic MOA and therefore its potency should be modeled according to a linear low-dose model. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) note the following: "A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses ….." (p. 3-23). 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;
2. concurs with the decision not to use the Union Carbide Cohort data for unit risk derivation, but suggests that the agency discuss the weight of the evidence of the UCC, NIOSH, and Swedish sterilization workers studies. More suggestions regarding the Swedish sterilization workers study can be found in the response to charge question 6;
3. suggests that the EPA consider using the same model for both environmental and occupational exposures; and
4. agrees with the decision not to move the contents of Appendix A to the main body of the draft assessment.

The SAB supports the expanded discussion of endogenous EtO provided in the draft assessment and has suggestions for further improvement; agrees with the decision not to include a toxicity value for EtO based upon nonlinear extrapolation, but recommends a more balanced and objective discussion of the subject; and recognizes and agrees with revisions to strengthen support for a classification of EtO as "carcinogenic to humans."

Completeness and Clarity of Appendix J – New Studies

In general, the literature review of new studies presented in Appendix J appears complete. The logic and progression of the review is clearly supported. The clarity can be improved by distinguishing between statements made by study authors and statements made by the EPA. The SAB concurs that inclusion of the new studies would not substantially alter the findings of the assessment, with the exception of the Swedish sterilization workers study. This study used detailed exposure data at low doses and documented substantial effects on breast cancer, which has stronger implications than suggested in the draft assessment. The strong breast cancer results at low dose exposures in the Swedish sterilization workers study greatly add to the overall findings. The observation of a 2.5 to 3.5–fold increased risk of breast cancer associated with low cumulative exposure in this study demonstrates strong evidence of carcinogenicity.

EPA Response to Public Comments

Appendix L presents public comments on the July 2013 draft of the assessment and EPA responses to the public comments. The SAB finds that overall, the EPA has been very responsive to the public comments. The responses are thorough, clear, and appropriate. There were also some public comments on the 2006 draft assessment in Appendix H. The SAB finds that the revisions made to the draft assessment and the EPA response in Appendix L adequately and appropriately address the issues raised in the public comments in Appendix H.

2. INTRODUCTION

2.1. Background

The U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment (NCEA) has developed a draft carcinogenicity assessment of ethylene oxide (EtO) in support of the agency's Integrated Risk Information System (IRIS), *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft – August 2014)*. An earlier version of the draft carcinogenicity assessment received public comment and underwent external peer review by the SAB in 2007. The assessment was revised and underwent public comment in July 2013. Primarily because of the new modeling of epidemiologic data done in response to the SAB recommendations, the EPA has decided to seek additional SAB peer review. A summary of the public and SAB peer review comments from 2007 and EPA's disposition of the comments is presented in Appendix H of the current draft assessment. A summary of the 2013 public comments and EPA responses can be found in Appendix L of the current draft assessment.

IRIS is a human health assessment program that evaluates scientific information on effects that may result from exposure to specific chemical substances in the environment. IRIS is prepared and maintained by the NCEA within the Office of Research and Development (ORD). Through IRIS, the EPA provides science-based human health assessments to support the agency's regulatory activities and decisions to protect public health. IRIS assessments contain information for chemical substances that can be used to support the first two steps (hazard identification and dose-response assessment) of the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for chronic health effects (including cancer and effects other than cancer). Government and others combine IRIS toxicity values with exposure information to characterize public health risks of chemical substances; this information is then used to support risk management decisions designed to protect public health.

The draft carcinogenicity assessment of EtO presents an evaluation of the cancer hazard and the derivation of quantitative cancer risk estimates from exposure to EtO by inhalation. The hazard assessment (Chapter 3) includes a review of epidemiologic studies, rodent cancer bioassays, and mechanistic studies, e.g., genotoxicity studies. The quantitative assessment includes exposure-response modeling for the derivation of inhalation unit risk estimates of cancer risk at low (generally environmental) exposure concentrations (Sections 4.1 – 4.5) and estimates of the cancer risk associated with some occupational exposure scenarios (Section 4.7).

2.2. Charge to the Science Advisory Board

The EPA requested comments on how the agency responded to the SAB (2007) recommendations, including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and transparency of the revised draft assessment. The EPA also requested comments on other scientific issues related to the hazard identification and dose-response assessment associated with the inhalation carcinogenicity of EtO.

In response to the EPA's request, the SAB augmented the Chemical Assessment Advisory Committee (CAAC) with additional experts to conduct the review. The Augmented CAAC for the Ethylene Oxide Review held a public teleconference on September 30, 2014, and a face-to-face meeting on November 18-20, 2014, to discuss and deliberate on the charge questions and to consider public comments. The Augmented CAAC held a follow-up teleconference on February 20, 2015, to discuss its draft advisory report and the Chartered SAB conducted a quality review of the report and approved the report on June 8, 2015.

The EPA's charge to the SAB focused on review of those sections of the revised draft assessment that deal with the exposure-response modeling of the epidemiologic data from the NIOSH study (Steenland et al., 2003, 2004) and development of (1) the inhalation unit risk estimates of cancer risk at low (generally environmental) exposure concentrations and (2) estimates of the cancer risk associated with occupational exposures. The charge also asked the SAB to review the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the sections that were either new or had been substantially revised since the 2007 review, and to comment on whether scientific issues that were raised by the public in July 2013 as described in Appendix L have been adequately addressed by the EPA.

The charge questions in their entirety are presented in Appendix A. The charge questions are presented individually (in italics) in the next section followed by the SAB response.

3. RESPONSE TO CHARGE QUESTIONS

3.1. Exposure Lagging

Charge Question 1: Exposure-response modeling was conducted separately for lymphohematopoietic cancer mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox proportional hazards models, a lag period was used to represent an interval before cancer death (or diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was disregarded because it was not considered relevant for the development of the cancer outcome observed. The lag period for each of the different cancer types was selected empirically based on statistical fit. These exposure lag periods were included in EPA's exposure-response analyses using other model forms for the derivation of cancer risk estimates. Please comment on whether the use of lagged exposure estimates in the derivation of cancer risk estimates and the selection of the lag periods used are clearly described and scientifically appropriate.

The draft assessment and appendices clearly describe the nature of the modeled latency for cancer incidence/death and the time lag that is applied to the cumulative exposure measures in the preferred models of risk. The draft assessment and Appendix D describe many new and varied trials at modeling dose response for EtO exposures, but the final selected models all retain the exposure lag periods identified in the earlier published analyses (Steenland et al., 2003, 2004) of the National Institute for Occupational Safety and Health (NIOSH) data: lymphoid cancer and lymphohematopoietic cancer - 15 years; breast cancer mortality - 20 years; breast cancer incidence - 15 years.

The SAB agrees that it is scientifically plausible, and even likely, for there to be a period of latency between biologically important exposures and subsequent cancer incidence or mortality, however, the NIOSH epidemiological data do not provide a strong biological argument in support of or against the 15-year latency periods for breast and lymphoid cancers that are adopted in the statistical modeling of relative risks and estimates of unit risks in the draft assessment.

The existence and length of a latency period for the cancers in question remain a scientific uncertainty in the risk assessment and the EPA is encouraged to continue to address it as such in the assessment. Given this uncertainty, the SAB recommends the methods used to determine minimum latency estimates in the CDC 9/11 Working Group Guidelines (CDC, 2013) as a good framework for assessing latency in cancer onset. However, the disease-specific latency selections in the guidelines are specific to the World Trade Center Health Program and 9/11 agents, and are not relevant to the EtO draft assessment.

With scientific uncertainty over the latency between exposures to EtO and any associated cancer incidence or mortality, there is certainly statistical uncertainty in how latency should be reflected in the modeling of exposure risk. The draft assessment argues strongly for modeling exposure risk using 15-year latency periods for breast cancer incidence and lymphoid cancer mortality. Given no strong statistical support for choosing one lag period over another in modeling breast cancer risk, the draft assessment (pp. 4-31 – 4-32) concludes "The log cumulative exposure model with no lag was considered less biologically realistic than the corresponding model with a 15-year lag because some lag period would be expected for the development of breast cancer." The SAB encourages the EPA to refine the discussion of this uncertainty with a paragraph in the body of the assessment and a summary of an analysis (detailed in an appendix) that examines the sensitivity of estimates of unit risks over the plausible range of latency periods (i.e., 0-20 years). Appendix D (pp. D-24 to D-29) presents detailed SAS® output from a new trial of fitting Cox regression (nested case control) models for incident breast cancer to cumulative exposure and log cumulative exposure with varying lag periods (lags of 0, 5, 10, 15, and 20 years). Although there is no discussion of this trial or its evaluation in Appendix D, the results for the models fitted to the log of cumulative exposures show very little to distinguish the fit between the model that imposed a 15-year lag and the model that used no lag in cumulative exposure. This analysis matches the results of the original Steenland et al. (2003) analysis, which found nearly equivalent quality of model fits for log cumulative exposure models with 0- or 15-year lags. The SAB encourages the EPA to formalize the presentation and discussion of the quantitative results for the sensitivity analysis of exposure lags that is currently included in Appendix D, focusing on the sensitivity of the EPA's recommended models and a strongest competitor(s) to the length of the assumed latency period. The body of the draft assessment should include a short summary of the quantitative results of the sensitivity analysis described in detail in the appendix, accompanied by a qualitative discussion of how the results of the sensitivity analysis should factor into an overall assessment of the biological and statistical uncertainty of the unit risk estimates derived under the alternative models of exposure risk.

In summary, the SAB agrees that it is scientifically plausible, and even likely, for there to be a period of latency between biologically important exposures and subsequent cancer incidence or mortality.

3.2. Breast Cancer Incidence – Model Selection

Charge Question 2: As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

2a: Please comment on whether the considerations used for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence for the purposes of estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

There is not enough detail provided for the NIOSH exposure data for the SAB to determine the appropriateness of the data. Therefore the SAB response is conditional on the assumption that the NIOSH exposure data are appropriate. The SAB requests that the EPA provide better documentation of the NIOSH data, particularly with respect to exposure. The response to Charge Question 4 provides a discussion of considerations of the adequacy of the results not conditional on the appropriateness of the exposure data.

