

**Science Advisory Board (SAB) Draft Report (January 7, 2015) to Assist
Meeting Deliberations -- Do Not Cite or Quote –**

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the chartered SAB and does not represent EPA policy.

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6 EPA-SAB-15-xxx

7
8 The Honorable Gina McCarthy
9 Administrator
10 U.S. Environmental Protection Agency
11 1200 Pennsylvania Avenue, N.W.
12 Washington, D.C. 20460

13
14 Subject: Science Advisory Board Review of the EPA's *Evaluation of the Inhalation*
15 *Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014)*
16

17 Dear Administrator McCarthy:
18

19 The U.S. Environmental Protection Agency's National Center for Environmental Assessment requested
20 a peer review of the draft carcinogenicity assessment developed in support of the Integrated Risk
21 Information System, *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External*
22 *Review Draft - August 2014)*. An earlier version of the draft assessment was peer reviewed by the SAB
23 in 2007. The draft assessment was revised in accordance to the SAB recommendations and, due
24 primarily to additional modeling of the epidemiologic data, the agency requested an additional SAB peer
25 review.
26

27 The SAB was asked to comment on how the agency responded to the 2007 SAB recommendations,
28 including the exposure-response modeling of epidemiologic data, and the accuracy, objectivity, and
29 transparency of the revised draft assessment. The SAB was also asked to comment on other scientific
30 issues related to the hazard identification and dose-response assessment associated with the inhalation
31 carcinogenicity of ethylene oxide. In response to the EPA's request, the SAB augmented the Chemical
32 Assessment Advisory Committee (CAAC) with additional experts to conduct the review. The enclosed
33 report provides the SAB's consensus advice and recommendations. This letter briefly conveys the major
34 findings.
35

36 Overall the SAB finds the agency has been highly responsive to the 2007 SAB recommendations. The
37 SAB finds that the National Institute of Occupational Safety and Health (NIOSH) dataset is still the
38 most appropriate dataset to use and concurs with the agency in not using the Union Carbide Corporation
39 cohort data. The statistical and epidemiological issues in this assessment are complex and the agency is
40 to be commended for conducting the additional exposure-response modeling in response to the 2007
41 SAB recommendations.
42

43 The draft assessment employed lagged exposure estimates in the derivation of cancer risk estimates.
44 Although there is a scientific rationale for a period of latency between biologically important exposures

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1 and subsequent cancer incidence or mortality, the SAB did not find a strong biological or statistical
2 argument supporting the particular selected latency periods applied for breast and lymphoid cancers. The
3 EPA is encouraged to perform a sensitivity analysis of various latency periods to determine what effect
4 this selection had on risk estimates.

5
6 A number of different statistical models were examined for estimating breast cancer incidence risk from
7 low exposure to EtO. The draft assessment presents a number of considerations used in the selection of
8 the preferred model. The SAB generally concurs with the selection of the two-piece spline model for
9 estimating breast cancer incidence. However, the SAB has recommendations on improving the
10 considerations used for model selection, including less reliance on the Akaike information criterion
11 (AIC), more informed use of the AIC, and a better balance between assessment of model fit, *a priori*
12 considerations regarding the nature of the functional form being applied, and biologic plausibility.
13 Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression
14 models with more local fits in the low exposure range (e.g., spline models). The draft assessment also
15 presents risk estimates from other “reasonable models.” Although much of this approach is scientifically
16 appropriate, the SAB finds lacking a clear definition of “reasonable models” and encourages some
17 modifications and more transparency in the presentation. The SAB also provides recommendations on
18 prioritizing statistical considerations in the selection of models.

19
20 For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose
21 categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO.
22 The SAB prefers the use of continuous individual-level exposure data over the use of categorical results.
23 The linear regression of categorical results should not be selected unless the individual exposure model
24 results are biologically implausible. The SAB recommends inclusion of multiple estimates of the unit
25 risk in sensitivity analyses and an updated justification of model selection. If a linear regression of
26 categorical results is used, then the use of more dose categories and category medians rather than the
27 means is recommended, as they provide a better representation of exposure in each category, particularly
28 the highest exposure category. The SAB suggests consideration of using the same model for both
29 environmental and occupational exposures. The use of different models for environmental and
30 occupational exposures should only be done with sufficient justification.

31
32 The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be
33 improved and extended. Considerations about uncertainty directly pertaining to the analyses reported
34 can be separated into uncertainty due to the data themselves (particularly from reliance on a single
35 dataset), and uncertainty of the results given the data. The SAB recommends adding descriptive
36 summaries of the characteristics of the NIOSH cohort, better quantification of the results from the
37 various models (such as reporting unit risk estimates and comparisons in sensitivity analyses), and
38 downweighting epidemiologic results based on external standards due to the healthy worker effect.

