

**Comments from Drs. Sheppard and Heeringa on 01/07/15 Draft Report
to Facilitate Discussion on 2/20/15 Teleconference**

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EPA-SAB-15-xxx

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 SAB in 2007. The draft assessment was revised in accordance 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. 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 in not using 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.

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

7
8 A number of different statistical models were examined for estimating breast cancer incidence risk from
9 low exposure to EtO. The draft assessment presents a number of considerations used in the selection of
10 the preferred model. The SAB generally concurs with the selection of the two-piece spline model for
11 estimating breast cancer incidence. However, the SAB has recommendations on improving the
12 considerations used for model selection, including less reliance on the Akaike information criterion
13 (AIC), more informed use of the AIC, and a better balance between assessment of model fit, *a priori*
14 considerations regarding the nature of the functional form being applied, and biologic plausibility.
15 Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression
16 models with more local fits in the low exposure range (e.g., spline models). The draft assessment also
17 presents risk estimates from other “reasonable models.” Although much of this approach is scientifically
18 appropriate, the SAB finds lacking a clear definition of “reasonable models” and encourages some
19 modifications and more transparency in the presentation. The SAB also provides recommendations on
20 prioritizing statistical considerations in the selection of models.

21
22 For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose
23 categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO.
24 The SAB prefers the use of continuous individual-level exposure data over the use of categorical results.
25 The linear regression of categorical results should not be selected unless the individual exposure model
26 results are biologically implausible. The SAB recommends ~~inclusion-presentation~~ of multiple estimates
27 of the unit risk in sensitivity analyses and an updated justification of model selection. ~~If a linear~~
28 ~~regression of categorical results is used, then the use of more dose categories and category medians~~
29 ~~rather than the means is recommended, as they provide a better representation of exposure to individuals~~
30 ~~in each category, particularly the highest exposure category.~~ The SAB suggests consideration of using
31 the same model for both environmental and occupational exposures. The use of different models for
32 environmental and occupational exposures should only be done with sufficient justification.

33
34 The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be
35 improved and extended. Considerations about uncertainty directly pertaining to the analyses reported
36 can be separated into uncertainty due to the data themselves (particularly from reliance on a single
37 dataset), and uncertainty of the results given the data. The SAB recommends adding descriptive
38 summaries of the characteristics of the NIOSH cohort, better quantification of the results from the
39 various models (such as reporting unit risk estimates and comparisons in sensitivity analyses), and
40 downweighting epidemiologic results based on external standards ~~that may be subject to bias~~ due to the
41 healthy worker effect.
42

Commented [sgh21]: Suggest deleting. Statement is accurate but this recommendation is conditional (on a method we do not want) and secondary to some of the more important recommendation in the cover letter.

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1 The draft assessment presents an accurate, objective, and transparent summary of published studies on
2 EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological
3 studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the
4 carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of
5 action. The SAB finds that several areas of the draft assessment can be improved to enhance the clarity
6 of presentation and to provide a more detailed interpretation of findings within the context of more
7 recent advances in the understanding of the biology of cancer and has specific recommendations and
8 suggestions for revision detailed in the report.
9

10 Appendix H of the draft assessment provides a summary of the 2007 SAB comments and the EPA's
11 response to the comments. The responses are transparent, objective, and for the most part, accurate
12 (exceptions are noted in the current report). In particular, the SAB supports the expanded discussion of
13 endogenous EtO provided in the draft assessment and has suggestions for further improvement; agrees
14 with the decision not to include a unit risk value for EtO based upon nonlinear extrapolation, but
15 recommends a more balanced and objective discussion of the subject; and recognizes and agrees with
16 revisions to strengthen support for a classification of EtO as "carcinogenic in humans."
17

18 In general, the literature review of new studies presented in Appendix J appears complete. The logic and
19 progression of the review is clearly supported. The clarity can be improved by distinguishing between
20 statements made by study authors and statements made by the EPA. The SAB concurs that inclusion of
21 the new studies would not substantially alter the findings of the assessment, with the exception of the
22 Mikoczy study of Swedish workers, which can strengthen support for the hazard characterization of EtO
23 and provide support for the modeling of the NIOSH data.
24

25 Appendix L presents public comments on the July 2013 draft of the assessment and EPA responses to
26 the public comments. The SAB finds that overall, the EPA has been very responsive to the public
27 comments. The responses are thorough, clear, and appropriate.
28

29 The SAB appreciates the opportunity to provide the EPA with advice and looks forward to the agency's
30 response.
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32
33 Sincerely,
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42 Enclosure

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NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board (SAB), a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use. Reports of the SAB are posted on the EPA website at <http://www.epa.gov/sab>

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

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2 Public Health, Hartford, CT

3
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6
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10 **SCIENCE ADVISORY BOARD STAFF**

11 **Mr. Aaron Yeow**, Designated Federal Officer, U.S. Environmental Protection Agency, Science
12 Advisory Board, Washington, DC

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Acronyms and Abbreviations

1		
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4	ADAF	age-dependent adjustment factor
5	AIC	Akaike information criterion
6	CAAC	Chemical Assessment Advisory Committee
7	EC	effective concentration
8	EPA	U.S. Environmental Protection Agency
9	EtO	ethylene oxide
10	HERO	Health and Environmental Research Online
11	IRIS	Integrated Risk Information System
12	IRR	incidence rate ratio
13	LH	lymphohematopoietic
14	MOA	mode of action
15	NCEA	National Center for Environmental Assessment
16	NIOSH	National Institute for Occupational Safety and Health
17	ORD	Office of Research and Development
18	POD	point of departure
19	ppm	parts per million
20	RfC	reference concentration
21	RfD	reference dose
22	SAB	Science Advisory Board
23	UCC	Union Carbide Corporation
24		

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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 accordance 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. 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 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 ethylene oxide (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 EPA is encouraged to revise the discussion of the Cox model, or more generally, relative risk models, to use terminology that can be

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1 directly linked with the published literature. Terminology describing the behavior of the models at the
2 low-exposure range should be clearly defined, particularly terms that are used to make judgments, such
3 as “unstable.”
4

5 The SAB has recommendations on improving the considerations used for model selection, including less
6 reliance on the Akaike information criterion (AIC), more informed use of the AIC, and a better balance
7 between assessment of model fit, *a priori* considerations regarding the nature of the functional form
8 being applied, and biologic plausibility. Specifically, the SAB recommends prioritizing functional forms
9 of the exposure that allow regression models with more local fits in the low exposure range (e.g., spline
10 models). Within the class of spline functions, appropriate use of AICs and/or p-values can help choose
11 between certain fitted models. Any model that is to be considered reasonable for risk assessment must
12 have a dose-response form that is both biologically plausible and ~~reasonably~~ consistent with the
13 observed data.
14

15 The draft assessment also presents risk estimates from other “reasonable models.” Although much of
16 this approach is scientifically appropriate, the SAB finds a lacking of a clear definition of “reasonable
17 models” and encourages some modifications and more transparency in the presentation. Discarding a
18 model because the fitted curve is “too steep” needs scientific justification. Furthermore, follow-up by the
19 EPA is needed to clearly articulate the criteria for determining that models are reasonable as well as
20 providing transparent definitions for frequently used terms such as “too steep,” “unstable,”
21 “problematic,” and “credible.” The SAB recommends assigning weight to certain types of models based
22 on a modified combination of biologic plausibility and statistical considerations, and using somewhat
23 different considerations for comparing AICs than those currently employed in the draft assessment.
24

25 Regarding statistical considerations about various models, the SAB recommends a different set of
26 priorities for establishing the most reasonable models and gives guidance on the preference for their
27 ordering. First, prioritization should be given to regression models that directly use individual-level
28 exposure data. Second, among models fit to individual-level exposure data, models that are more tuned
29 to local behavior in the data should be relied on more heavily. Third, the principle of parsimony should
30 be considered.
31

32 **Lymphoid Cancer – Model Selection**
33

34 For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose
35 categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO.
36 The SAB does not concur with this choice and prefers the use of continuous individual-level exposure
37 data over the use of categorical results. The SAB recommends inclusion presentation of multiple
38 estimates of the unit risk in sensitivity analyses and an updated justification of model selection. If a
39 linear regression of categorical results is used, then the SAB suggests EPA consider using of more dose
40 categories and recommends the use of category medians rather than the means is recommended, as they
41 provide a better representation of exposure to individuals in each category, particularly the highest
42 exposure category.
43

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1 Overall, the SAB finds the rationale for the selection of the preferred exposure-response model for
2 lymphoid cancer to be lacking and not transparently communicated. The SAB suggests that the EPA
3 consider using the same model for both environmental and occupational exposures. The use of different
4 models is acceptable only with sufficient justification. ~~The draft assessment should include the results of
5 all models and on the sensitivity of the results, for all models, not just for the model selected.~~

Commented [LS2]: I suggest deleting here as this is said in the previous paragraph.

Commented [sgh23]: Agree

Uncertainty in the Cancer Risk Estimates

8 The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be
9 improved and extended. Considerations about uncertainty directly pertaining to the analyses reported
10 can be separated into uncertainty due to the data themselves (particularly from reliance on a single
11 dataset), and uncertainty of the results given the data. The SAB recommends that in order to provide a
12 deeper understanding of the data source, the EPA should obtain and archive the NIOSH data and include
13 several tables or figures with descriptive summaries of the characteristics of the NIOSH cohort. The
14 uncertainty arising from the use of a single data source can be reduced by highlighting how the Swedish
15 data help support the conclusions reached from the NIOSH data.

Commented [sgh24]: Here and throughout the report we need to be more specific. We can regularly cite this as the Mikoczy (2011) study or initially site it and then refer to it as the Swedish sterilization worker study.