Although generally the EPA's model selection for breast cancer incidence is scientifically appropriate, it could be described more clearly and transparently. The EPA is encouraged to revise the discussion of the Cox model, or more generally, relative risk models, to use terminology that can be directly linked with the published literature. Prentice (1985) provides examples of this terminology and a discussion of relative risk models. Terminology describing the behavior of the models at the low-exposure range should be clearly defined, particularly terms that are used to make judgments, such as "unstable."

The EPA's considerations for model selection included exploration of a range of different models, assessment of their fit using Akaike information criterion (AIC) and/or p-values (and for linear splines, comparison of likelihoods for alternative knot locations), and judgment of their results based on the steepness of the dose-response function at low doses. Fits that produced slope estimates in the low-dose exposure range that were considered too steep (but details of exactly how this determination was made were not given) were not considered further for estimation of the unit risk estimates. In selecting models for use in risk assessment, the SAB recommends less reliance on the AIC. However, if AIC is used for model selection, it should be used appropriately. (The response to Charge Question 2b discusses important considerations in using AICs for model selection, which may have some bearing on the appropriateness of using AIC to choose between linear and exponential relative risk model fits.). There should be *a priori* considerations regarding the nature of the functional form being applied. Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low-exposure range (e.g., spline models; these are preferred over more global functions, such as untransformed or log-transformed cumulative exposure, that give more weight to the high exposures in the estimated dose response). Within the class of spline functions, appropriate use of AICs and/or p-values can help choose between certain fitted models (see response to Charge Question 2b). Finally, any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data. These comments should be helpful for considering how to revise Table 4-12.

The SAB supports the prioritization of incidence data and the choice of data to use for the breast cancer incidence analyses. The SAB also concurs with the reliance on analyses based on the individual estimates of cumulative exposure for risk assessment (in contrast to categorized exposure or other exposure metrics such as duration). Exposure duration is not as informative for risk assessment because the magnitude of exposure is not part of duration. Using an exposure lag is more biologically plausible than using no lag. The SAB commends the EPA for considering and documenting the results for a variety of different model specifications in terms relevant for the ultimate risk assessment. In particular, a good choice is the linear spline structure used to parameterize the exposure covariate in the relative risk function under an exponential (exp(f(x))) or linear (1+f(x)) relative risk model. A spline parameterization of f(x) has the advantage of allowing the shape of the relative risk function to vary over the range of exposure while ensuring that the behavior of the function in the low-exposure range is not unduly influenced by the highest exposures. The linear spline parameterization has the disadvantage that it has a "corner" and a smooth dose-response function would be preferred. The draft assessment uses a cubic spline model to address this, but ultimately the simpler linear spline model was selected as the preferred model. The EC_{01} from the cubic spline model is similar to the one from the linear spline model and the SAB concurs with the EPA's preference for the much simpler linear spline model parameterization, recognizing the virtue of simplicity and transparency of reporting.

Alternatives to using cumulative exposure in the model as a single untransformed term are log-transformation and square root transformation. These alternatives are less desirable because they produce more global fits to the entire exposure range, which would give the higher exposures more influence (compared to the more local spline models) on the fitted dose-response in the low-exposure range of the data. Although it is worthwhile observing from the fits (e.g., Figure 4-5) that the log and square root transformations also exhibit a similar behavior to the linear spline at low exposures (namely that the risk increases rapidly at low exposures and then continues to increase at higher exposures, but much less rapidly), the global nature of these estimates makes them less desirable for estimation of unit risks.

There are clear advantages to relying on parsimonious regression models directly fit to the individual-level cumulative exposure data using spline models to parameterize exposure. It is straightforward to compute unit and excess risk estimates directly from these fitted results. Furthermore, spline models have the advantage of being sensitive to local behavior in the data. They can also be chosen to be parsimonious (an example is a 2-piece linear spline). Models fit to exposure categories are similarly sensitive to local behavior in the data, but they require more parameters to be estimated and are thus less parsimonious than the spline models considered in the assessment. They also impose the implausible assumption that the risk is constant within each exposure category. Furthermore, it is not straightforward to translate the relative risk estimates from a categorical relative risk regression model to unit and excess risk estimates. This requires the less desirable additional step of summarizing the categorical model fit by translating its results into a functional form that can be used in a risk assessment. (See the response to Charge Questions 2b and 3 for further detail.)

The SAB has some concern about the number of models that were fit to the data because over-reliance on the best-fitting results can lead to statistical artifacts (such as "random high bias" which has been defined in the context of hypothesis testing; e.g., see Fleming (2010)). Many of the model fitting evaluations came from the initial peer-reviewed published reports, although additional models were fit by Dr. Steenland under contractual direction from EPA. At this stage of the EtO risk assessment, the SAB's concern with the large number of models that have been explored can best be addressed by striving for comprehensive reporting of model results; i.e., sensitivity analyses should be reported for a range of results. These should include sensitivity to the functional form of the model (both the choice of relative risk function and the functional form of exposure within). Other aspects of the analysis should also be considered such as inclusion of confounding variables, choice of lag, and cohort (full cohort vs. those with interviews). The SAB recommends inclusion of tables documenting the various estimates of the target parameter of interest (which is predominantly the unit risk estimate) from the many models that were considered for the risk assessment. Although not all models are equally reasonable from a risk assessment perspective, full and transparent reporting of the target parameters of interest provides valuable context. Appropriate use of appendices and thoughtfully designed tables in the main report can minimize the potential for confusion that may result from reporting so many estimates. The SAB notes that the EPA already addressed this recommendation to some degree in its draft assessment by including the EC_{01} and LEC_{01} estimates for many models. These are useful but require an additional transformation before the target quantity of interest can be considered.

As a final comment, the draft assessment states that low-dose extrapolation was performed for risk assessment, but the document does not state whether or not the doses considered for the unit risk estimates were outside the range of the NIOSH exposure data. For instance, as given by the conversion shown in footnote "e" of Table 4-13, 5,800 ppm-days corresponds to 0.075 ppm (with the correction to the formula that one divides by 365). The tenth percentile of the breast cancer incidence data corresponds to 157 ppm-days of exposure and 17 incident cases have nonzero exposure at or below this level (using a 15-year lag; see Table D-1a). Using the same formula, this corresponds to 0.00202 ppm. The LEC_{01} from the preferred model is 0.00576 ppm, more than twice 0.00202 ppm, suggesting there is no low-dose extrapolation in these data. Because there is no low-dose extrapolation in these data, there is less uncertainty of the unit risk estimate than would be otherwise present.

In conclusion, the SAB concurs with the EPA's selected model for the breast cancer incidence data. However, it could be described more clearly and transparently and the SAB prefers a somewhat different set of criteria for selecting the most appropriate model. There are clear advantages to relying on parsimonious regression models directly fit to the individual-level cumulative exposure data using spline models to parameterize exposure. In addition, biologic plausibility and other external information (such as corroborating information from other studies) should help inform the model selection. For example, the incidence rate ratio (IRR) results reported for the Swedish sterilization workers study by Mikoczy et al. (2011) could be used to support the selected model. The task of selecting a final model is more challenging when a set of plausible models gives widely disparate unit risk estimates. The response to

Charge Question 2c provides further advice on how to prioritize potentially plausible models. Ultimately though, the SAB expects that this preferred approach will result in selecting the same or a very similar model to the one selected by the EPA.

Summary of recommendations:

- The SAB requests that the EPA provide better documentation of the NIOSH data, particularly with respect to exposure.
- In selecting models for use in risk assessment, the SAB recommends less reliance on the AIC for model selection. If AIC is used for model selection, it should be used appropriately (as detailed in the response to Charge Questions 2b).
- The SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low-exposure range (e.g., spline models).
- Any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.
- Sensitivity analyses should be reported for a range of results and should include the target quantity of interest (unit risk, excess risk). Although not all models are equally reasonable from a risk assessment perspective, full and transparent reporting of the target parameters of interest provides valuable context.

2b: For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.

The SAB understands that the EPA considered four "reasonable" models for providing unit risk estimates; these all have unit risk estimates reported in Table 4-13. A few additional models are described in Tables 4-12 and 4-13, some of which could also be considered reasonable. The presentation of "reasonable" models considers model fit and some *a priori* (but not clearly articulated) notion about the acceptable shape of the dose-response function in the low-dose region. Because the data do not appear to conform to the *a priori* notion, the draft assessment also considers models based on an untransformed continuous exposure term or a linear regression of the categorical results as reasonable. However, these models do a poorer job reflecting the patterns in the data. Although much of the approach is scientifically appropriate, the SAB does not agree with all of the judgments. In order to strengthen the assessment and presentation, some modifications are suggested to the approach for comparing models and choosing which models are reasonable. The SAB recommends that the discussion be revised to provide more clarity and transparency as well as making the disposition easier to follow. In general, discussion of statistical significance should occur in a more nuanced fashion so that important perspective about the results is not lost in the tendency to turn the statistical evidence into a binary categorization of significant vs. not significant. (This can mislead readers into interpreting a pair of results as inconsistent when their *p*-values, effect estimates, and 95% confidence intervals are very similar but the two *p*-values happen to be on opposite sides of 0.05.) Consideration of reasonable models should address the quality of fit in the region of interest for risk assessment. Prioritizing sufficiently flexible exposure parameterizations (e.g., not linear) and exposure functions with more local behavior (e.g., splines, linear and cubic) reduces the impact of highly exposed individuals on the risk estimates for lower exposures. Discarding a model because the fitted curve is "too steep" needs scientific justification. Furthermore, follow-up by the EPA is needed to clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible" (p. 4-38). The SAB recommends assigning weight to certain types of models based on a modified combination of biologic plausibility and statistical considerations, and using somewhat different considerations for comparing AICs than those currently employed in the draft assessment.

Regarding statistical considerations about various models, the SAB recommends a different set of emphases in the priorities for the most reasonable models and gives guidance on the preference for their ordering. First, priority should be given to regression models that directly use individual-level exposure data. Because the NIOSH cohort has rich individual-level exposure data, linear regression of the categorical results should be de-emphasized in favor of models that directly fit individual-level exposure data. Second, among models fit to individual-level exposure data, models that are more tuned to local behavior in the data should be relied on more heavily. Thus, spline models should be given higher priority over transformations of the exposure. Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited. Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example. Use of AIC can assist with adhering to this principle of parsimony, but its application cannot be used naïvely and without also including scientific considerations. (See further discussion below.) Beyond these recommendations for choosing among models, one advantage of fitting and examining a wide range of models is to get a better understanding of the behavior of the data in the exposure regions of interest. For instance, the models shown in Table 4-13 and Figures 4-5 and 4-6 can be compared, ideally with one or more of these presentations augmented with a few more model fits, including the square root transformation of cumulative exposure, linear regression of categorical results given more categories, and several additional 2-piece linear spline models with different knots. From the comparisons, it is clear that these data suggest a general pattern of the risk rising very rapidly for low-dose exposures and then continuing to rise much more slowly for higher exposures. It is reassuring to observe that many of the fitted models reflect this pattern even though they have different sensitivity to local data.

Results of statistical analyses do not always conform to an *a priori* understanding of biologic plausibility. When this is the case, investigators need to reassess whether the data are correct, a different approach to model fitting should be employed, or whether the prevailing notion of biologic plausibility should be re-examined. When sufficient exploration of the fitted models has been conducted and a range of models with different properties all suggest a dose-response relationship that would not have been predicted in advance (as is the case in these NIOSH data analyses), then the remaining two considerations should be reviewed. The response to Charge Question 4 further discusses uncertainty in the exposure data. The SAB also encourages finding opportunities to use other evidence from the literature to support the observed dose-response relationship. Specifically, the SAB encourages a discussion of the Swedish sterilization workers study results using the internal comparison group.

The application of AIC for selecting models is acceptable within some constraints as outlined in the following discussion. Burnham and Anderson (2004) is an additional reference that discusses the use of AIC for model selection. (The following discussion is intended to be fairly comprehensive and thus covers points that the SAB did not identify as problematic in the draft assessment.) AIC is an appropriate tool to use for model selection for both nested and non-nested models, provided these models use the same likelihood formulation and the same data. AIC is not the preferred way to characterize model fit. For model selection, (1) AIC is not an appropriate tool for comparing across different models that are fit using different measures, such as comparing a Poisson vs. least squares fit to count data; (2) one should not use AICs to compare models using different transformations of the outcome variable; and (3) comparing AICs from models estimated using different software tools, including different implementations within the same statistical package can be challenging because many calculations of AIC remove constants in the likelihood from the estimated AIC. These AIC features require that users interested in comparing AICs across different software routines (even those within one statistical package) understand exactly what likelihood is being maximized and how the AIC is calculated. AIC can be used to compare the same regression model with the same outcome variable and different predictors whether or not these models are nested. This gives a consistent estimate of the mean-squared prediction error (MSPE), which is one criterion for choosing a model. Finally, the theory behind this MSPE criterion can break down with a large number of models. Thus, naïve applications of AIC for model selection can be problematic (but are not necessarily so in any particular application). In particular, differences in AICs could be an artifact of how the calculation was done. This is a possible difference between the linear and exponential relative risk models applied to the breast cancer incidence data. Although the EPA provided some clarification about its approach in its February 19, 2015 memo to the SAB, the SAB still does not have sufficient information to determine whether or not this is the case.

In conclusion, although the SAB concurs with the EPA's selected model, it believes that aspects of EPA's approach to model selection can be refined and that more transparency in the presentation is needed.

Summary of recommendations:

- Revise the discussion to provide more clarity and transparency as well as making the disposition easier to follow.
- Discarding a model because the fitted curve is "too steep" is only acceptable when there is scientific justification.
- Clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible".
- Assign weight to various models based on a modified combination of biological plausibility and statistical considerations; use somewhat different considerations for comparing AICs than those currently employed in the draft assessment.
- Use a different set of emphases in the priorities for the most reasonable models; detailed suggestions are provided by the SAB in this response.

2c: For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.

The method used to identify the knots involves a sequential search over a range of plausible knots to identify the value at which the likelihood is maximized. This is scientifically appropriate and a practical solution that is transparently described.

3.3. Lymphoid Cancer – Model Selection

Charge Question 3: EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

The SAB has general concerns that pertain to this charge question and these concerns may overlap with other charge questions as well. These could be addressed by including a better introduction to the NIOSH worker sample and worker exposure data, before the statistical modeling is described. The NIOSH data source may contain more details, but the present assessment would greatly benefit by including basic statistical summaries from the database in the Draft Assessment. The response to Charge Question #4 provides specific examples of the descriptive statistics on worker and exposure characteristics that might be included in such a background summary of the NIOSH data.

Overall, the SAB suggests that the EPA revise the text, including more clearly providing the rationale for the methods that were used. At present, the text contains disjointed remarks made to address the SAB (2007) report, but the narrative does not read as a cohesive document.

3a: 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 (Section 4.1.1.2).

The SAB recommends that the linear regression of categorical estimates not be selected unless the individual exposure model results are biologically implausible (for which evidence is not presented in the draft assessment). Instead, the SAB prefers the use of individual-level continuous exposure data. The models developed using individual-level continuous exposure data appear to be appropriate even though the draft assessment states that they are unsuitable. The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures. These are summarized in Figure 4-2. The SAB does not agree with the conclusion that the linear regression of the categorical results is a preferable model over the other, better-fitting models using individual-level exposure data.

If the final assessment proceeds with a linear regression of categorical risk, then the SAB suggests the EPA also explore and describe the effects of fitting the model to more categories (narrower ranges) of exposure rather than simply quintiles of the exposure distribution. Also, if the linear regression of categorical risk is selected as the preferred model to derive unit risk estimates for lymphoid cancer, the SAB suggests that the draft assessment include a table of descriptive statistics that summarizes the characteristics of the workers and distribution of exposures in each category. For example, what is the median estimated exposure, age, and years of employment in each of the categories? The extent of confounding of exposure with the subjects' age, years of employment, and their age at start of employment cannot be determined in the draft assessment.

If linear regression of categorical results is chosen, then the use of category median exposure rather than the mean exposure is recommended, as they provide a better representation of exposure to individuals in each category, particularly the highest exposure category. (The SAB acknowledges the highest category was not used in the linear regression of categorical results.)

The SAB recommends presentation of multiple estimates of the unit risk derived under the alternative models for individual and categorized exposures including a summary of any sensitivity analysis conducted for specific model forms (e.g., number of exposure categories or use of median vs. mean exposure as the category exposure metric). This expanded presentation of model results should be accompanied by an updated justification of lymphoid cancer model uncertainty and selection.

Summary of recommendations:

- The SAB recommends that the linear regression of categorical estimates of lymphoid cancer mortality risk not be selected as the preferred model unless the individual exposure model results are biologically implausible.
- In deriving unit risk estimates under a linear regression model for risk by exposure category the use of category median exposure rather than the mean exposure is recommended.
- The SAB recommends presentation of multiple estimates of the unit risk derived under the alternative models for individual and categorized exposures.

3b: Please comment on whether the considerations used for model selection and their application in the selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

Overall, the SAB finds the rationale for the selection of the preferred exposure-response model for lymphoid cancer to be lacking and not transparently communicated. As discussed in the response to Charge Question 3a, the SAB does not concur with the EPA's choice of the linear regression of categorical risks model and recommends that it be avoided unless stronger justification can be provided. The SAB suggests that the EPA consider using the same model for both environmental and occupational exposures. The use of different models needs sufficient justification. As discussed in the response to Charge Questions 2a and 2b, the SAB prefers a somewhat different set of criteria for selecting the most appropriate model for risk assessment; please see those responses for details. The SAB also reiterates the recommendation that the draft assessment should include the results of multiple models so readers can understand the sensitivity of the results and put that in context with the final model selected.

Summary of recommendations:

- As noted in the response to Charge Question 3a, the SAB recommends that the linear regression of categorical estimates of lymphoid cancer mortality risk not be selected as the preferred model unless the individual exposure model results are biologically implausible.
- The SAB finds the rationale for the selection of the preferred exposure-response model for lymphoid cancer to be lacking and not transparently communicated. The SAB refers to the response to Charge Questions 2a and 2b for general recommendations to strengthen the model selection rationale and transparency in the discussion of model inputs and model fitting for the lymphoid cancer data.

3c: EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).
The approach used for deriving risk estimates for lymphoid cancer incidence and the rationale for using this approach are explained transparently and are scientifically appropriate.

However, if the draft assessment were also intended for a broad audience, the approach could be more transparently described. The SAB suggests the EPA go through some more crudely estimated approaches so general readers can understand clearly all the different aspects of obtaining the unit risk and excess risk estimates without having to rely on the more complex life table analyses. If the EPA judges it to be informative, the SAB suggests that extra lifetime risk be presented in terms of the number of lymphoid cancers that are due to the exposure to EtO in the cohort. As another suggestion, the risk estimates (Table 4-5, for example) would benefit by expressing these in scientific notation, rather than a list of leading zeros.

3.4. <u>Uncertainty in the Cancer Risk Estimates</u>

Charge Question 4: Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

The uncertainty discussions are generally clear, objective, and scientifically appropriate but they can be improved and extended. Considerations about uncertainty directly pertaining to the analyses reported can be separated into 1) uncertainty due to the data (particularly from reliance on a single dataset), and 2) uncertainty of the results. Suggestions are provided on how to enhance the presentation and to encompass additional considerations from the SAB.

<u>Uncertainty due to the data (particularly from reliance on a single dataset)</u>
The SAB supports the use of the NIOSH EtO worker cohort described in Steenland et al. (2003, 2004) as the primary data source for the modeling of cancer risk from EtO exposures. This is consistent with the support for the data source in the previous SAB (2007) review. The support of the NIOSH data is founded on study documentation of the original exposure measurements, procedures for exposure estimation (Hornung et al., 1994) and historical modeling (prediction) of exposures that occurred before the time period in which actual exposure measurements were systematically collected. All such model-based reconstructions of exposure data are subject to variable and potentially systematic sources of error (i.e., bias). No statistical treatment of data is expected to be unaffected by such errors and, as noted in the responses to the previous charge questions, any complete statistical treatment should transparently describe both the results of the analysis and the implications of any uncertainty in the data inputs or the assumed statistical model. The previous SAB (2007) review identified several areas of data and modeling uncertainty that should be addressed further. Appendices D and H of the current draft assessment provide a comprehensive response to most of the key questions of data or model uncertainty that were raised in the SAB (2007) review (see the response to Charge Question 5b). For example, a key question raised concerns about the extent to which the introduction of 15- and 20-year lags in cumulative exposure measures (to account for latency) would make the modeled exposure measures heavily dependent on historical time predictions from the Hornung et al. (1994) regression model.