17 The qualitative discussion of uncertainty can be improved by better quantification of the results from the
18 various models (such as reporting unit risk estimates and comparisons in sensitivity analyses). The SAB
19 recommends downweighting epidemiologic results based on external standards (e.g., standardized
20 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

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

Response to the 2007 SAB Comments

39 Appendix H of the draft assessment provides a summary of the 2007 SAB comments and the EPA's
40 response to the comments. Overall the SAB finds that the EPA was highly responsive to the comments
41 and recommendations. The responses are transparent, objective, and for the most part, accurate
42
43

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(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 unit risk;
2. using the Union Carbide cohort data 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 conditions for including a non-linear assessment per EPA *Guidelines for Carcinogen Risk Assessment* (EPA, 2005) are not met in the case of EtO, and therefore a non-linear modeling approach need not be included;
2. concurs with the decision not to use the Union Carbide Cohort data for unit risk derivation, but suggests that the agency discuss the extent to which this study and others (e.g., the Swedish study) corroborate results from the NIOSH study;
3. suggests that the EPA consider using the same model for both environmental and occupational exposures;
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 unit risk 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 in 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 study. The Swedish study has 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 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

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1 comments. The responses are thorough, clear, and appropriate. There were also some public comments
2 on the 2006 draft assessment in Appendix H. The SAB finds that the revisions made to the draft
3 assessment and the EPA response in Appendix L adequately and appropriately address the issues raised
4 in the public comments in Appendix H.
5

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1
2
2. INTRODUCTION

3 **2.1. Background**

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

15
16 IRIS is a human health assessment program that evaluates scientific information on effects that may
17 result from exposure to specific chemical substances in the environment. IRIS is prepared and
18 maintained by the NCEA within the Office of Research and Development (ORD). Through IRIS, the
19 EPA provides science-based human health assessments to support the agency's regulatory activities and
20 decisions to protect public health. IRIS assessments contain information for chemical substances that
21 can be used to support the first two steps (hazard identification and dose-response assessment) of the
22 human health risk assessment process. When supported by available data, IRIS provides health effects
23 information and toxicity values for chronic health effects (including cancer and effects other than
24 cancer). Government and others combine IRIS toxicity values with exposure information to characterize
25 public health risks of chemical substances; this information is then used to support risk management
26 decisions designed to protect public health.

27
28 The draft carcinogenicity assessment of ethylene oxide presents an evaluation of the cancer hazard
29 and the derivation of quantitative cancer risk estimates from exposure to ethylene oxide by inhalation.
30 The hazard assessment (Chapter 3) includes a review of epidemiologic studies, rodent cancer bioassays,
31 and mechanistic studies, e.g., genotoxicity studies. The quantitative assessment includes exposure-
32 response modeling for the derivation of inhalation unit risk estimates of cancer risk at low (generally
33 environmental) exposure concentrations (Sections 4.1 – 4.5) and estimates of the cancer risk associated
34 with some occupational exposure scenarios (Section 4.7).
35

36 **2.2. Charge to the Science Advisory Board**

37 The EPA requested comments on how the agency responded to the SAB (2007) recommendations,
38 including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and
39 transparency of the revised draft assessment. The EPA also requested comments on other scientific

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1 issues related to the hazard identification and dose-response assessment associated with the inhalation
2 carcinogenicity of ethylene oxide.

3
4 In response to the EPA's request, the SAB augmented the Chemical Assessment Advisory Committee
5 (CAAC) with additional experts to conduct the review. The Augmented CAAC for the Ethylene Oxide
6 Review held a public teleconference on September 30, 2014, a face-to-face meeting on November 18-
7 20, 2014, a follow-up teleconference on [DATE], to discuss and deliberate on the charge questions and
8 to consider public comments. The Chartered SAB conducted a quality review of the report and
9 [DISPOSITION] the report on [DATE].

10
11 The EPA's primary goal was to obtain a review of those sections of the revised draft assessment that
12 deal with the exposure-response modeling of the epidemiologic data from the NIOSH study (Steenland
13 et al., 2003, 2004) and development of (1) the inhalation unit risk estimates of cancer risk at low
14 (generally environmental) exposure concentrations and (2) estimates of the cancer risk associated with
15 occupational exposures.

16
17 A secondary goal is to obtain review of the accuracy, objectivity, and transparency of the revised draft
18 assessment, with particular emphasis on the following sections, which are either new or have been
19 substantially revised since the 2007 external peer review. An additional goal is to obtain comment as to
20 whether there are scientific issues that were raised by the public in July 2013 as described in Appendix L
21 that may not have been adequately addressed by the EPA.

22
23 The charge questions in their entirety are presented in Appendix A. The charge questions are presented
24 individually (in italics) in the next section followed by the SAB response.

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1 **3. RESPONSE TO CHARGE QUESTIONS**
2

3 **3.1. Exposure Lagging**

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

14
15 The draft assessment and appendices clearly describe the nature of the modeled latency for cancer
16 incidence/death and the time lag that is applied to the cumulative exposure measures in the preferred
17 models of risk. The draft assessment and Appendix D describe many new and varied trials at modeling
18 dose response for ethylene oxide exposures, but the final selected models all retain the exposure lag
19 periods identified in the earlier published analyses (Steenland et al., 2003,2004) of the National Institute
20 for Occupational Safety and Health (NIOSH) data: lymphoid cancer and lymphohematopoietic cancer -
21 15 years; breast cancer mortality - 20 years; breast cancer incidence - 15 years.

22
23 The SAB agrees that it is scientifically plausible, and even likely, for there to be a period of latency
24 between biologically important exposures and subsequent cancer incidence or mortality, however, the
25 NIOSH epidemiological data do not provide a strong biological argument in support of or against the
26 15-year latency periods for breast and lymphoid cancers that are adopted in the statistical modeling of
27 relative risks and estimates of unit risks in the draft assessment.

28
29 The existence and length of a latency period for the cancers in question remain a scientific uncertainty in
30 the risk assessment and the EPA is encouraged to continue to address it as such in the assessment. Given
31 this uncertainty, the SAB recommends the CDC 9-11 Working Group Guidelines (CDC, 2013) as a
32 good model for a discussion of the process of assessing latency in cancer onset. However, the SAB does
33 not find the disease-specific discussions in the CDC document to be relevant to the draft assessment.

34
35 With scientific uncertainty over the latency between exposures to ethylene oxide and any associated
36 cancer incidence or mortality, there is certainly statistical uncertainty in how latency should be reflected
37 in the modeling of exposure risk. The draft assessment argues strongly for modeling exposure risk using
38 15-year latency periods for breast cancer incidence and lymphoid cancer mortality. Given no strong
39 statistical support for choosing one lag period over another in modeling breast cancer risk, the draft
40 assessment (pp. 4-31 – 4-32) concludes “The log cumulative exposure model with no lag was considered

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1 less biologically realistic than the corresponding model with a 15-year lag because some lag period
2 would be expected for the development of breast cancer.” The SAB encourages the EPA to refine the
3 discussion of this uncertainty with a paragraph in the body of the assessment and a summary of an
4 analysis (detailed in an appendix) that examines the sensitivity of estimates of unit risks over the
5 plausible range of latency periods (i.e., 0-20 years). Appendix D (pp. D-24 - D-29) presents detailed
6 SAS® output from a new trial of fitting Cox regression (nested case control) models for incident breast
7 cancer to cumulative exposure and log cumulative exposure with varying lag periods (lags of 0, 5, 10,
8 15, and 20 years). Although there is no discussion of this trial or its evaluation in Appendix D, the
9 results for the models fitted to the log of cumulative exposures show very little to distinguish the fit
10 between the model that imposed a 15-year lag and the model that used no lag in cumulative exposure.
11 This analysis matches the results of the original Steenland et al. (2003) analysis, which found nearly
12 equivalent quality of model fits for log cumulative exposure models with 0- or 15-year lags. The SAB
13 encourages the EPA to formalize the presentation and discussion of the quantitative results for the
14 sensitivity analysis of exposure lags that is currently included in Appendix D, focusing on the sensitivity
15 of the EPA’s recommended models and a strongest competitor(s) to the length of the assumed latency
16 period. The body of the draft assessment should include a short summary of the quantitative results of
17 the sensitivity analysis described in detail in the appendix, accompanied by a qualitative discussion of
18 how the results of the sensitivity analysis should factor into an overall assessment of the biological and
19 statistical uncertainty of the unit risk estimates derived under the alternative models of exposure risk.
20

21 **3.2. Breast Cancer Incidence – Model Selection**

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

27
28 *2a: Please comment on whether the considerations used for model selection and their application in the*
29 *selection of preferred exposure-response models for breast cancer incidence for the purposes of*
30 *estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures*
31 *(Section 4.7) are clearly and transparently described and scientifically appropriate.*
32

33 There is not enough detail provided for the NIOSH exposure data for the SAB to determine the
34 appropriateness of the data. Therefore the SAB response is conditional on the assumption that the
35 NIOSH exposure data are appropriate. The SAB requests that the EPA provide better documentation of
36 the NIOSH data, particularly with respect to exposure. The response to Charge Question 4 provides a
37 discussion of considerations of the adequacy of the results not conditional on the appropriateness of the
38 exposure data.
39

40 Although generally the EPA’s model selection for breast cancer incidence is scientifically appropriate, it
41 could be described more clearly and transparently. The EPA is encouraged to revise the discussion of

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1 the Cox model, or more generally, relative risk models, to use terminology that can be directly linked
2 with the published literature. Prentice (1985) provides examples of this terminology and a discussion of
3 relative risk models. Terminology describing the behavior of the models at the low-exposure range
4 should be clearly defined, particularly terms that are used to make judgments, such as “unstable.”
5

6 The EPA’s considerations for model selection included exploration of a range of different models,
7 assessment of their fit using Akaike information criterion (AIC) and/or p-values (and for linear splines,
8 comparison of likelihoods for alternative knot locations), and judgment of their results based on the
9 steepness of the dose-response function at low doses. Fits that produced slope estimates in the low-dose
10 exposure range that were considered too steep (but details of exactly how this determination was made
11 were not given) were not considered further for estimation of the unit risk estimates. In selecting models
12 for use in risk assessment, the SAB recommends less reliance on the AIC, more informed use of AIC,
13 and most importantly, a better balance between assessment of model fit, *a priori* considerations
14 regarding the nature of the functional form being applied, and biologic plausibility considerations of the
15 resulting dose-response estimate. (The response to Charge Question 2b discusses important
16 considerations in using AICs for model selection, which may have some bearing on the appropriateness
17 of using AIC to choose between linear and exponential relative risk model fits.) Specifically, the SAB
18 recommends prioritizing functional forms of the exposure that allow regression models with more local
19 fits in the low-exposure range (e.g., spline models; these are preferred over more global functions, such
20 as untransformed or log-transformed cumulative exposure, that give more weight to the high exposures
21 in the estimated dose response). Within the class of spline functions, appropriate use of AICs and/or p-
22 values can help choose between certain fitted models (see response to Charge Question 2b). Finally, any
23 model that is to be considered reasonable for risk assessment must have a dose-response form that is
24 both biologically plausible and **reasonably** consistent with the observed data. These comments should be
25 helpful for considering how to revise Table 4-12.
26

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

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

9
10 There are clear advantages to relying on parsimonious regression models directly fit to the individual-
11 level cumulative exposure data using spline models to parameterize exposure. It is straightforward to
12 compute unit and excess risk estimates directly from these fitted results. Furthermore, spline models
13 have the advantage of being sensitive to local behavior in the data. They can also be chosen to be
14 parsimonious (an example is a 2-piece linear spline). Models fit to exposure categories are similarly
15 sensitive to local behavior in the data, but they require more parameters to be estimated and are thus less
16 parsimonious than the spline models considered in the assessment. They also impose the implausible
17 assumption that the risk is constant within each exposure category. Furthermore, it is not straightforward
18 to translate the relative risk estimates from a categorical relative risk regression model to unit and excess
19 risk estimates. This requires the less desirable additional step of summarizing the categorical model fit
20 by translating its results into a functional form that can be used in a risk assessment. (See the response to
21 Charge Questions 2b and 3 for further detail.)