Appendix H provides a comprehensive response on the issue of estimation of exposures prior to 1975 (in the absence of any sampling data prior to 1975). It addresses the implication of the original exposure prediction model assumption (Hornung et al., 1994) that calendar time effects (year) which were significant after 1978 but were absent prior to 1978 - allowing the predictions to pre-1978 exposures to be a function of the 1978 time effect (Figure 1 in Hornung et al., 1994) and additive effects of other predictors in the model of log exposure (exposure category, product type, product age, engineering controls, air volume of work area, etc.).

Based on the draft assessment, supporting materials, and discussion at the November public meeting, the SAB understands that:

1. Hornung et al. (1994) document the workplace constructs and regression model used to fit the exposure prediction model;
2. the original data used to develop the Hornung et al. (1994) exposure model and generate historical predictions of exposures for individual workers cannot be recovered;
3. the Hornung et al. (1994) regression model was cross-validated for workplace exposure data collected during the period 1978-1985 but not for the several decades preceding the study; and
4. the EPA does not currently have a copy of the NIOSH modeled exposure data set to use in conducting exploratory analyses (see below) that would be useful to examine the predicted distributions of historical exposures in the worker cohort.

Recognizing these four points, the SAB recommends that the EPA consolidate the current discussion of exposure uncertainty that appears in various sections of Appendices D and H and also to include in the body of the draft assessment a qualitative discussion of the statistical uncertainty that is associated with the model-based predictions of annual exposures. Furthermore, the SAB recommends that in order to provide a deeper understanding of the data source, the EPA should obtain and archive the NIOSH modeled exposure dataset and include in the revised report several tables or figures with descriptive summaries of the characteristics of the NIOSH cohort and the distributions of predicted exposures in the NIOSH dataset. Although not a true means of assessing the precision or accuracy of the historical prediction of exposures from the regression model, these descriptive summaries will provide insight on historical trends and patterns of variability in the model-generated measures of annual EtO exposure for workers in the study cohort.

Key characteristics of the NIOSH cases and controls that should be analyzable from the study dataset and could be summarized in descriptive tables or figures include the following distributions:

- Gender distribution over time
- Year of entry to the EtO workforce
- Age of entry to the EtO workforce
- Duration of employment in the EtO cohort
- Age and year of departure/retirement from the EtO cohort

A useful descriptive summary of the exposure characteristics for cases and controls could include the following:

- Box plot of cumulative total and peak exposures for individual cases and controls
- Time (individual years or 5-year intervals) plot of the distribution of computed mean, median, and 25th, 75th, and 95th percentile values for annual exposures among the currently working subpopulations of cases and controls
- Summary of percent of total case and control individual exposures in the worker histories that are excluded when various lags are imposed (e.g., 5, 10,15 and 20 years)

Given the approach of using a nested case-control design in the NIOSH cohort analyses as an approximation to the proportional hazards model with a time-dependent covariate, the SAB recognizes that without the analysis datasets that were used, precise reproduction of the “controls” in the analyses is challenging. An alternative solution is to mimic the nested case-control sampling and select controls from the remaining at-risk cohort each time a new case occurs.

The SAB is also concerned that public commenters had exposure data from the NIOSH cohort that the EPA did not have. For instance, a few selected graphs were presented in public comments to the Augmented CAAC that indicated exposure predictions for four jobs in two of the fourteen plants showed lower exposures in some or all years prior to 1975. The SAB was provided only a few carefully selected examples, and thus was unable to assess the extent of these surprising data. This is an uncertainty that can easily be ruled out. Upon reviewing the model equation in Hornung et al. (1994), the SAB finds the surprising historical behavior to be unlikely and could be explained by changes in processes in specific plants, rather than some failure of the model to capture historically larger exposures. The EPA should ensure that they obtain all relevant data released from NIOSH to members of the public.

Although the SAB concurs with the EPA's decision to rely solely on the NIOSH dataset for the risk assessment, the use of only one dataset is a source of uncertainty. This uncertainty can be reduced by highlighting how the Swedish sterilization workers data (Mikoczy et al., 2011) help support the conclusions reached from the NIOSH data.

Uncertainty of the results

The SAB recommends better quantification of the results from the models that were fit as a way of improving the qualitative discussion of uncertainty. In particular, as has been noted in responses to previous charge questions, the unit risks should be reported and compared in sensitivity analyses for a rich set of models. This could include analyses that e.g., differ according to the various outcomes, subcohorts, link functions, functional forms of the exposure (i.e., exposure parameterizations), exposure metrics, exposure lags (see response to Charge Question 1), confounder adjustments, and standard error estimation approaches (Wald vs. profile likelihood). Such information would provide context for the unit risk behavior across the range of plausible models. The SAB also encourages consideration of focusing the reporting of sensitivity analyses on the target parameters of interest (unit risk, excess risk).

If feasible, consideration of additional analyses using alternative exposure metrics is suggested. The December 4, 2014 EPA memo (U.S. EPA, 2014) notes that four exposure metrics were already considered by the agency. If additional metrics are available, it would be valuable to consider these as well.

Additional considerations related to qualitative uncertainty assessment

The SAB encourages consideration of the following points in the document, either directly in the uncertainty discussion, or in other places, as appropriate. The first two points are observations, the third is a recommendation.

1. The dose-response model indicated by the NIOSH cohort that suggests risk increases sharply for low exposures and then increases further but less steeply for higher exposures. The biologic plausibility of this functional form is uncertain, and evidence that there are mechanistic explanations that support this form will inform the risk assessment.
2. The analysis of NIOSH data relies on cumulative exposure as the dose metric. Given the status of the exposure data, it is unlikely that other more refined exposure information can be used to better understand the mechanisms of EtO exposure in cancer initiation. Furthermore, it is often difficult to determine mechanisms from epidemiological data, particularly when these data are limited.
3. The SAB recommends down-weighting all epidemiological results that are based on external standards (e.g., standardized mortality ratio, standardized incidence ratio). The presence of the

healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases.

Summary of recommendations:

- The SAB recommends that the EPA consolidate the current discussion of exposure uncertainty that appears in various sections of Appendices D and H and also to include in the body of the draft assessment a qualitative discussion of the statistical uncertainty that is associated with the model-based predictions of annual exposures.
- To better characterize the NIOSH worker samples and their exposure profiles, the SAB recommends that key demographic, work history and exposure characteristics of the NIOSH cases and controls be summarized in descriptive tables or figures in the body of the EtO risk assessment report.
- The EPA should ensure that they obtain a copy of the NIOSH individual data including all relevant data released from NIOSH to members of the public.
- The SAB repeats its recommendation from previous charge questions that there be improvements in the quantification of the results from the models that were fit as a way of improving the qualitative discussion of uncertainty. Specifically, unit risks should be reported and compared in sensitivity analyses for a rich set of models.
- The SAB recommends down-weighting all epidemiological results that are based on external standards (e.g., standardized mortality ratio, standardized incidence ratio).

3.5. Accuracy, Objectivity, and Transparency of the Revised Draft Assessment

Charge Question 5: Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:

5a: Section 3.3.3 and Appendix C (genotoxicity)

Section 3.33 and Appendix C of the draft assessment present an accurate, objective and transparent summary of the results of research studies published up to July 2013 on EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of action (MOA). Indeed, the genotoxicity database has firmly established that EtO is a direct-acting agent, as evidenced by the formation of DNA adducts and highly reproducible, positive effects in a variety of *in vitro* and *in vivo* mutation and clastogenesis assays. The genotoxic studies examined showed adducts, mutagenesis, or clastogenesis at the bioassay doses and in some cases lower (Donner et al., 2010; Mardsen et al., 2009; Recio et al., 2004; Walker et al., 1997), providing evidence of dose-response concordance for a mutagenic mode of action.

However, several areas of the draft assessment can be improved to enhance the clarity of presentation and to provide a more detailed interpretation of findings within the context of more recent advances in the understanding of the biology of cancer. Specific recommendations and suggestions for revision include:

Recommendations

- Table 3.6 should be revised to specify the sites involved and the relative importance (weight) assigned to each of the individual studies presented. In addition, a new table should be added to show the dose-response relationships for the formation of DNA adducts and the *in vivo* genotoxic effects in humans and comparative model systems.

- 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.
- Although the description of the database was found to be adequate, the synthesis of the information used to support a mutagenic MOA should be presented in a more systematic and complete manner. Section 3.4 should be reorganized around a broader evidence base for a mutagenic MOA to more clearly establish the framework for defining mutagenic MOA. Key elements of this framework, as informed by a recent review by Eastmond (2012) should include:
    - o <u>Characterization of Molecular Alterations</u>: Does the chemical interact with protein and/or DNA, undergo redox cycling, or modulate cell cycle/rates of cell replication, apoptosis, signaling pathways? What are the doses required to induce these changes? In the case of EtO, the primary effect appears to be direct interaction with DNA to produce a variety of DNA adducts. Other effects occur, and include protein adducts and likely oxidative stress.
    - o <u>Characterization of mutagenic or clastogenic effects</u>: Which biological systems are involved and what are the doses required for adduct formation? In the case of EtO, genotoxic effects occur at doses well below those required to induce cytotoxicity or tumorigenesis. It would be helpful to clarify whether specific DNA adducts are associated with genotoxic effects, but the absence of these data does not negate a mutagenic MOA for EtO.
- In the absence of further mechanistic information, evidence for DNA interactions coupled with consistency in the occurrence of mutagenic/clastogenic effects provides a sound basis for applying a mutagenic MOA to risk assessment. Additional data that may be informative in revising the draft to support a mutagenic MOA includes:
    - o <u>Genotoxic Effects in Cancer Target Organs</u>: These effects can include DNA adducts (weight increased if they are known to be promutagenic DNA adducts), mutational and clastogenic effects in the target organ. In the case of EtO there is evidence for mutational effects in several target tissues. For example, EtO-induced breast tumor tissue from mouse cancer bioassays has shown altered mutational spectra (Houle et al. 2006), as well as altered mutational spectra in lung and other target tissue tumors (Hong et al. 2007). The fact that EtO-induced mutational spectra changes occur in tumor suppressor genes and oncogenes provides additional weight for a mutagenic MOA. Regarding lymphoid tumors, there is evidence from several studies for genotoxic effects of EtO in bone marrow and peripheral blood lymphocytes. On a more general basis, if target organ data do not exist, consideration should be given as to whether toxicokinetic or physico-chemical factors exist that would prevent access to the cancer target organ. This does not appear to be the case for EtO.
    - o <u>Non-linearities</u>: Are there non-linearities that would suggest that the mutagenic MOA does not continue to be operative at low- or high-dose levels? In the case of EtO, the DNA adduct dose-response extends to very low doses, well below the cancer effect level (Marsden et al., 2009).
    - o <u>Temporal Relationships</u>: Do DNA adducts and genotoxic effects precede the carcinogenic effect? In the case of EtO, as cited in the draft assessment, short-term and subchronic studies find evidence of genotoxic effects.
    - o <u>Alternative Mechanisms</u>: Are there other effects that might account for the oncogenic effects, at what doses do they occur, and how robust are these findings? In the case of

EtO, cytotoxicity, oxidative stress, and alterations of signaling pathways may occur, but evidence is lacking that these effects would become a primary effect at low doses.
  - Summary of the Cancer MOA: This summary of the key events should describe how they combine to yield a mutagenic basis for cancer causation. As presented in the draft assessment, key events appear to be: (a) DNA adduct formation; (b) mutation/clastogenesis; (c) clonal expansion of altered cells; and (d) tumor formation.

Suggestions

- Inclusion of additional experimental details about the separation of endogenous from exogenous adducts as reported by Marsden et al. (2009) would help provide biological perspective for issues related to risk assessment considerations, especially linearity versus non-linearity of dose-response relationships.
- The genotoxicity section would be improved by consideration of the role that differences in DNA repair capacity between different target cells in different tissues plays in relative vulnerability to mutagenesis. For example, genes known to regulate vulnerability of breast cancer in women, such as BRAC1, BRAC2 and XRCC1, are known to regulate DNA repair pathways in breast tissue (Shi et al., 2004; Hu et al., 2002). This line of thinking can help to inform the biological bases to better understand the shape of the dose response in the low-dose region of the NIOSH dataset.
- In light of the above discussion, the organization of the text can also be revised to include information about known differences in mutagenic and carcinogenic pathways for EtO at different tumor sites, as well as the degree to which biochemical differences at the cellular or tissue level differentially impact MOA. Furthermore, references made in page 3-29 to the levels of different adducts are presented without making a clear and necessary distinction between the putative or assigned biological impact for N-7 versus O-6 DNA adducts.

5b: Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard characterization (p. H-3).

Appendix H provides a summary of the SAB (2007) peer review comments, followed by the agency's response. Overall, the EPA was highly responsive to the comments and recommendations presented in the SAB (2007) report. Responses are transparent, objective, and for the most part, accurate (exceptions are noted in the current review). The agency should be commended for this effort because this was a particularly challenging undertaking given the lack of consensus in the SAB (2007) report on several issues critical to key outcomes of the draft assessments. The EPA not only addressed all major consensus recommendations but also responded specifically to both the majority and minority opinions whenever divergent views were expressed.

There are some recommendations or suggestions of the SAB (2007) peer review that are not implemented in the current draft assessment, including:

1. use of a non-linear modeling approach for deriving a toxicity value;
2. use of the Union Carbide cohort data (Greenberg et al., 1990; Teta et al., 1993; Benson and Teta, 1993) for unit risk derivation;
3. use of a single model to fit the occupational and environmental exposure-relevant regions of the dose-response curve; and
4. moving the contents of Appendix A to the main body of the assessment.

Feedback regarding these agency decisions is provided in the detailed response to this charge question and in responses to other charge questions. This feedback can be summarized as follows:

1. The SAB finds that EtO likely acts by a mutagenic MOA and therefore its potency should be modeled according to a linear low-dose model. EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005) note the following: "A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses ….." (p. 3-23). The SAB finds that the empirical data for EtO and its 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.
2. The SAB concurs with the decision not to use the Union Carbide Cohort data for unit risk derivation, but suggests that the agency discuss the weight of the evidence of the UCC, NIOSH, and Swedish sterilization workers studies. More suggestions regarding the Swedish sterilization workers study can be found in the response to charge question 6.
3. The SAB suggests that the EPA consider using the same model for both environmental and occupational exposures.
4. The SAB agrees with the decision to not move the contents of Appendix A to the main body of the draft assessment.

This charge question asks specifically about responses to comments on endogenous EtO (p. H-4), a nonlinear approach (P. H-13 to H-17), and the cancer hazard characterization. Each of these topics is addressed in the detailed response to the charge question, but can be summarized as follows: (1) The SAB supports the expanded discussion of endogenous EtO provided in the draft assessment and has suggestions for further improvement; (2) as noted above, the SAB agrees with the decision not to include a toxicity value for EtO based upon nonlinear extrapolation, but recommends a more balanced and objective discussion of the subject; and (3) the SAB recognizes and agrees with revisions to strengthen support for a classification of EtO as "carcinogenic to humans."

A more extensive discussion of EPA's responses to the comments and recommendations in SAB (2007) report follows. Comments and recommendations from the SAB in 2007, hereafter referred to as the "2007 SAB" are summarized, followed by a summary of the EPA's responses and the current SAB evaluation of the responses.

Summary of SAB (2007) comments on Charge Question 1a – Carcinogenic Hazard

A majority of the 2007 SAB judged that the weight of the mutagenicity, animal and epidemiology evidence included in the EPA 2006 assessment supported the characterization of EtO as "Carcinogenic to Humans." Although they agreed with the use of internal comparisons for estimating cancer risks, and with characterization of the epidemiology data as "less than completely conclusive", there was a divergence of opinion on the strength of the epidemiology evidence, with a minority of members considering it too weak so that, in light of insufficient data on precursor events in humans, the hazard descriptor "Likely to be Carcinogenic to Humans" would be more appropriate. The 2007 SAB recommended strengthening the assessment by improving the introduction to the hazard identification section, including the addition of an initial summary; enhancing the description and clarifying the criteria for quality descriptors of the epidemiology data, and moving materials presented in Appendix A of the assessment into the body of the assessment. They also requested clarification of the apparent incongruence between the descriptor of the magnitude of the unit risk estimate as "weak" in light of estimated magnitude.

Summary of EPA Response

In response to the SAB (2007) comments, the EPA revised the Hazard Identification chapter by expanding the description, discussion, and strength of the human studies evidence (Sections 3.1 and 3.5.1). The EPA clearly states the criteria for judging strengths and weaknesses of the epidemiology studies, which are summarized in a general form at the beginning of 3.1 but also applied clearly (and repeatedly) in the justification for selection of the NIOSH cohort studies as key for derivation of unit risk elsewhere in the document. Section 3.1.1 now provides better-supported conclusions on the human carcinogenic potential of EtO. EPA also added discussion of studies of precursor events in animals and humans (see response to question 1c. below) that, although limited, support the characterization of EtO as mutagenic to humans. The introductory paragraph summarizing the contents of Chapter 3 that was added improves the readability of the assessment. Another related recommendation was to add "a more inclusive summary figure and/or table at the beginning of Chapter 3.0". The EPA did not address this comment specifically. The EPA also did not move material from Appendix A into the main body of the assessment.

The SAB realizes that the recommendation to add the summary figure/table at the beginning of Chapter 3 was perhaps not clear. The recommendation was meant to include a brief summary of the key findings of the Hazard Assessment at the beginning of the chapter in some form. This is consistent with the new format for IRIS assessments, which includes a grey box at the beginning of chapters in the assessment highlighting the main conclusions of the Hazard Identification section. A similar addition should be considered for Chapter 4 of the current draft assessment.

The SAB agrees with the decision not to transfer *in toto* materials from Appendix A – Critical Review of the Epidemiological Evidence to the main body of the assessment. The addition of the two brief summary tables on the hematopoietic and breast cancer studies is a good alternative for strengthening the chapter. This choice is consistent with the National Research Council (2011) recommendations that the main body of the assessment focus on the critical data, rationales, and analyses used to support the unit risk derivation and that, as much as possible, detailed description of key and other studies or analyses be summarized in appendices with appropriate cross-referencing in the main body of the assessment. If anything, the current document could benefit from transferring more materials to appendices, although it is acknowledged that the current draft assessment is not intended to conform completely to the new format for IRIS assessments.

The EPA also clarified its designation of the unit risk estimate as "weak" in the prior draft assessment, and section 3.5.1 of the current draft assessment provides a good evaluation of the strength of the weight of the evidence in term of Hill's criteria for causality.

Summary of SAB (2007) Comments on Charge Question 1b – Additional Studies/Reports

The 2007 SAB found several key areas of the supporting information for the characterization of EtO as a carcinogenic hazard to be incomplete and/or insufficiently discussed, including endogenous metabolic production of EtO and background adducts, and EtO exposure-associated DNA adduct formation. Some members also suggested consideration of external ethylene exposure because it is metabolized to EtO and provided a list of 34 additional references that could be relevant to the assessment.

Summary of EPA Response

The EPA has included additional literature and expanded the discussion in the supportive evidence section (3.3) of the assessment that describe endogenous EtO metabolic production as well as EtO-DNA adduct formation from external and internal sources (including from endogenous ethylene formation). Section 3.3.2 of the draft assessment and Appendix C provide a more transparent and critical description of the available data (including studies that were not available at the time of the 2006 draft assessment) and recognize its limitations, especially as they relate to the application of analytical techniques that can resolve and quantify the differential contribution of external and endogenous EtO to formation of protein and DNA adducts. The EPA concluded that although endogenous EtO is likely to contribute to measurable risk - even significantly more so at low external exposure levels - it is unlikely to overwhelm the effect from external exposure. With regard to consideration of EtO metabolic formation from external exposure to ethylene, as recommended by a minority of the members, the EPA judged that it would not be useful based on the limitations of studies suggested, therefore, made no changes in the assessment.