22
23 The SAB has some concern about the number of models that were fit to the data because over-reliance
24 on the best-fitting results can lead to statistical artifacts (such as “random high bias” which has been
25 defined in the context of hypothesis testing; e.g., see Fleming (2010)). Many of the model fitting
26 evaluations came from the initial peer-reviewed published reports, although additional models were fit
27 by Dr. Steenland under contractual direction from EPA. At this stage of the EtO risk assessment, the
28 SAB’s concern with the large number of models that have been explored can best be addressed by
29 striving for comprehensive reporting of model results; i.e., sensitivity analyses should be reported for a
30 range of results. These should include sensitivity to the functional form of the model (both the choice of
31 relative risk function and the functional form of exposure within that). Other aspects of the analysis
32 should also be considered such as inclusion of confounding variables, choice of lag, and cohort (full
33 cohort vs. those with interviews). The SAB recommends inclusion of tables documenting the various
34 estimates of the target parameter of interest (which is predominantly the unit risk estimate) from the
35 many models that were considered for the risk assessment. Although not all models are equally
36 reasonable from a risk assessment perspective, full and transparent reporting of the target parameters of
37 interest provides valuable context. Appropriate use of appendices and thoughtfully designed tables in the
38 main report can minimize the potential for confusion that may result from reporting so many estimates.
39 The SAB notes that the EPA already addressed this recommendation to some degree in its draft
40 assessment by including the EC_{01} and LEC_{01} estimates for many models. These are useful but require an
41 additional transformation before the target quantity of interest can be considered.

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1 In conclusion, the SAB generally concurs with EPA's selected model for the breast cancer incidence
2 data. However, a somewhat different set of criteria for selecting the most appropriate model would be
3 preferred. A preferred approach would prioritize the most parsimonious model that fits the data well
4 among exposure parameterizations that are not unduly reliant on data in the high exposure range. In
5 other words, spline functions are preferred over global fits that result from transformations of the
6 exposure. In addition, biologic plausibility and other external information (such as corroborating
7 information from other studies) should be incorporated into the model selection. For example, the
8 incidence rate ratio (IRR) results reported by Mikoczy et al. (2011) could be used to support the selected
9 model. The task of selecting a final model is more challenging when a set of plausible models gives
10 widely disparate unit risk estimates. The response to Charge Question 2c provides further advice on how
11 to prioritize potentially plausible models. Ultimately though, using this preferred approach may result in
12 selection of a model very similar to the one selected by the EPA.

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

24
25 *2b: For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as*
26 *well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3*
27 *and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable*
28 *models" is clearly and transparently described and scientifically appropriate.*
29

30 The SAB interprets the draft assessment's description of "reasonable" models for providing unit risk
31 estimates as those that appear in Table 4-13. A few additional models are described in Table 4-12, some
32 of which could also be considered reasonable. The presentation of "reasonable" models considers model
33 fit and some *a priori* (and not clearly articulated) notion about the acceptable shape of the dose-response
34 function in the low-dose region. Because the data do not appear to conform to the *a priori* notion, the
35 draft assessment also considers models based on an untransformed continuous exposure term or a linear
36 regression of the categorical results as reasonable. However, these models do a poorer job reflecting the
37 patterns in the data. Although much of the approach is scientifically appropriate, the SAB does not
38 completely agree with all of the judgments. In order to strengthen the assessment and presentation, some
39 modifications to the approach to comparing models and choosing which models are reasonable are
40 encouraged. The discussion should be revised to provide more clarity and transparency as well as
41 making the disposition easier to follow. In general, discussion of statistical significance should occur in
42 a more nuanced fashion so that important perspective about the results is not lost in the tendency to turn
43 the statistical evidence into a binary categorization of significant vs. not significant. (This can mislead

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1 readers into interpreting a pair of results as inconsistent when their p-values, effect estimates, and 95%
2 confidence intervals are very similar but the two p-values happen to be on opposite sides of 0.05.)
3 Consideration of reasonable models should address the quality of fit in the region of interest for risk
4 assessment. Prioritizing sufficiently flexible exposure parameterizations (e.g., not linear) and exposure
5 functions with more local behavior (e.g., splines, linear and cubic) reduces the impact of highly exposed
6 individuals on the risk estimates for lower exposures. Discarding a model because the fitted curve is
7 “too steep” needs scientific justification. Furthermore, follow-up by the EPA is needed to clearly
8 articulate the criteria for determining that models are reasonable as well as providing transparent
9 definitions for frequently used terms such as “too steep,” “unstable,” “problematic,” and “credible” (p.
10 4-38). The SAB recommends assigning weight to certain types of models based on a modified
11 combination of biologic plausibility and statistical considerations, and using somewhat different
12 considerations for comparing AICs than those currently employed in the draft assessment.

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

41
42 Results of statistical analyses do not always conform to *a priori* understanding of biologic plausibility.
43 When this is the case, investigators need to reassess whether the data are correct, a different approach to

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1 model fitting should be employed, or whether the prevailing notion of biologic plausibility should be re-
2 examined. When sufficient exploration of the fitted models has been conducted and a range of models
3 with different properties all suggest a dose-response relationship that would not have been predicted in
4 advance (as is the case in these NIOSH data analyses), then the remaining two considerations should be
5 reviewed. The response to Charge Question 4 further discusses uncertainty in the exposure data. The
6 SAB also encourages finding opportunities to use other evidence from the literature to support the
7 observed dose-response relationship. Specifically the SAB encourages a discussion of the Mikoczy et al.
8 (2011) results using the internal comparison group.
9

10 The application of AIC for selecting models is acceptable within some constraints, however this not a
11 preferred way to characterize model fit. AIC is an appropriate tool to select between nested models
12 because it allows tradeoff for parsimony. It is not an appropriate tool for comparing across different
13 models that are fit using different measures, such as comparing a Poisson vs. least squares fit to count
14 data. Similarly one should not use AICs to compare models using different transformations of the
15 outcome variable. There can be a third challenge with comparing AICs from models estimated using
16 different software tools, including different functions within the same statistical package, because many
17 implementations of AIC remove constants in the likelihood from the estimated AIC. AIC can be used to
18 compare the same regression model with the same outcome variable and different predictors. This gives
19 a consistent estimate of the mean-squared prediction error which is one criterion for choosing a model.
20 Finally, the theory behind this criterion can break down with a large number of models. Thus, naïve
21 application of AIC for model selection can be problematic. Differences in AICs could be an artifact of
22 how the calculation was done. This is a possible difference between the linear and exponential relative
23 risk models applied to the breast cancer incidence data, but the information provided to the SAB is
24 insufficient to determine whether or not this is the case.
25

26 In conclusion, the SAB finds that much of the approach to model selection is scientifically appropriate,
27 but encourages some modifications and more transparency in the presentation.
28

29 *2c: For analyses using a two-piece spline model, please comment on whether the method used to*
30 *identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically*
31 *appropriate.*
32

33 The method used to identify the knots involves a sequential search over a range of plausible knots to
34 identify the value at which the likelihood is maximized. This is scientifically appropriate and a practical
35 solution that is transparently described.
36

37 **3.3. Lymphoid Cancer – Model Selection**

38 *Charge Question 3: EPA attempted to develop additional models of the continuous data for lymphoid*
39 *cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for*
40 *the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the*
41 *categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer*

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1 (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous
2 data was selected as the preferred model (Section 4.7).
3

4 The SAB has general concerns that pertain to this Charge Question and these concerns may overlap with
5 others as well. These could be addressed by including a better introduction to the data, before the
6 statistical analysis is described. The NIOSH data source may contain more details, but the present
7 assessment would greatly benefit by repeating some of this information. As examples it would be
8 helpful to build the following tables:

- 9 • Marginal summaries of workers' ages, exposures, and years of entry to employment
- 10 • Cumulative exposure to EtO by duration of employment
- 11 • Cumulative exposure to EtO by year of entry to employment
- 12 • Cumulative exposure to EtO in each of the risk categories

13
14 Overall, the SAB suggests that the EPA revise the text, including more clearly providing the rationale
15 for the methods that were used. At present, the text contains disjointed remarks made to address the
16 SAB (2007) report, but the narrative does not read as a cohesive document.

17
18 *3a: Please comment on EPA's rationale for its use of the linear regression of the categorical results as*
19 *the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer*
20 *(Section 4.1.1.2).*

21
22 The SAB does not prefer the use of linear regression of categorical risks, but rather prefers the use of
23 individual-level continuous exposure data. The models developed using individual-level continuous
24 exposure data appear to be appropriate even though the draft assessment states that they are unsuitable.
25 The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk
26 rises rapidly with a small amount of exposure and then rises much more gradually for even higher
27 exposures. These are summarized in Figure 4-2. The SAB does not agree with the conclusion that the
28 linear regression of the categorical results is a preferable model over the other, better-fitting models
29 using individual-level exposure data.