Based on the discussion presented in the assessment and considering the weight of the evidence from human and animal studies, the SAB finds EPA's conclusion on endogenous exposure to EtO to be supported. Nonetheless (and also in light of the analyses presented on pages H-15 to H-17 and further insights derived from the SAB recommendations in the response to Charge Question 5a – Section 3.5 of this report), it appears that recognizing this source of metabolic EtO and briefly expanding on its relevance to the assessment would complete the description of sources of endogenous EtO and their relative importance for adduct formation. This could be readily done in detail in Appendix C with the expanded, but succinct description added to Chapter 3.0 and cross-referenced to the appendix.

The EPA added 24 of the 34 additional references recommended by the panel. There was no explanation for the reasons for not including 10 of the references suggested for inclusion.

Summary of SAB (2007) Comments on Charge Question 1c – MOA Conclusions

The 2007 SAB agreed with the EPA's conclusion on a mutagenic MOA for EtO. However, they found that the discussion was incomplete and not sufficiently balanced as to the series of events leading to EtO-induced mutagenesis.

Summary of EPA Response

The EPA expanded sections of the assessment discussing the evidence for formation of DNA adducts, mutagenicity, and possible mechanisms in Chapter 3 (sections 3.3.3 and 3.4 and sections C1-C5 of Appendix C).

The SAB finds that the EPA has been responsive in providing an expanded and more balanced discussion of human and animal studies of precursor events that support a mutagenic MOA. However, the supportive evidence for a mutagenic MOA needs further enhancement and discussion as indicated in the SAB response to Charge Question 5a (Section 3.5 of this report).

Summary of SAB (2007) Comments on Charge Question 1d – Hazard Characterization Discussion

The 2007 SAB did not reach consensus on this question. Some members judged that the hazard characterization discussion of EtO was scientifically balanced and sound, while some members, although agreeing with the mutagenic MOA, considered the lack of data on precursor events in humans at expected levels of EtO exposure to be an important weakness that needed to be addressed in more detail.

Summary of EPA Response

The EPA responded by enhancing relevant sections of the assessment and essentially indicating that, lacking evidence to the contrary, key precursor events observed in the animal studies would be anticipated to occur in humans.

The EPA's enhancements to the relevant sections of the draft assessment have improved the assessment, but the sections relevant to MOA need further support. Please refer to the response to Charge Question 5a (Section 3.5 of this report) for further detail.

Summary of SAB (2007) Comments on Charge Question 2a – Epidemiological Data

The 2007 SAB concurred with the EPA that the NIOSH retrospective cohort studies provide the most robust set of data for estimating the magnitude of carcinogenic risk to humans environmentally exposed to EtO. However, they also recommended that the EPA consider the full range of available epidemiology studies, with special emphasis on the Union Carbide retrospective cohort. They also recommended that the EPA explore the potential for instabilities resulting from the interaction between the chosen time metric in the dose-response model and the treatment of time in the log cumulative with 15-year lag exposure model estimates.

Summary of EPA Response

The EPA expanded the sections describing the epidemiology studies in Chapter 4 and Appendix A and added Table 4-1 ("Considerations used in this assessment for selecting epidemiology studies for quantitative risk estimates") to summarize the criteria for selection of epidemiology studies. The EPA did not include the Union Carbide data and provided the rationale for that decision. Regarding comments about the reliability of the cumulative exposure with a 15-year lag metric used in the dose-response assessment, the EPA provided a response from Dr. Steenland on pages H-8 to H-10 of Appendix H.

The selection of the NIOSH cohort and the decision not to combine these data with the Union Carbide cohort is better and more transparently justified in the revised draft assessment. The draft assessment notes several shortcomings of the UCC data including:

- The UCC cohort is about one-tenth the size of the NIOSH cohort;
- The number of cases is small compared to the NIOSH study;
- The UCC study has a less extensive exposure assessment than the NIOSH study;
    - The UCC exposure assessment was relatively crude;
    - It was based on a small number of department-specific (high-, medium-, and low-exposure intensity) and time-period-specific (1925-1939, 1940-1956, 1957-1973, and 1974-1988) categories;
    - Exposure estimates derived from actual measurements are only available for a few of the categories;
- The UCC study did not include female workers;
- The UCC study contained occupational co-exposures;
- Lack of comparability between the exposure estimates across the UCC and NIOSH studies make grouping together the two cohorts for a rigorous, combined quantitative risk assessment impossible.

The SAB concurs with this assessment of the UCC data and concurs with the decision not to include the UCC data. However, the SAB considers that a more detailed description of the NIOSH cohort is needed as it relates to the derivation of exposure metrics, as indicated in the SAB response to Charge Question 2 (Section 3.2 of this report) for the current draft assessment.

It is not known if Dr. Steenland received only the comment as presented in the Executive Summary of the SAB (2007) report, or the more detailed discussion in pages 20-22 of the SAB (2007) report. The SAB considers that, although consultation with Dr. Steenland on the technical aspects of this recommendation is appropriate because of his intimate knowledge of the exposure model developed for the NIOSH EtO cohort studies, the EPA should have provided its own response to the SAB (2007) recommendation. Dr. Steenland indicates that he was not completely sure about the meaning of the recommendation and proceeded to present a set of reasonable arguments as to why the bias introduced by using this metric would not alter the analysis appreciably. It is also important to note that the exposure estimates likely to be of lower reliability (because there were no exposure measurement data that could be included in the exposure model prior to 1979) are also likely to be higher than the more recent exposures and, therefore, would play a less important role in the current derivation of the point of departure (POD). The response, however, has not completely clarified the issue of potential estimate instabilities introduced by interactions between time-varying predictor variables and the log cumulative exposure with a 15-year lag exposure estimate. This issue is addressed in the SAB response to Charge Question 2 (Section 3.2 of this report) for the current draft assessment.

> <u>Summary of SAB (2007) Comments on Charge Question 2b - Modeling</u>
> The 2007 SAB provided very extensive comments and recommendations in response to this charge question. They were unanimous in recommending that: (1) the EPA not use the categorical results but instead develop risk models using the original individual exposure and cancer data of the NIOSH cohort, and (2) analysis should be made by lymphohematopoietic (LH) cancer subtype. The 2007 SAB did not reach consensus on the appropriateness of linear or non-linear model fit of the data within the observed range and for calculation of the POD, so it was recommended that the EPA explore the use of a range of models (with a preference for biologically-based models). Likewise, they agreed that the EPA did not provide a clear justification for basing LH risk estimates on males only and recommended that gender differences should be explored (there were different opinions on the procedural aspects of incorporating gender differences).

The EPA was highly responsive in addressing concerns about the use of categorical data for POD derivation and contracted with Dr. Steenland, the principal investigator of the NIOSH studies, to perform multiple analyses of the NIOSH cohort data (including use of individual and categorical exposure estimates) using alternative modeling approaches. In addition, there was also an attempt to expand on the error analysis of the NIOSH cohort exposure estimation, although this could not be accomplished because the data files used in that assessment were no longer available. Results from the extensive additional analysis are detailed and well described in the current draft assessment, both in Chapter 4 and in Appendix D, together with the rationale for supporting the decisions by EPA in model selection. Problems with the implementation of the recommendations are described clearly. Outcomes from alternative models are summarized both in tables and graphical form, with justification for the preferred models. It is important to emphasize that Dr. Steenland's involvement in the additional analyses is a strength of the revised draft not only because of his intimate familiarity with the NIOSH cohort studies but his expertise in exposure modeling and occupational epidemiology. The revised assessment for breast cancer risk incidence is based on continuous exposure data. The analysis for LH cancer subtype is based on the NIOSH cohort lymphoid cancer results (results for all LH cancers are also presented) for both genders (no statistically significant gender differences were found). Results for individual and categorical data models are presented; EPA preferred the non-categorical model.

Although there are still significant concerns with the final selection of modeling approaches for derivation of unit risk in the current draft assessment (see the responses to Charge Questions 1-4, Sections 3.1-3.4 of this report), the EPA should be commended for the effort and the commitment of resources to address the comments and recommendations in the SAB (2007) report. Likewise, the EPA considered the SAB's extensive comments on the rationale for non-linear low-dose extrapolation including additional analysis of experimental animal data on mutations by EtO (pages H-15 to H-19 of Appendix H), concluding that the evidence did not indicate low-dose, non-linear extrapolation or threshold dose-response patterns. Thus, the rationale (including more expansion on EPA guidance) for using low-dose, linear extrapolation is improved and stronger in the current assessment, but some concerns remain (see responses to Charge Questions 1-3 and 6, Sections 3.1-3.3 and Section 3.6 of this report).

Concerns about the suitability of life table methodology for determination of LEC_{01} have been addressed. The EPA provides a convincing rationale (especially since alternative approaches are not available) for using the BEIR IV algorithm. The response to the request to present the range unit risk estimates for the upper and lower 95% confidence limits of the EC_{01} is also reasonable.

The EPA also responded in detail to the comments provided in Appendix A of the SAB (2007) report. Many of the comments referred to the use of categorical exposure metrics and regression on group data that are also the subject of the current SAB review and are reflected in the responses to Charge Questions 1-3 (Sections 3.1-3.3 of this report).

> <u>Summary of SAB (2007) Comments on Charge Question 2c – Age-dependent Adjustment Factors (ADAFs)</u>
> The 2007 SAB agreed with the application of default ADAFs because of a lack of data, but indicated that the description in the assessment was insufficient.
>
> <u>Summary of EPA Response</u>
> EPA expanded the section on the application of ADAFs (Section 4.4).

The SAB finds this to be responsive to the SAB (2007) comment.

> <u>Summary of SAB (2007) Comments on Charge Question 2d – Different Models for Occupational and Environmental Exposures</u>
> The 2007 SAB panel agreed that the use of two models was transparently described but disagreed with the use of different models for fitting the lower and higher level of the dose-response curve, recommending that a single model be used.
>
> <u>Summary of EPA Response</u>
> EPA has expanded Section 4.7 to clarify the use of different models for fitting the data applicable to occupational exposure scenarios (i.e., higher exposure range) and to environmental exposures (i.e., lower exposure scenarios).

The SAB suggests that the EPA consider using the same model for both environmental and occupational exposures. (Please refer to the response to Charge Question 3 – Section 3.3 of this report).

<u>Summary of SAB (2007) Comments on Charge Question 2e – Rodent Data</u>
The 2007 SAB agreed with the use of the ppm equivalency method for rodent to human interspecies scaling of EtO exposure, and advised the use of more sophisticated approaches (e.g., PBPK modeling) should the animal data become the basis for unit risk derivation.