30
31 ~~The inclusion of a diverse number of cancers into the classification of lymphoid cancers also suggests~~
32 ~~that the data represent a heterogeneous collection of related outcomes. Similarly, this is another~~
33 ~~justification for the use of individual level data, rather than grouping risk levels into a small number of~~
34 ~~quintiles. The SAB recommends that the linear regression of categorical estimates should not be selected~~
35 ~~unless the individual exposure model results are biologically implausible. The draft assessment does not~~
36 ~~present evidence of biological implausibility.~~

37
38 If the final assessment proceeds with a linear regression of categorical risk, then ~~it should~~the SAB
39 suggests EPA also explore the effects of including more categories, rather than quintiles. In the final
40 chosen model, ~~there should be~~the SAB suggests EPA include tables identifying the characteristics of
41 individuals in each of the risk categories. For example, what is the median estimated exposure, age, and
42 years of employment in each of the categories? The extent of confounding of exposure with the subjects'

Commented [LS5]: I'm not sure I understand why this is true. Delete? SGH- I agree.

Commented [LS6]: I also don't see how this follows. Also delete? SGH I agree.

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1 age, years of employment, and their age at start of employment are unable to be determined in the draft
2 assessment. ~~It is likely that these are all highly correlated but the draft assessment does not allow~~
3 ~~identification of these relationships.~~

4
5 The SAB recommends ~~inclusion-presentation~~ of multiple estimates of the unit risk in sensitivity analyses
6 and an updated justification of model selection. If linear regression of categorical results is chosen, then
7 the use of category medians rather than the means are recommended, as they provide a better
8 representation of exposure to individuals in each category, particularly the highest exposure category.
9 *3b: Please comment on whether the considerations used for model selection and their application in the*
10 *selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating*
11 *low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section*
12 *4.7) are clearly and transparently described and scientifically appropriate.*

13
14 Overall, the SAB finds the rationale for the selection of the preferred exposure-response model for
15 lymphoid cancer to be lacking and not transparently communicated. As discussed in our response to
16 Charge Question 3a, the SAB does not concur with EPA's choice of the linear regression of categorical
17 risks model and recommends that it be avoided unless stronger justification can be provided. The SAB
18 suggests that the EPA consider using the same model for both environmental and occupational
19 exposures. The use of different models ~~is acceptable only with~~ needs sufficient justification. As
20 discussed in our response to Charge Questions 2a and 2b, the SAB prefers a somewhat different set of
21 criteria for selecting the most appropriate model for risk assessment; please see those responses for
22 details. ~~The~~ We also reiterate our recommendation that the draft assessment should include the results of
23 all-multiple models and so readers can understand the sensitivity of the results, ~~for all models, not just~~
24 for and put that in context with the final model selected.

25
26 ~~The spline allows different functions of risk for low and high exposure, relies more on local, rather than~~
27 ~~global, behavior of the data. It is not advisable to use one model for risk assessment for part of the~~
28 ~~exposure range and a different model for another part of the exposure range. The report demonstrates~~
29 ~~that it is difficult to estimate the location of the changepoint (or knot). This is a well-known statistical~~
30 ~~problem. How sensitive are the risk estimates to the final choice of the changepoint? The answer to this~~
31 ~~question would allow the determination of whether the spline model is more of a measure of global or~~
32 ~~local behavior. Biologically, the spline model may not have a mechanistic underpinning, but the fitted~~
33 ~~model may not be far from the true behavior.~~

34
35 ~~There seems to be some a priori notion that using a rapidly increasing function to model risk assessment~~
36 ~~is unacceptable. However, all the evidence in the data suggests that there is a very steep dose-response~~
37 ~~in the low-dose range. This general pattern is supported in multiple analyses and by both local and more~~
38 ~~global parameterizations of the exposure. It suggests that it should be trusted and used in the risk~~
39 ~~assessment.~~

40
41 ~~The lack of statistically significant p-values (p. 4-7) is not evidence of a poor-fitting model. Failure to~~
42 ~~find a statistically significant relationship between exposure and risk is not an indication of the failure of~~
43 ~~the model. Neither is the use of AIC a proper measure of a good-fitting model. The AIC only allows~~

Commented [LS7]: OK but not very helpful. I suggest deleting SGH I agree

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~~comparisons of the statistically significant contribution of additional parameters in a pair of nested models, but does not indicate that either model is appropriate.~~

~~Instead, there are model diagnostics that could be explored to validate the adequacy of the fit. The risk equation (Equation 4-2) is assumed to be constant for age, but this assumption can be checked by including a regression term for age in the Cox regression model. In addition, there are definitions of residuals for proportional hazards models of individual level data that can be plotted to identify unusual observations. These are used to locate unusual values of the explanatory variables in the Cox regression. These might identify, for example, a number of very young workers with lymphoid cancer.~~

~~The draft assessment should identify and cite guidance for the use of low dose/low exposure extrapolation in risk assessment and indicate how consistent the draft assessment is with the guidance.~~

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. ~~It could be helpful to~~ The SAB suggests EPA go through some more crudely estimated ~~alternatives 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. ~~It is suggested~~ If 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. ~~The~~ 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.

~~This exercise will help interpreting the steep slope discussed in Charge Question 3b. Specifically, for the spline model, what is the risk associated with higher levels of exposure? Expressed in easily understood terms, this answer might suggest that exposure does indeed rise quickly at low doses but reaches either a high or low plateau. This conclusion would make the results more easily understood.~~

3.4. Uncertainty in the Cancer Risk Estimates

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.

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

6
7 Uncertainty due to the data (particularly from reliance on a single dataset)

8 The SAB supports the use of the NIOSH ethylene oxide worker cohort described in Steenland et al.
9 (2003, 2004) as the primary data source for the modeling of cancer risk from ethylene oxide exposures.
10 This is consistent with the support for the data source in the previous SAB (2007) review. The support
11 of the NIOSH data is founded on study documentation of the original exposure measurements,
12 procedures for exposure estimation (Hornung et al., 1994) and historical modeling (prediction) of
13 exposures that occurred before the time period in which actual exposure measurements were
14 systematically collected. All such model-based reconstructions of exposure data are subject to variable
15 and potentially systematic sources of error (i.e. bias). No statistical treatment of data is expected to be
16 unaffected by such errors and, as noted in the responses to the previous Charge Questions, any complete
17 statistical treatment should transparently describe both the results of the analysis and the implications of
18 any uncertainty in the data inputs or the assumed statistical model. The previous SAB (2007) review
19 identified several areas of data and modeling uncertainty that should be addressed further. Appendices D
20 and H of the current draft assessment provide a comprehensive response to most of the key questions of
21 data or model uncertainty that were raised in the SAB (2007) review (see the response to Charge
22 Question 5b). For example, a key question raised concerns about the extent to which the introduction of
23 15- and 20-year lags in cumulative exposure measures (to account for latency) would make the modeled
24 exposure measures heavily dependent on historical time predictions from the Hornung et al. (1994)
25 regression model.

26
27 Appendix H provides a comprehensive response on the issue of estimation of exposures prior to 1975 (in
28 the absence of any sampling data prior to 1975). It addresses the implication of the original exposure
29 prediction model assumption (Hornung et al., 1994) that calendar time effects (year) which were
30 significant after 1978 but were absent prior to 1978 - allowing the predictions to pre-1978 exposures to
31 be a function of the 1978 time effect (Figure 1 in Hornung et al., 1994) and additive effects of other
32 predictors in the model of log exposure (exposure category, product type, product age, engineering
33 controls, air volume of work area, etc.).

34
35 Based on the draft assessment, supporting materials, and discussion in the public meeting, the SAB
36 understands that:

- 37 1. Hornung et al. (1994) document the workplace constructs and regression model used to fit the
38 exposure prediction model;
- 39 2. the original data used to develop the Hornung et al. (1994) exposure model and generate
40 historical predictions of exposures for individual workers cannot be recovered;
- 41 3. the Hornung et al. (1994) regression model was cross-validated for workplace exposure data
42 collected during the period 1978-1985 but not for the several decades preceding the study; and

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- 1 4. the EPA does not currently have a copy of the NIOSH modeled exposure data set to use in
2 conducting exploratory analyses (see below) that would be useful to examine the predicted
3 distributions of historical exposures in the worker cohort.
4

5 Recognizing these four points, the SAB recommends that the EPA consolidate the current discussion of
6 exposure uncertainty that appears in various sections of Appendices D and H and also to include in the
7 body of the draft assessment a qualitative discussion of the statistical uncertainty that is associated with
8 the model-based predictions of annual exposures. Furthermore, the SAB recommends that in order to
9 provide a deeper understanding of the data source, the EPA should obtain and archive the NIOSH
10 modeled exposure data set and include in the revised report several tables or figures with descriptive
11 summaries of the characteristics of the NIOSH cohort and the distributions of predicted exposures in the
12 NIOSH data set. Although not a true means of assessing the precision or accuracy of the historical
13 prediction of exposures from the regression model, these descriptive summaries will provide insight on
14 historical trends and patterns of variability in the model-generated measures of annual EtO exposure for
15 workers in the study cohort.
16

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

- 19 • Gender distribution over time
20 • Year of entry to the EtO workforce
21 • Age of entry to the EtO workforce
22 • Duration of employment in the EtO cohort
23 • Age and year of departure/retirement from the EtO cohort
24

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

- 27 • Box plot of cumulative total and peak exposures for individual cases and controls
28 • Time (individual years or 5-year intervals) plot of the distribution of computed Q25, Q50, mean,
29 Q75, Q95 values for annual exposures among the currently working subpopulations of cases and
30 controls
31 • Summary of % of total case and control individual exposures in the worker histories that are
32 excluded when the EPA- chosen lag of 15 years is imposed
33

34 Given the approach of using a nested case-control design in the NIOSH cohort analyses as an
35 approximation to the proportional hazards model with a time-dependent covariate, the SAB recognizes
36 that without the analysis datasets that were used, precise reproduction of the “controls” in the analyses is
37 challenging. An alternative solution is to mimic the nested case-control sampling and select controls
38 from the remaining at risk cohort each time a new case occurs.
39

40 The SAB is also concerned that the public had exposure data from the NIOSH cohort that the EPA did
41 not have. For instance, a few selected graphs were presented by the public that indicated exposure
42 predictions for 4 jobs in two of the fourteen plants showed lower exposures in some or all years prior to

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1 1975. The SAB was provided only a few carefully selected examples, and thus was unable to assess the
2 extent of these surprising data. This is an uncertainty that can easily be ruled out. Upon reviewing the
3 model equation in Hornung et al. (1994), the SAB finds the surprising historical behavior to be unlikely
4 and could be explained by changes in processes in specific plants, rather than some failure of the model
5 to capture historically larger exposures. The EPA should ensure that they obtain all relevant data
6 released from NIOSH to members of the public.

7
8 Although the SAB concurs with the EPA's decision to rely solely on the NIOSH dataset for the risk
9 assessment, the use of only one dataset is a source of uncertainty. This uncertainty can be reduced by
10 highlighting how the Swedish data (Mikoczy et al., 2011) help support the conclusions reached from the
11 NIOSH data.

12
13 Uncertainty of the results given the data

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

23
24 If feasible, consideration of additional analyses using alternative exposure metrics is suggested. The
25 December 4, 2014 EPA memo (U.S. EPA, 2014) notes that four exposure metrics were already
26 considered. If additional metrics are available, it would also be valuable to consider these as well.

27
28 Additional considerations related to qualitative uncertainty assessment

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

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

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1 healthy worker effect cannot be denied in these occupational data and the use of an external
2 standard for comparison does not avoid healthy worker types of biases.
3

4 **3.5. Accuracy, Objectivity, and Transparency of the Revised Draft Assessment**

5 *Charge Question 5: Please comment on the accuracy, objectivity, and transparency of the revised draft*
6 *assessment, with particular emphasis on the following sections, which are either new or substantially*
7 *revised since the 2007 external peer review:*
8

9 *5a: Section 3.3.3 and Appendix C (genotoxicity)*
10

11 Section 3.33 and Appendix C of the draft assessment present an accurate, objective and transparent
12 summary of the results of research studies published up to July 2013 on EtO genotoxicity. The SAB
13 agrees that the weight of the scientific evidence from epidemiological studies, laboratory animal studies
14 and in vitro studies supports the general conclusion that the carcinogenicity of EtO in laboratory animals
15 and humans is mediated through a mutagenic mode of action (MOA). Indeed, the genotoxicity database
16 has firmly established that EtO is a direct-acting agent, as evidenced by the formation of DNA adducts
17 and highly reproducible, positive effects in a variety of in vitro and in vivo mutation and clastogenesis
18 assays.
19

20 However, several areas of the draft assessment can be improved to enhance the clarity of presentation
21 and to provide a more detailed interpretation of findings within the context of more recent advances in
22 the understanding of the biology of cancer. Specific recommendations and suggestions for revision
23 include:
24

25 Recommendations

- 26 • Table 3.6 should be revised to specify the sites involved and the relative importance (weight)
27 assigned to each of the individual studies presented. In addition, a new table should be added to
28 show the dose-response relationships for the formation of DNA adducts and the in vivo
29 genotoxic effects in humans and comparative model systems.
- 30 • The rationale for decisions made regarding model selection for calculations of unit risk should be
31 presented in this section, and elsewhere, within the context of MOA considerations and the initial
32 key biological events involved in mutagenesis and carcinogenesis. The evidence for mutagenic
33 MOA can be used to explain the behavior of the data in low dose regions and the subsequent
34 extrapolation for risk assessment.
- 35 • Although the description of the database was found to be adequate, the synthesis of the
36 information used to support a mutagenic MOA should be presented in a more systematic and
37 complete manner. Section 3.4 should be reorganized around a broader evidence base for a
38 mutagenic MOA to more clearly establish the framework for defining mutagenic MOA. Key
39 elements of this framework, as informed by a recent review by Eastmond (2012) should include:
 - 40 ○ Characterization of Molecular Alterations: Does the chemical interact with protein and/or
41 DNA, undergo redox cycles, or modulate cell cycle/rates of cell replication, apoptosis,

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1 signaling pathways? What are the doses required to induce these changes? In the case of
2 EtO, the primary effect appears to be direct interaction with DNA to produce a variety of
3 DNA adducts. Other effects occur include, protein adducts and likely oxidative stress.

4 ○ Characterization of mutagenic or clastogenic effects: Which biological systems and what
5 are the doses required for adduct formation? In the case of EtO, genotoxic effects occur at
6 doses well below those required to induce cytotoxicity or tumorigenesis. It would be
7 helpful to clarify whether specific DNA adducts are associated with genotoxic effects,
8 but the absence of these data does not negate a mutagenic MOA for EtO.

- 9 • In the absence of further mechanistic information, evidence for DNA interactions coupled with
10 consistency in the occurrence of mutagenic/clastogenic effects provides a sound basis for
11 applying a mutagenic MOA to risk assessment. Additional data that may be informative in
12 revising the draft to support a mutagenic MOA includes:

13 ○ Genotoxic Effects in Cancer Target Organs: These effects can include DNA adducts
14 (weight increased if they are known to be promutagenic DNA adducts), mutational and
15 clastogenic effects in the target organ. In the case of EtO there is evidence for mutational
16 effects in several target tissues. For example, EtO-induced breast tumor tissue from
17 mouse cancer bioassays has shown altered mutational spectra (Houle et al. 2006), as well
18 as altered mutational spectra in lung and other target tissue tumors (Hong et al. 2007).

19 The fact that EtO-induced mutational spectra changes occur in tumor suppressor genes
20 and oncogenes provides additional weight for a mutagenic MOA. Regarding lymphoid
21 tumors, there is evidence from several studies for genotoxic effects of EtO in bone
22 marrow and peripheral blood lymphocytes. On a more general basis, if target organ data
23 do not exist, consideration should be given as to whether toxicokinetic or physico-
24 chemical factors exist that would prevent access to the cancer target organ. This does not
25 appear to be the case for EtO.

26 ○ Non-linearities: Are there non-linearities that would suggest that the mutagenic MOA
27 does not continue to be operative at low or high dose levels? In the case of EtO, the DNA
28 adduct dose response extends to very low doses, well below the cancer effect level
29 (Marsden et al., 2009).

30 ○ Temporal Relationships: Do DNA adducts and genotoxic effects precede the
31 carcinogenic effect? In the case of EtO, as cited in the draft assessment, short-term and
32 subchronic studies find evidence of genotoxic effects.

33 ○ Alternative Mechanisms: Are there other effects that might account for the oncogenic
34 effects, at what doses do they occur, and how robust are these findings? In the case of
35 EtO, cytotoxicity, oxidative stress, alterations of signaling pathways may occur, but
36 evidence is lacking that these effects would become a primary effect at low doses.

37 ○ Summarization of the Cancer MOA: This summary of the key events should describe
38 how the key events combine to yield a mutagenic basis for cancer causation. As
39 presented in the draft assessment, key events appear to be: (a) DNA adduct formation; (b)
40 mutation/clastogenesis; (c) clonal expansion of altered cells; (d) tumor formation.

41 Suggestions

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- 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 that are not implemented in the current draft assessment, including:

1. use a non-linear modeling approach for deriving a unit risk;
2. use of the Union Carbide cohort data for unit risk derivation;
3. use 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 decisions [are-is](#) provided in the detailed response to this charge question and in responses to other charge questions. This feedback can be summarized as follows:

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- 1 1. The SAB does not insist that a non-linear approach be included in the assessment. The SAB
2 agrees with the agency that EtO has a genotoxic mode of action (see response to Charge
3 Question 5a) and finds that conditions for including a non-linear assessment per EPA *Guidelines*
4 *for Carcinogen Risk Assessment* (U.S. EPA, 2005) are not met in the case of EtO. However, the
5 SAB recommends that the issue be treated in a manner that is much more balanced and
6 objective.
- 7 2. The SAB concurs with the decision not to use the Union Carbide Cohort data for unit risk
8 derivation, but suggests that the agency discuss the extent to which this study and others (e.g.,
9 the Swedish study) corroborate results from the NIOSH study.
- 10 3. The SAB suggests that the EPA consider using the same model for both environmental and
11 occupational exposures.
- 12 4. The SAB agrees with the decision to not move the contents of Appendix A to the main body of
13 the draft assessment.

14
15 This charge question asks specifically about responses to comments on endogenous EtO (p. H-4), a
16 nonlinear approach (P. H-13 to H-17), and the cancer hazard characterization. Each of these topics is
17 addressed in the detailed response to the charge question, but can be summarized as follows: (1) The
18 SAB supports the expanded discussion of endogenous EtO provided in the draft assessment and has
19 suggestions for further improvement; (2) As noted above, the SAB agrees with the decision not to
20 include a unit risk value for EtO based upon nonlinear extrapolation, but recommends a more balanced
21 and objective discussion of the subject; and (3) the SAB recognizes and agrees with revisions to
22 strengthen support for a classification of EtO as “carcinogenic in humans.”

23
24 A more extensive discussion of EPA’s responses to the comments and recommendations in SAB (2007)
25 report follows. Comments and recommendations from the SAB (2007) report are summarized, followed
26 by a summary of the EPA’s responses and the SAB evaluation of the responses.

27
28 Summary of SAB (2007) comments on Charge Question 1a – Carcinogenic Hazard

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

Commented [sgh28]: Here and throughout this series of comment/response paragraphs I recommend clearly identifying the 2007 SAB when it is the agent. Otherwise we run the risk of readers confusing the 2007 review with the present SAB recommendations.

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1 Summary of EPA Response

2 In response to the SAB (2007) comments, the EPA revised the Hazard Identification chapter by
3 expanding the description, discussion, and strength of the human studies evidence (Sections 3.1
4 and 3.5.1). The EPA clearly states the criteria for judging strengths and weaknesses of the
5 epidemiology studies, which are summarized in a general form at the beginning of 3.1 but also
6 applied clearly (and repeatedly) in the justification for selection of the NIOSH cohort studies as
7 key for derivation of unit risk elsewhere in the document. Section 3.1.1 now provides better
8 supported conclusions on the human carcinogenic potential of EtO. EPA also added discussion
9 of studies of precursor events in animals and humans (see response to question 1c. below) that,
10 although limited, support the characterization of EtO as mutagenic to humans.