<u>Summary of EPA Response</u>
The current assessment is based on human data only. Estimates based on animal data are only provided for comparison, so EPA considered that the use of more sophisticated models was not required for this purpose.

The SAB agrees with EPA's response.

<u>Summary of SAB (2007) Comments on Charge Question 3 - Uncertainty</u>
The 2007 SAB did not respond specifically to this question because it considered that the issues were addressed as part of their responses to Charge Questions 1 and 2.

<u>Summary of EPA Response</u>
The EPA did not have a response.

SAB comments on uncertainty in the current draft assessment are reflected in the response to Charge Question 4 (Section 3.4 of this report).

In summary, the SAB recommends the EPA:

- Consider adding a brief introductory summary of purpose and highlights to each chapter 2, 3 and 4 to improve the readability of the assessment document.
- Expand the description of endogenous sources of EtO to include formation from external exposure to ethylene.
- Summarize the key highlights of Dr. Steenland's further analysis as they reflect on the reliability of the cumulative exposure with 15-year lag metric used in the dose-response assessment.

3.6. <u>Completeness and Clarity of Appendix J – New Studies</u>

Charge Question 6: Please comment on the completeness and clarity of the appendix describing major new studies published since the first external review draft but not included in the revised assessment (Appendix J) and on the conclusion presented in that appendix that the inclusion of these new studies would not substantially alter the hazard or quantitative findings of the assessment.

In general, the logic and progression of the literature review are clearly supported. However, in the descriptions and assessments of the new studies, it is not entirely clear which statements are made by the study authors and which are made by the EPA. The discussion of the Kiran et al. (2010) case-control study is thorough. The conclusion that the Kiran et al. (2010) study overall supports the draft assessment is reasonable. The conclusion that small numbers of participants in the Morgan et al. (1981) and Ambroise et al. (2005) studies preclude more detailed analysis, but warrant inclusion in the review is reasonable. The summary of the Valdez-Flores and Sielken (2013) study discussion in Appendix J-3 is thorough, but parts of the discussion should be moved to the main body of the draft assessment. The SAB generally agrees that the new studies in Appendix J do not substantially alter the findings of the assessment with the exception of the Swedish sterilization workers study (Hagmar et al., 1991; Mikoczy et al., 2011). This study of EtO sterilization workers, with detailed exposure data at low doses with documented substantial effects on breast cancer has stronger implications than suggested in the draft assessment. The strong breast cancer results at low-dose exposures in this study greatly add to the overall findings. The observation of a 2.5-3.5-fold significantly elevated risk of breast cancer associated with low cumulative exposure in this study demonstrates strong evidence of carcinogenicity.

Specific suggestions for expanded inclusion of the Swedish sterilization workers study results (Mikoczy et al., 2011) for breast cancer include:

- Discussion of the study should be moved to a more central position in the draft assessment.
- The Swedish sterilization worker study should be incorporated into an overall weight of evidence assessment of EtO effects at low doses.
- Consideration of using the word "strong" in its Bradford-Hill strength of association analysis.
- Consideration of characterizing the exposure assessment as high quality in light of the results of the exposure matrix for the early period of the study being validated by hemoglobin adduct levels (Hagmar et al., 1991).
- Consideration of a quantitative risk assessment based on the breast cancer data in the study.
- Alternately, consideration of applying NIOSH estimates to the Swedish sterilization workers study to assess the consistency of findings with:
    - Low dose exposure
    - Attenuation of risk with higher exposures
    - The observation of increased breast cancer risk with 16 more years of follow-up (latency)

Other specific suggestions include:

- Consideration of separating agency interpretation of study findings from those of the studies' authors;
- Consideration of an expanded review of recent studies, including summary reviews, with specific focus on issues related to mode of action;
- Consideration of emphasizing the importance of internal comparisons in occupational studies.

3.7. <u>EPA Response to Public Comments</u>

Charge Question 7: EPA solicited public comments on a July 2013 public comment draft of the IRIS carcinogenicity assessment of EtO and has revised the assessment to respond to the scientific issues raised in the comments. A summary of the major public comments and EPA's responses are provided in Appendix L. Has EPA adequately addressed the scientific issues raised in the public comments? For example, please comment on EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a total cancer unit risk estimate.

Appendix L presents a summary of the EPA responses to public comments on the July 2013 draft assessment. The section begins with a brief and clear summary of the comments received.

Before assessing the responses of the EPA to each of the specific comments, a general assessment of the nature of the comments received by the EPA, which primarily came from industry or industry organizations, is presented. In addressing this charge question, the primary focus is to evaluate the quality and thoroughness with which the EPA responded to the public comments rather than to evaluate the issues raised as these are covered in the responses to the other charge questions in the current report.

Comment #1: This comment claims that the EPA failed to follow NRC (2011) guidelines and failed to apply a systematic and weight-of-evidence approach. The EPA response is clear but could be even stronger. There are several places in the draft assessment where the weight-of-evidence approach is discussed and justified. To strengthen the response to this question, some more detail listing places in the draft assessment where NRC (2011) and EPA guidelines as well as the systematic and weight-of-evidence approach are explained and justified would be helpful. There was additional comment on the use of NIOSH breast cancer incidence data that were not publically available. The EPA response clearly described their adherence to the EPA Information Quality Act Guidelines, which do not require all raw epidemiology data be publically available. Constraints due to confidentiality were also noted.

Comment #2: The comment states that the EPA did not properly explain the criteria used to evaluate studies and deem them to be of high quality for inclusion in their analysis. A summary of the characteristics used by EPA in the EtO assessment was revised in order to more clearly respond to this public comment. Criteria used to evaluate data quality are now discussed in much more detail than in the previous document.

Comment #3: The comment states that lymphohematopoietic and lymphoid cancers should not be grouped because they are derived from different cells of origin. The response clearly states the rationale for grouping these together and notes that the SAB (2007) report agreed with the logic of that grouping for comparison purposes. This response is clear and appropriate.

Comment #4: The comment states that the evidence for breast cancer is too weak. The response notes that the document acknowledges that the breast cancer database is more limited than that for other cancers. Further, the response notes that the SAB (2007) report accepted the derivation of a unit risk factor based on that database. This response is clear and appropriate. Additionally, the EPA could also discuss the animal model data (NTP, 1987; Parsons et al., 2013) and Swedish sterilization workers study data (Mikoczy et al., 2011) to provide further support for breast cancer as a potential hazard from EtO exposure.

Comment #5: The comment notes that EtO is a weak mutagen. Both the response and the draft assessment never claim that EtO is a strong mutagen. The "weakness" of EtO as a mutagen as compared to many anti-cancer compounds and other reactive epoxides is clearly stated. In their response, the EPA provides further justification by noting that there is seldom a good correlation between mutagenic and carcinogenic potencies. This response is clear and appropriate.

Comment #6: The comment states that a mutagenic MOA is not supported by the most recent scientific evidence; other MOAs, specifically oxidative stress and cell proliferation, should be considered. There are two major issues here with regard to the MOA. First, the database concerning the MOA is rather complex, which the draft assessment and the EPA response acknowledge. Second, and most significantly, the Parsons et al. (2013) study cited in the comment is considered to be flawed and does not adequately argue that other MOAs besides direct mutagenesis are involved. The response clearly states that there is no support for the conclusions in Parsons et al. (2013). In the response, the EPA cites another recent study (Nagy et al., 2013) that does not support oxidative stress. The response also provides a detailed discussion of the problems of inferring too much from K-ras mutation data. Even fewer data exist to support a proliferative MOA. The EPA response methodically presents the reasoning behind this conclusion.

Comment #7: The comment criticizes the EPA for failing to incorporate the Union Carbide Corporation (UCC) data into the dose-response assessment. It goes on to state that the NIOSH exposure assessment also suffered from limitations. 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.

Comment #8: This comment criticizes the EPA for using summary data rather than the individual data in the modeling of breast cancer mortality and lymphoid cancer despite the SAB (2007) recommendations. Two key points are made in the response. First, the rationale for the modeling procedures used and their consistency with the previous recommendations in the SAB (2007) report are noted. Second, the response notes that the current document adds additional models based on continuous exposure data and has added them to the assessment for comparison purposes. This response is appropriate. However, the SAB suggests that the model should only apply to low-dose exposures and that a range of doses should be specified over which the model applies.

Comment #9: A comment from two sources criticized the EPA for using a non-peer-reviewed supralinear spline model. The response notes that the model was published in 2011. Further, the response notes that use of the model will receive additional review by the SAB. This response is clear and appropriate.

Comment #10: A comment was made regarding other concerns about the modeling procedures used and how they lead to over-prediction of cancer deaths in the NIOSH study. In response to concerns raised by the two publications cited in the comment, the EPA provided additional discussion in Appendix J to specifically address concerns raised with respect to the Valdez-Flores and Sielken (2013) study. The response further suggested that the referenced citations did not provide convincing evidence of flaws in the modeling. Further, the EPA notes that the potential degree of over-prediction is far less than that claimed in the comment and the two papers. This response is appropriate.

Comment #11: A comment was made from three sources that the EPA should present both linear and nonlinear extrapolation approaches. This subject is discussed at great length in the draft assessment and in Appendix H. The response further notes that the SAB (2007) report agreed that there was presently insufficient evidence to support use of a nonlinear extrapolation approach. This response is appropriate.

Comment #12: A comment was made from two sources that combining breast cancer and lymphoid cancer unit risk estimates is not justified, and that the EPA did not discuss competing risks, different background populations, incidence vs. mortality, and the use of different exposure-response models. In their response, the EPA first notes that breast cancer and lymphoid cancers were first modeled separately and then combined. The rationale for combining these unit risk estimates is explained in detail in the draft assessment. Further, the subject of competing and background risks is also discussed in detail in the draft assessment. Finally, the response concludes by noting the distinction between cancer incidence and cancer status. Standard practice in IRIS assessments is to estimate total cancer risk and not just the risk from individual cancer types; this practice is consistent with EPA guidelines and NRC recommendations. This response is appropriate.

Comment #13: A comment was made from three sources that the EPA should reexamine its risk determination given background and endogenous levels of EtO and that the EPA's risk estimates are unrealistically high. The EPA response explains how background rates for the cancers of interest have been taken into account in the risk determination. They also note that in one of the comments an unrealistic exposure concentration was used in arguing their point. This response is appropriate.

Comment #14: Two sources commented that the EPA should not be deriving occupational exposure limits for EtO. The EPA response makes two clarifications. First, the EPA's Office of Pesticide Programs (OPP) is indeed responsible for deriving occupational exposure limits. Second, and more importantly, the response notes that such a derivation was not conducted in the present risk determination. Rather, the response notes that with the models used for the EtO cancer data, the unit risk estimate is not appropriate for the full range of occupational exposure scenarios of interest to OPP. For the purposes of OPP, the assessment provides sample risk estimates for exposure scenarios of interest to OPP for its own risk assessment of sterilization uses of EtO.

Overall Analysis of EPA Response to Public Comments in Appendix L: The responses provided by the EPA are focused, generally complete, and appear to be delivered in good faith.

In addition to evaluating the EPA response (Charge Question 7) to public comments received on the July 2013 draft assessment, the EPA also presented their responses to public comments received on the 2006 draft assessment (U.S. EPA, 2006) in Appendix H. Some of the comments were addressed by changes made in the current assessment. For example, one criticism was that the 2006 draft assessment (U.S. EPA, 2006) had an improper reliance on data from only one sex. The current draft assessment uses data from both sexes. Another example was the EPA response to Comment #7 regarding the modeling procedures. Although the EPA response to the comment on the 2006 draft assessment (U.S. EPA, 2006) was very brief and lacked sufficient detail, these issues are extensively addressed in the current draft assessment and the accompanying appendices. Several other comments were redundant with public comments made on the 2013 draft assessment. Examples include comments on EtO mutagenicity, lack of use of the UCC database, and the use of summary data versus individual data. In summary, the previous EPA responses in Appendix H as well as the changes that were instituted in the current draft assessment adequately and appropriately respond to the public comments on the 2006 draft assessment (U.S. EPA, 2006).

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APPENDIX A: CHARGE TO THE SAB

Charge to the Science Advisory Board for the IRIS Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft—August 2014)

The U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment has developed a draft carcinogenicity assessment of ethylene oxide in support of the Agency's Integrated Risk Information System (IRIS). An earlier version of the carcinogenicity assessment received public comment and underwent external peer review by a panel of EPA's Science Advisory Board (SAB) in 2007. A revised draft assessment has been developed in accordance with the SAB panel recommendations. Primarily because of the new modeling of epidemiologic data done in response to the SAB recommendations, EPA has decided to seek additional SAB peer review. EPA requests comments on how the Agency responded to the 2007 SAB panel recommendations, including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and transparency of the revised draft assessment. EPA will also consider the SAB panel's comments on other scientific issues related to the hazard identification and dose-response assessment associated with the inhalation carcinogenicity of ethylene oxide. A summary of the public and SAB peer review comments from 2007 and EPA's disposition of the comments is presented in Appendix H of the revised draft assessment. The revised draft assessment has also undergone additional public comment in July 2013 and was discussed at an IRIS Bimonthly Public Science meeting in December 2013. A summary of the 2013 public comments and EPA responses can be found in Appendix L.

Goal:

EPA's primary goal is to obtain a review of those sections of the revised draft assessment that deal with the exposure-response modeling of the epidemiologic data from the NIOSH study (Steenland et al., 2004; Steenland et al., 2003) and development of (1) the inhalation unit risk estimates of cancer risk at low (generally environmental) exposure concentrations and (2) estimates of the cancer risk associated with occupational exposures. The specific sections with text pertaining to these issues include:

- Chapter 4 (Cancer Dose-Response Assessment for Inhalation Exposure)
- Appendix D (Reanalyses and Interpretation of Ethylene Oxide Exposure-Response Data)
- Appendix H (Summary of 2007 External Peer Review and Public Comments and Disposition; particularly responses pertaining to SAB comments on issue #2 of the 2006 charge)

A secondary goal is to obtain review of the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or have been substantially revised since the 2007 external peer review:

- Section 3.3.3 and Appendix C (Genotoxicity and Mutagenicity of Ethylene Oxide)
- Appendix H (Summary of 2007 External Peer Review and Public Comments and Disposition)
- Appendix J (Summary of Major New Studies Since the Literature Cutoff Date)

An additional goal is to obtain comment as to whether there are scientific issues that were raised by the public in July 2013 as described in Appendix L that may not have been adequately addressed by EPA.

Background:

The carcinogenicity assessment of ethylene oxide presents an evaluation of the cancer hazard and the derivation of quantitative cancer risk estimates from exposure to ethylene oxide by inhalation.

The hazard assessment (Chapter 3) includes a review of epidemiologic studies, rodent cancer bioassays, and mechanistic studies, e.g., genotoxicity studies. The quantitative assessment includes exposure-response modeling for the derivation of inhalation unit risk estimates of cancer risk at low (generally environmental) exposure concentrations (Sections 4.1 – 4.5) and estimates of the cancer risk associated with some occupational exposure scenarios (Section 4.7).

Based on the hazard assessment, ethylene oxide is characterized as "carcinogenic to humans", and a majority of the SAB Panel agreed with that conclusion (SAB, 2007). This characterization does not rely solely on the evidence from human studies but is based on the total weight of evidence. A further conclusion from the hazard assessment is that there is sufficient evidence to support a mutagenic mode of action for ethylene oxide carcinogenicity, and the SAB agreed with this conclusion (SAB, 2007). To strengthen the hazard evaluation presented in the draft assessment document, the discussion of genotoxicity was substantially revised and expanded, as was the discussion of endogenous ethylene oxide, as recommended by the SAB (SAB, 2007). For the quantitative assessment, exposure-response modeling was conducted for lymphohematopoietic and lymphoid cancer mortality in males and females and for breast cancer incidence and mortality in females, using the occupational data of Steenland et al. (2003) and Steenland et al. (2004), the best single epidemiologic data set with which to study the relationship between ethylene oxide and cancer, according to the SAB (SAB, 2007). For lymphohematopoietic cancers, EPA's primary analysis focused on the lymphoid cancer subtype, as recommended by the SAB (SAB, 2007). The SAB also recommended that EPA's modeling of lymphohematopoietic and lymphoid cancer mortality include female subjects (SAB, 2007), and EPA has conducted exposure-response analyses for these cancer types on both sexes combined. For breast cancer incidence in females, analyses focused on the incidence data from the subcohort with interviews, because this subcohort had more complete case ascertainment than the full incidence cohort and had additional information on potential breast cancer confounders that was not available for the full cohort.

For the exposure-response analyses, EPA did not rely solely on the published categorical data and continuous data analyses but conducted additional analyses using the continuous data[1], as recommended by the SAB (SAB, 2007). A number of different statistical models were examined, including Cox proportional hazards models (using continuous data), two-piece linear and log-linear spline models (using continuous data), and weighted linear regression models of the categorical results. The exposure-response modeling included consideration of lagged exposure periods. For breast cancer incidence, exposure-response modeling included terms for date of birth, parity, and having a first-degree relative with breast cancer.

The selection of the preferred models for developing risk estimates for lymphoid cancer mortality and for breast cancer incidence was based on considerations of statistical fit, assessed by AICs and likelihood ratio p-values, visual inspection of fit, and biological plausibility, making specific choices for estimates of risk in the range of the occupational exposures of concern and for estimates of risk at exposures well below the occupational range of concern (the latter estimates are referred to as unit risk estimates). Sensitivity analyses were performed comparing various model forms and data selection choices, and uncertainties in the quantitative estimates are discussed.

Some of the new modeling work has been published in a peer-reviewed journal (Steenland et al., 2011); however, some of it has received no prior peer review, and this review is the only peer review anticipated.

[1] "Continuous data" refers to data on the individual workers based on exposure values expressed on a continuous scale, as opposed to data for groups of workers in categorical exposure groups that reflect a range of exposure values.

Charge Questions:

The first four charge questions (1-4) pertain to the review of those sections of the draft assessment that deal with the exposure-response modeling of the epidemiologic data and development of cancer risk estimates. The final two questions (5-6) are more general and refer to the accuracy, objectivity, and transparency of the revised draft.

Questions 1-4:

In general, these charge questions seek comment on the methods, results, and conclusions from EPA's cancer dose-response assessment of the epidemiologic data (Chapter 4, omitting Section 4.2, and Appendix D) in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate for the purposes of estimating risk for lymphoid cancer and for breast cancer, and in terms of how well the 2007 SAB recommendations and public comments on these topics (Chapter 4 and Issue 2 of Appendix H) were addressed. In particular, please address the following issues:

1. **Exposure lagging.** Exposure-response modeling was conducted separately for lymphohematopoietic cancer mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox proportional hazards models, a lag period was used to represent an interval before cancer death (or diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was disregarded because it was not considered relevant for the development of the cancer outcome observed. The lag period for each of the different cancer types was selected empirically based on statistical fit. These exposure lag periods were included in EPA's exposure-response analyses using other model forms for the derivation of cancer risk estimates. Please comment on whether the use of lagged exposure estimates in the derivation of cancer risk estimates and the selection of the lag periods used are clearly described and scientifically appropriate.

2. **Breast cancer incidence – model selection.** As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

    2.a. Please comment on whether the considerations used for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence for the purposes of estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

    2.b. For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.

2.c. For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.

3. **Lymphoid cancer – model selection.** EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

   3.a. 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 (Section 4.1.1.2).

   3.b. Please comment on whether the considerations used for model selection and their application in the selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

   3.c. EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).

4. **Uncertainty in the cancer risk estimates.** Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

Questions 5-6:

5. Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:
   - Section 3.3.3 and Appendix C (genotoxicity)
   - Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard characterization (p. H-3).

6. Please comment on the completeness and clarity of the appendix describing major new studies published since the first external review draft but not included in the revised assessment (Appendix J) and on the conclusion presented in that appendix that the inclusion of these new studies would not substantially alter the hazard or quantitative findings of the assessment.

7. EPA solicited public comments on a July 2013 public comment draft of the IRIS carcinogenicity assessment of EtO and has revised the assessment to respond to the scientific issues raised in the comments. A summary of the major public comments and EPA's responses are provided in Appendix L. Has EPA adequately addressed the scientific issues raised in the public comments? For example, please comment on EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a total cancer unit risk estimate.

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