11 The introductory paragraph summarizing the contents of Chapter 3 that was added improves the
12 readability of the assessment. Another related recommendation was to add “a more inclusive
13 summary figure and/or table at the beginning of Chapter 3.0”. The EPA did not address this
14 comment specifically. The EPA also did not move material from Appendix A into the main body
15 of the assessment.

16
17 The SAB realizes that the recommendation to add the summary figure/table at the beginning of Chapter
18 3 was perhaps not clear. The recommendation was meant to include a brief summary of the key findings
19 of the Hazard Assessment at the beginning of the chapter in some form. This is consistent with the new
20 format for IRIS assessments, which includes a grey box at the beginning of this chapter (and the rest of
21 the chapters in the assessment) highlighting the main conclusions of the Hazard Identification section. A
22 similar addition should be considered for Chapter 4 of the current draft assessment.

23
24 The SAB agrees with the decision to not transfer *in toto* materials from Appendix A – Critical Review of
25 the Epidemiological Evidence to the main body of the assessment. The addition of the two brief
26 summary tables on the hematopoietic and breast cancer studies is a good alternative for strengthening
27 the chapter. This choice is consistent with the National Research Council (2011) recommendations that
28 the main body of the assessment focus on the critical data, rationales, and analyses used to support the
29 unit risk derivation and that, as much as feasibly possible, detailed description of key and other studies
30 or analyses be summarized in appendices with appropriate cross-referencing in the main body of the
31 assessment. If anything, the current document could benefit from transferring more materials to
32 appendices, although it is acknowledged that the current draft assessment is not intended to conform
33 completely to the new format for IRIS assessments.

34
35 EPA also clarified its designation of the unit risk estimate as “weak” in the prior draft assessment, and
36 section 3.5.1 of the current draft assessment provides a good evaluation of the strength of the weight of
37 the evidence in term of Hill’s criteria for causality.

38
39 Summary of SAB (2007) Comments on Charge Question 1b – Additional Studies/Reports

40 The SAB found several key areas of the supporting information for the characterization of EtO
41 as a carcinogenic hazard to be incomplete and/or insufficiently discussed, including endogenous
42 metabolic production of EtO and background adducts, and EtO exposure-associated DNA adduct
43 formation. Some members also suggested consideration of external ethylene exposure because it

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1 is metabolized to EtO and provided a list of 34 additional references that could be relevant to the
2 assessment.

3
4 Summary of EPA Response

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

19
20 Based on the discussion presented in the assessment and considering the weight of the evidence from
21 human and animal studies, the SAB finds EPA's conclusion on endogenous exposure to EtO to be
22 supported. Nonetheless (and also in light of the analyses presented on pages H-15 to H-17 and further
23 insights derived from the SAB recommendations in the response to Charge Question 5a – Section 3.5 of
24 this report), it appears that recognizing this source of metabolic EtO and briefly expanding on its
25 relevance to the assessment would complete the description of sources of endogenous EtO and their
26 relative importance for adduct formation. This could be readily done in detail in Appendix C with the
27 expanded, but succinct description added to Chapter 3.0 and cross-referenced to the appendix.

28
29 The EPA added 24 of the 34 additional references recommended by the panel. There was no explanation
30 as the reasons for not including 10 of the references suggested for inclusion.

31
32 Summary of SAB (2007) Comments on Charge Question 1c – MOA Conclusions

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

36
37 Summary of EPA Response

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

41
42 The SAB finds that the EPA has been responsive in providing an expanded and more balanced
43 discussion of human and animal studies of precursor events that support a mutagenic MOA. However,

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1 the supportive evidence for a mutagenic MOA needs further enhancement and discussion as indicated in
2 the SAB response to Charge Question 5a (Section 3.5 of this report).

3
4 Summary of SAB (2007) Comments on Charge Question 1d – Hazard Characterization

5 Discussion

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

11
12 Summary of EPA Response

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

16
17 The EPA's enhancements to the relevant sections of the draft assessment have improved the assessment,
18 but the sections relevant to MOA need further support. Please refer to the response to Charge Question
19 5a (Section 3.5 of this report) for further detail.

20
21 Summary of SAB (2007) Comments on Charge Question 2a – Epidemiological Data

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

29
30 Summary of EPA Response

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

38
39 The selection of the NIOSH cohort and the decision not to combine these data with the Union Carbide
40 cohort is better and more transparently justified in the revised draft assessment and the SAB concurs
41 with this decision. However, the SAB considers that a more detailed description of the NIOSH cohort is
42 needed as it relates to the derivation of exposure metrics, as indicated in the SAB response to Charge
43 Question 2 (Section 3.2 of this report) for the current draft assessment.

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1
2 It is not known if Dr. Steenland received only the comment as presented in the Executive Summary the
3 SAB (2007) report, or the more detailed discussion in pages 20-22 of the SAB (2007) report. The SAB
4 considers that, although consultation with Dr. Steenland on the technical aspects of this recommendation
5 is appropriate because of his intimate knowledge of the exposure model developed for the NIOSH EtO
6 cohort studies, the EPA should have provided its own response to the SAB (2007) recommendation. Dr.
7 Steenland indicates that he was not completely sure about the meaning of the recommendation and
8 proceeded to present a set of reasonable arguments as to why the bias introduced by using this metric
9 would not alter the analysis appreciably. It is also important to note that the exposure estimates likely to
10 be of lower reliability (because there were no exposure measurement data that could be included in the
11 exposure model prior to 1979) are also likely to be higher than the more recent exposures and, therefore,
12 would play a less important role in the current derivation of the POD. The response, however, has not
13 completely clarified the issue of potential estimate instabilities introduced by interactions between time-
14 varying predictor variables and the log cumulative exposure with a 15-year lag exposure estimate. This
15 issue is addressed in the SAB response to Charge Question 2 (Section 3.2 of this report) for the current
16 draft assessment.

17
18 Summary of SAB (2007) Comments on Charge Question 2b - Modeling

19 The SAB provided very extensive comments and recommendations in response to this charge
20 question. The panel was unanimous in recommending that: (1) the EPA not use the categorical
21 results but instead develop risk models using the original individual exposure and cancer data of
22 the NIOSH cohort, and (2) analysis should be made by lymphohematopoietic (LH) cancer
23 subtype. The SAB did not reach consensus on the appropriateness of linear or non-linear model
24 fit of the data within the observed range and for calculation of the POD, so it was recommended
25 that the EPA explore the use of a range of models (with a preference for biologically-based
26 models). Likewise, the SAB agreed that the EPA did not provide a clear justification for basing
27 LH risk estimates on males only and recommended that gender differences should be explored
28 (there were different opinions on the procedural aspects of incorporating gender differences).
29

30 The EPA was highly responsive in addressing concerns about the use of categorical data for POD
31 derivation, including obtaining the individual data for the NIOSH cohort and subcontracting with Dr.
32 Steenland, the principal investigator of the NIOSH studies, to perform multiple analyses with these of the
33 NIOSH cohort data (including use of individual and categorical exposure estimates) using alternative
34 modeling approaches. In addition, there was also an attempt to expand on the error analysis of the
35 NIOSH cohort exposure estimation (this could not be accomplished because the data files used in that
36 assessment were no longer available). Results from the extensive additional analysis are detailed and
37 well described in the current draft assessment, both in Chapter 4 and in Appendix D, together with the
38 rationale for supporting the decisions by EPA in model selection. Problems with the implementation of
39 the recommendations are described clearly. Outcomes from alternative models are summarized both in
40 tables and graphical form, with justification for the preferred models. It is important to emphasize that
41 Dr. Steenland's involvement in the additional analyses is a strength of the revised draft not only because
42 of his intimate familiarity with the NIOSH cohort studies but his expertise in exposure modeling and
43 occupational epidemiology. The revised assessment for breast cancer risk incidence is based on

Commented [sgh29]: I don't believe the EPA actually requested or received the individual data. The purpose of the contract with Dr. Steenland was in part to take advantage of his access to the NIOSH individual data (in addition to his expertise in the analysis of the data).

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1 continuous exposure data. The analysis for LH cancer subtype is based on the NIOSH cohort lymphoid
2 cancer results (results for all LH cancers are also presented) for both genders (no statistically significant
3 differences gender differences were found). Results for individual and categorical data models are
4 presented (EPA preferred the non-categorical model).
5

6 Although there are still significant concerns with the final selection of modeling approaches for
7 derivation of unit risk in the current draft assessment (see the responses to Charge Questions 1-4,
8 Sections 3.1-3.4 of this report), the EPA should be commended for the effort and the commitment of
9 resources to address the comments and recommendations SAB (2007) report. Likewise, the EPA
10 considered the SAB's extensive comments on the rationale for non-linear low dose extrapolation
11 including additional analysis of experimental animal data on mutations by EtO (pages H-15 to H-19 of
12 Appendix H), concluding that the evidence did not indicate low dose non-linear extrapolation or
13 threshold dose-response patterns. Thus, the rationale (including more expansion on EPA guidance) for
14 using low dose linear extrapolation is improved and stronger in the current assessment, but some
15 concerns remain (see responses to Charge Questions 1-3 and 6, Sections 3.1-3.3 and Section 3.6 of this
16 report).
17

18 Concerns about the suitability of life table methodology for determination of LEC_{01} have been
19 addressed. The EPA provides a convincing rationale (especially since alternative approaches are not
20 available) for using the BEIR IV algorithm. The response to the request to present the range unit risk
21 estimates for the upper and lower 95% confidence limits of the EC_{01} is also reasonable.
22

23 EPA also responded in detail to the comments provided in Appendix A of the SAB (2007) report. Many
24 of the comments referred to the use of categorical exposure metrics and regression on group data that are
25 also the subject of the current SAB review and are reflected in the responses to Charge Questions 1-3
26 (Sections 3.1-3.3 of this report).
27

28 Summary of SAB (2007) Comments on Charge Question 2c – Age-dependent Adjustment
29 Factors (ADAFs)

30 The SAB agreed with the application of default ADAFs because of a lack of data, but indicated
31 that the description in the assessment was insufficient.
32

33 Summary of EPA Response

34 EPA expanded the section on the application of ADAFs (Section 4.4).
35

36 The SAB finds this to be responsive to the SAB (2007) comment.
37

38 Summary of SAB (2007) Comments on Charge Question 2d – Different Models for
39 Occupational and Environmental Exposures

40 The 2007 SAB panel agreed that the use of two models was transparently described but
41 disagreed with the use of different models for fitting the lower and higher level of the dose-
42 response curve, recommending that a single model be used.
43

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1 Summary of EPA Response

2 EPA has expanded Section 4.7 to clarify the use of different models for fitting the data
3 applicable to occupational exposure scenarios (i.e., higher exposure range) and to environmental
4 exposures (i.e., lower exposure scenarios).

5
6 The SAB suggests that the EPA consider using the same model for both environmental and occupational
7 exposures. (Please refer to the response to Charge Question 3 – Section 3.3 of this report).

8
9 Summary of SAB (2007) Comments on Charge Question 2e – Rodent Data

10 The 2007 SAB panel agreed with the use of the ppm equivalency method for rodent to human
11 interspecies scaling of EtO exposure, and advised the use of more sophisticated approaches (e.g.,
12 PBPK modeling) should the animal data become the basis for unit risk derivation.

13 Summary of EPA Response

14 The current assessment is based on human data only. Estimates based on animal data are only
15 provided for comparison, so EPA considered that the use of more sophisticated models was not
16 required for this purpose.

17
18 The SAB agrees with EPA's response.

19
20 Summary of SAB (2007) Comments on Charge Question 3 - Uncertainty

21 The SAB did not respond specifically to this question because it considered that the issues were
22 addressed as part of their responses to Charge Questions 1 and 2.

23
24 Summary of EPA Response

25 The EPA did not have a response.

26
27 SAB comments on uncertainty in the current draft assessment are reflected in the response to Charge
28 Question 4 (Section 3.4 of this report).

29 **3.6. Completeness and Clarity of Appendix J – New Studies**

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

34
35 In general, the logic and progression of the literature review are clearly supported. However, in the
36 descriptions and assessments of the new studies, it is not entirely clear which statements are made by the
37 study authors and which are made by EPA staff. The discussion of the Kiran et al. (2010) case-control
38 study is thorough. The conclusion that the Kiran et al. (2010) study overall supports the draft assessment
39 is reasonable. The conclusion that small numbers of participants in the Morgan et al. (1981) and
40 Ambroise et al. (2005) studies preclude more detailed analysis, but warrant inclusion in the review is
41 reasonable. The summary of the Valdez-Flores and Sielken (2013) study discussion in Appendix J-3 is

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1 thorough, but parts of the discussion should be moved to the main body of the draft assessment. The
2 SAB generally agrees that the new studies in Appendix J do not substantially alter the findings of the
3 assessment with the exception of the Swedish study (Hagmar et al., 1991; Mikoczy et al., 2011). The
4 Swedish study of EtO sterilization workers, with detailed exposure data at low doses with documented
5 substantial effects on breast cancer has stronger implications than suggested in the draft assessment. The
6 strong breast cancer results at low dose exposures in the Swedish study greatly add to the overall
7 findings. The observation of a 2.5-3.5 significantly elevated risk of breast cancer associated with low
8 cumulative exposure in this study demonstrates strong evidence of carcinogenicity.

9
10 Specific suggestions for expanded inclusion of the Swedish study results for breast cancer include:

- 11 • Discussion of the Mikoczy et al. (2011) study should be moved to a more central position in the
12 draft assessment.
- 13 • Consideration of using the word “strong” in its Bradford-Hill strength of association analysis.
- 14 • Consideration of characterizing the exposure assessment as high quality in light of the results of
15 the exposure matrix for the early period of the study being validated by hemoglobin adduct
16 levels (Hagmar et al., 1991).
- 17 • Consideration of a quantitative risk assessment based on the breast cancer data in the study.
- 18 • Alternately, consideration of applying NIOSH estimates to the Swedish study to assess the
19 consistency of findings with:
 - 20 ○ Low dose exposure
 - 21 ○ Attenuation of risk with higher exposures
 - 22 ○ The observation of increased breast cancer risk with 16 more years of follow-up (latency)

23
24 Other specific suggestions include:

- 25 • Consideration of separating their interpretation of their findings from those of the studies’
26 authors;
- 27 • Consideration of an expanded review of recent studies, including summary reviews, with specific
28 focus on issues related to mode of action;
- 29 • Consideration of emphasizing the importance of internal comparisons in occupational studies.

30 **3.7. EPA Response to Public Comments**

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

38
39 Appendix L presents the EPA responses to public comments on the July 2013 draft assessment. The
40 section begins with a brief and clear summary of the comments received. Appendix L lists the source of

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1 the comments and notes that excluding the three requests to extend the public comment period, a total of
2 16 comments were received. Because there was some repetition, some comments are grouped together,
3 making 14 be the total number of unique comments to which the EPA responded.
4

5 Before assessing the responses of the EPA to each of the 14 specific comments, a general assessment of
6 the nature of the comments received by the EPA, which primarily came from industry or industry
7 organizations, is presented. In addressing this charge question, the primary focus is to evaluate the
8 quality and thoroughness with which the EPA responded to the public comments rather than to evaluate
9 the issues raised as these are covered in the responses to the other charge questions in the current report.
10

11 *Comment #1:* This comment claims that the EPA failed to follow NRC (2011) guidelines and failed to
12 apply a systematic and weight-of-evidence approach. The EPA response is clear but could be even
13 stronger. There are several places in the draft assessment where the weight-of-evidence approach is
14 discussed and justified. To strengthen the response to this question, some more detail listing places in
15 the draft assessment where NRC (2011) and EPA guidelines as well as the systematic and weight-of-
16 evidence approach are explained and justified would be helpful. There was additional comment on the
17 use of NIOSH breast cancer incidence data that were not publically available. The EPA response clearly
18 described their adherence to the EPA Information Quality Act Guidelines, which do not require all raw
19 epidemiology data be publically available. Constraints due to confidentiality were also noted.
20

21 *Comment #2:* The comment states that the EPA did not properly explain the criteria used to evaluate
22 studies and deem them to be of high quality for inclusion in their analysis. A summary of the
23 characteristics used by EPA in the EtO assessment was revised in order to more clearly respond to this
24 public comment. Criteria used to evaluate data quality are now discussed in much more detail than in the
25 previous document.
26

27 *Comment #3:* The comment states that lymphohematopoietic and lymphoid cancers should not be
28 grouped because they are derived from different cells of origin. The response clearly states the rationale
29 for grouping these together and notes that the SAB (2007) report agreed with the logic of that grouping
30 for comparison purposes. This response is clear and appropriate.
31

32 *Comment #4:* The comment states that the evidence for breast cancer is too weak. The response notes
33 that the document acknowledges that the breast cancer database is more limited than that for other
34 cancers. Further, the response notes that the SAB (2007) report accepted the derivation of a unit risk
35 factor based on that database. This response is clear and appropriate. Additionally, the EPA could also
36 discuss the animal model data (NTP, 1987; Parsons et al., 2013) and Swedish occupational data
37 (Mikoczy et al., 2011) to provide further support for breast cancer as a potential hazard from EtO
38 exposure.
39

40 *Comment #5:* The comment notes that EtO is a weak mutagen. Both the response and the draft
41 assessment never claim that EtO is a strong mutagen. The "weakness" of EtO as a mutagen as compared
42 to many anti-cancer compounds and other reactive epoxides is clearly stated. In their response, the EPA

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1 provides further justification by noting that there is seldom a good correlation between mutagenic and
2 carcinogenic potencies. This response is clear and appropriate.
3

4 *Comment #6:* The comment states that a mutagenic MOA is not supported by the most recent scientific
5 evidence; other MOAs, specifically oxidative stress and cell proliferation, should be considered. There
6 are two major issues here with regard to the MOA. First, the database concerning the MOA is rather
7 complex, which the draft assessment and the EPA response acknowledge. Second, and most
8 significantly, the Parsons et al. (2013) study cited in the comment is considered to be flawed and does
9 not adequately argue that other MOAs besides direct mutagenesis are involved. The response clearly
10 states that there is no support for the conclusions in Parsons et al. (2013). In the response, the EPA cites
11 another recent study (Nagy et al., 2013) that does not support oxidative stress. The response also
12 provides a detailed discussion of the problems of inferring too much from K-ras mutation data. Even
13 less data exist to support a proliferative MOA. The EPA response methodically presents the reasoning
14 behind this conclusion.
15

16 *Comment #7:* The comment criticizes the EPA for failing to incorporate the Union Carbide Corporation
17 (UCC) data into the dose-response assessment. It goes on to state that the NIOSH exposure assessment
18 also suffered from limitations. The EPA response is concise and clear. This issue is discussed in detail in
19 the draft assessment and was supported by the SAB (2007) report. The NIOSH study meets the criteria
20 of being a high-quality study much more strongly than the UCC data. This response is well-supported
21 and appropriate. The SAB concurs with the EPA decision to not combine UCC EtO exposure data with
22 those from the NIOSH study.
23

24 *Comment #8:* This comment criticizes the EPA for using summary data rather than the individual data in
25 the modeling of breast cancer mortality and lymphoid cancer despite the SAB (2007) recommendations.
26 Two key points are made in the response. First, the rationale for the modeling procedures used and their
27 consistency with the previous recommendations in the SAB (2007) report are noted. Second, the
28 response notes that the current document adds additional models based on continuous exposure data and
29 has added them to the assessment for comparison purposes. This response is appropriate. However, the
30 SAB suggests that the model should only apply to low-dose exposures and that a range of doses over
31 which the model applies should be specified.
32

33 *Comment #9:* A comment from two sources criticized the EPA for using a non-peer-reviewed
34 supralinear spline model. The response notes that the model was published in 2011. Further, the
35 response notes that use of the model will receive additional review by the SAB. This response is clear
36 and appropriate.
37

38 *Comment #10:* A comment was made regarding other concerns about the modeling procedures used and
39 how they lead to over-prediction of cancer deaths in the NIOSH study. In response to concerns raised by
40 the two publications cited in the comment, the EPA provided additional discussion in Appendix J to
41 specifically address concerns raised with respect to the Valdez-Flores and Sielken (2013) studies. The
42 response further suggested that the referenced citations did not provide convincing evidence of flaws in

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1 the modeling. Further, the EPA notes that the potential degree of over-prediction is far less than that
2 claimed in the comment and the two papers. This response is appropriate.

3
4 *Comment #11:* A comment was made from three sources that the EPA should present both linear and
5 nonlinear extrapolation approaches. This subject is discussed at great length in the draft assessment and
6 in Appendix H. The response further notes that the SAB (2007) report agreed that there was presently
7 insufficient evidence to support use of a nonlinear extrapolation approach. This response is appropriate.

8
9 *Comment #12:* A comment was made from two sources that combining breast cancer and lymphoid
10 cancer unit risk estimates is not justified, and that the EPA did not discuss competing risks, different
11 background populations, incidence vs. mortality, and the use of different exposure-response models. In
12 their response, the EPA first notes that breast cancer and lymphoid cancers were first modeled separately
13 and then combined. The rationale for combining these unit risk estimates is explained in detail in the
14 draft assessment. Further, the subject of competing and background risks is also discussed in detail in
15 the draft assessment. Finally, the response concludes by noting the distinction between cancer incidence
16 and cancer status. Standard practice in IRIS assessments is to estimate total cancer risk and not just the
17 risk from individual cancer types; this practice is consistent with EPA guidelines and NRC
18 recommendations. This response is appropriate.

19
20 *Comment #13:* A comment was made from three sources that the EPA should reexamine its risk
21 determination given background and endogenous levels of EtO and that the EPA's risk estimates are
22 unrealistically high. The EPA response explains how background rates for the cancers of interest have
23 been taken into account in the risk determination. They also note that in one of the comments an
24 unrealistic exposure concentration was used in arguing their point. This response is appropriate.

25
26 *Comment #14:* Two sources commented that the EPA should not be deriving occupational exposure
27 limits for EtO. The EPA response makes two clarifications. First, the EPA's Office of Pesticide
28 Programs (OPP) is indeed responsible for deriving occupational exposure limits. Second, and more
29 importantly, the response notes that such a derivation was not conducted in the present risk
30 determination. Rather, the response notes that with the models used for the EtO cancer data, the unit risk
31 estimate is not appropriate for the full range of occupational exposure scenarios of interest to OPP. For
32 the purposes of OPP, the assessment provides sample risk estimates for exposure scenarios of interest to
33 OPP for its own risk assessment of sterilization uses of EtO.

34
35 *Overall Analysis of EPA Response to Public Comments in Appendix L:* The responses provided by the
36 EPA are focused, generally complete, and delivered in good faith.

37
38 In addition to evaluating the EPA response (Charge Question 7) to public comments received on the July
39 2013 draft assessment, the EPA also presented their responses to public comments received on the 2006
40 draft assessment (EPA, 2006) in Appendix H. Some of the comments were addressed by changes made
41 in the current assessment. For example, one criticism was that the 2006 draft assessment (EPA, 2006)
42 had an improper reliance on data from only one sex. The current draft assessment uses data from both
43 sexes. Another example was the EPA response to Comment #7 regarding the modeling procedures.

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1 Although the EPA response to the comment on the 2006 draft assessment (EPA, 2006) was very brief
2 and lacked sufficient detail, these issues are extensively addressed in the current draft assessment and
3 the accompanying appendices. Several other comments were redundant with public comments made on
4 the 2013 draft assessment. Examples include comments on EtO mutagenicity, lack of use of the UCC
5 database, and the use of summary data versus individual data. In summary, the previous EPA responses
6 in Appendix H as well as the changes that were instituted in the current draft assessment adequately and
7 appropriately respond to the public comments on the 2006 draft assessment (U.S. EPA, 2006).
8
9
10
11
12

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APPENDIX A

**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.

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1 **Background:**

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

9
10 Based on the hazard assessment, ethylene oxide is characterized as “carcinogenic to humans”,
11 and a majority of the SAB Panel agreed with that conclusion ([SAB, 2007](#)). This characterization does not rely
12 solely on the evidence from human studies but is based on the total weight of evidence. A further conclusion
13 from the hazard assessment is that there is sufficient evidence to support a mutagenic mode of action for
14 ethylene oxide carcinogenicity, and the SAB agreed with this conclusion ([SAB, 2007](#)). To strengthen the hazard
15 evaluation presented in the draft assessment document, the discussion of genotoxicity was substantially
16 revised and expanded, as was the discussion of endogenous ethylene oxide, as recommended by the SAB ([SAB,](#)
17 [2007](#)). For the quantitative assessment, exposure-response modeling was conducted for lymphohematopoietic
18 and lymphoid cancer mortality in males and females and for breast cancer incidence and mortality in females,
19 using the occupational data of [Steenland et al. \(2003\)](#) and [Steenland et al. \(2004\)](#), the best single epidemiologic
20 data set with which to study the relationship between ethylene oxide and cancer, according to the SAB ([SAB,](#)
21 [2007](#)). For lymphohematopoietic cancers, EPA’s primary analysis focused on the lymphoid cancer subtype, as
22 recommended by the SAB ([SAB, 2007](#)). The SAB also recommended that EPA’s modeling of
23 lymphohematopoietic and lymphoid cancer mortality include female subjects ([SAB, 2007](#)), and EPA has
24 conducted exposure-response analyses for these cancer types on both sexes combined. For breast cancer
25 incidence in females, analyses focused on the incidence data from the subcohort with interviews, because this
26 subcohort had more complete case ascertainment than the full incidence cohort and had additional
27 information on potential breast cancer confounders that was not available for the full cohort.

28
29 For the exposure-response analyses, EPA did not rely solely on the published categorical data and continuous
30 data analyses but conducted additional analyses using the continuous data¹, as recommended by the SAB ([SAB,](#)
31 [2007](#)). A number of different statistical models were examined, including Cox proportional hazards models
32 (using continuous data), two-piece linear and log-linear spline models (using continuous data), and weighted
33 linear regression models of the categorical results. The exposure-response modeling included consideration of
34 lagged exposure periods. For breast cancer incidence, exposure-response modeling included terms for date of
35 birth, parity, and having a first-degree relative with breast cancer.

36
37 The selection of the preferred models for developing risk estimates for lymphoid cancer mortality and for
38 breast cancer incidence was based on considerations of statistical fit, assessed by AICs and likelihood ratio p-
39 values, visual inspection of fit, and biological plausibility, making specific choices for estimates of risk in the
40 range of the occupational exposures of concern and for estimates of risk at exposures well below the
41 occupational range of concern (the latter estimates are referred to as unit risk estimates). Sensitivity analyses

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.

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1 were performed comparing various model forms and data selection choices, and uncertainties in the
2 quantitative estimates are discussed.

3
4 Some of the new modeling work has been published in a peer-reviewed journal ([Steenland et al., 2011](#));
5 however, some of it has received no prior peer review, and this review is the only peer review anticipated.

6
7 **Charge Questions:**

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

12
13 **Questions 1-4:**

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

20
21 **1. Exposure lagging.** Exposure-response modeling was conducted separately for lymphohematopoietic cancer
22 mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox
23 proportional hazards models, a lag period was used to represent an interval before cancer death (or
24 diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was
25 disregarded because it was not considered relevant for the development of the cancer outcome observed.
26 The lag period for each of the different cancer types was selected empirically based on statistical fit. These
27 exposure lag periods were included in EPA's exposure-response analyses using other model forms for the
28 derivation of cancer risk estimates. Please comment on whether the use of lagged exposure estimates in
29 the derivation of cancer risk estimates and the selection of the lag periods used are clearly described and
30 scientifically appropriate.

31
32 **2. Breast cancer incidence – model selection.** As discussed in the Background section, a number of different
33 statistical models were examined and a number of considerations were used in the selection of the
34 preferred model (the two-piece linear spline model), which was selected for the derivation both of
35 estimates of risk in the range of the occupational exposures of concern and of estimates of risk at
36 exposures well below the occupational range of concern.

37
38 **2.a.** Please comment on whether the considerations used for model selection and their application in
39 the selection of preferred exposure-response models for breast cancer incidence for the purposes of
40 estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational
41 exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

42
43 **2.b.** For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as
44 well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3

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1 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the
2 “reasonable models” is clearly and transparently described and scientifically appropriate.
3

4 **2.c.** For analyses using a two-piece spline model, please comment on whether the method used to
5 identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.
6

7 **3. Lymphoid cancer – model selection.** EPA attempted to develop additional models of the
8 continuous data for lymphoid cancer mortality, as recommended by the SAB ([SAB, 2007](#)), but was unable
9 to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear
10 regression of the categorical results as the preferred model for derivation of the unit risk estimate for
11 lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of
12 the continuous data was selected as the preferred model (Section 4.7).
13

14 **3.a.** Please comment on EPA’s rationale for its use of the linear regression of the categorical results
15 as the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer
16 (Section 4.1.1.2).
17

18 **3.b.** Please comment on whether the considerations used for model selection and their application in
19 the selection of the preferred exposure-response models for lymphoid cancer for the purposes of
20 estimating low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational
21 exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.
22

23 **3.c.** EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for
24 the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the
25 approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for
26 using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).
27

28 **4. Uncertainty in the cancer risk estimates.** Please comment on whether the qualitative discussions of
29 uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.
30

31 **Questions 5-6:**

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

- 35 • Section 3.3.3 and Appendix C (genotoxicity)
- 36 • Appendix H (EPA’s responses to the 2007 external review comments), in particular the responses to the
37 comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard
38 characterization (p. H-3).
39
40

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- 1 6. Please comment on the completeness and clarity of the appendix describing major new studies published
2 since the first external review draft but not included in the revised assessment (Appendix J) and on the
3 conclusion presented in that appendix that the inclusion of these new studies would not substantially alter
4 the hazard or quantitative findings of the assessment.
5
- 6 7. EPA solicited public comments on a July 2013 public comment draft of the IRIS carcinogenicity assessment
7 of EtO and has revised the assessment to respond to the scientific issues raised in the comments. A
8 summary of the major public comments and EPA's responses are provided in Appendix L. Has EPA
9 adequately addressed the scientific issues raised in the public comments? For example, please comment on
10 EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates
11 derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a
12 total cancer unit risk estimate.
13
14
15

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31