39
40 The draft assessment presents an accurate, objective, and transparent summary of published studies on
41 EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological
42 studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the
43 carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of
44 action. The SAB finds that several areas of the draft assessment can be improved to enhance the clarity

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1 of presentation and to provide a more detailed interpretation of findings within the context of more
2 recent advances in the understanding of the biology of cancer and has specific recommendations and
3 suggestions for revision detailed in the report.
4

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

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

20 Appendix L presents public comments on the July 2013 draft of the assessment and EPA responses to
21 the public comments. The SAB finds that overall, the EPA has been very responsive to the public
22 comments. The responses are thorough, clear, and appropriate.
23

24 The SAB appreciates the opportunity to provide the EPA with advice and looks forward to the agency's
25 response.
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Sincerely,

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34
35
36
37 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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Acronyms and Abbreviations

1		
2		
3	ADAF	age-dependent adjustment factor
4	AIC	Akaike information criterion
5	CAAC	Chemical Assessment Advisory Committee
6	EC	effective concentration
7	EPA	U.S. Environmental Protection Agency
8	EtO	ethylene oxide
9	HERO	Health and Environmental Research Online
10	IRIS	Integrated Risk Information System
11	IRR	incidence rate ratio
12	LH	lymphohematopoietic
13	MOA	mode of action
14	NCEA	National Center for Environmental Assessment
15	NIOSH	National Institute for Occupational Safety and Health
16	ORD	Office of Research and Development
17	POD	point of departure
18	ppm	parts per million
19	RfC	reference concentration
20	RfD	reference dose
21	SAB	Science Advisory Board
22	UCC	Union Carbide Corporation
23		

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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 directly linked with the published literature. Terminology describing the behavior of the models at the

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1 low-exposure range should be clearly defined, particularly terms that are used to make judgments, such
2 as “unstable.”

3
4 The SAB has recommendations on improving the considerations used for model selection, including less
5 reliance on the Akaike information criterion (AIC), more informed use of the AIC, and a better balance
6 between assessment of model fit, *a priori* considerations regarding the nature of the functional form
7 being applied, and biologic plausibility. Specifically, the SAB recommends prioritizing functional forms
8 of the exposure that allow regression models with more local fits in the low exposure range (e.g., spline
9 models). Within the class of spline functions, appropriate use of AICs and/or p-values can help choose
10 between certain fitted models. Any model that is to be considered reasonable for risk assessment must
11 have a dose-response form that is both biologically plausible and reasonably consistent with the
12 observed data.

13
14 The draft assessment also presents risk estimates from other “reasonable models.” Although much of
15 this approach is scientifically appropriate, the SAB finds lacking a clear definition of “reasonable
16 models” and encourages some modifications and more transparency in the presentation. Discarding a
17 model because the fitted curve is “too steep” needs scientific justification. Furthermore, follow-up by the
18 EPA is needed to clearly articulate the criteria for determining that models are reasonable as well as
19 providing transparent definitions for frequently used terms such as “too steep,” “unstable,”
20 “problematic,” and “credible.” The SAB recommends assigning weight to certain types of models based
21 on a modified combination of biologic plausibility and statistical considerations, and using somewhat
22 different considerations for comparing AICs than those currently employed in the draft assessment.

23
24 Regarding statistical considerations about various models, the SAB recommends a different set of
25 priorities for establishing the most reasonable models and gives guidance on the preference for their
26 ordering. First, prioritization should be given to regression models that directly use individual-level
27 exposure data. Second, among models fit to individual-level exposure data, models that are more tuned
28 to local behavior in the data should be relied on more heavily. Third, the principle of parsimony should
29 be considered.

30
31 **Lymphoid Cancer – Model Selection**

32
33 For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose
34 categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO.
35 The SAB prefers the use of continuous individual-level exposure data over the use of categorical results.
36 The SAB recommends inclusion of multiple estimates of the unit risk in sensitivity analyses and an
37 updated justification of model selection. If a linear regression of categorical results is used, then the use
38 of more dose categories and category medians rather than the means is recommended, as they provide a
39 better representation of exposure in each category, particularly the highest exposure category.

40
41 Overall, the SAB finds the rationale for the selection of the preferred exposure-response model for
42 lymphoid cancer to be lacking and not transparently communicated. The SAB suggests that the EPA
43 consider using the same model for both environmental and occupational exposures. The use of different

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1 models is acceptable only with sufficient justification. The draft assessment should include the results of
2 all models and on the sensitivity of the results, for all models, not just for the model selected.

3
4 **Uncertainty in the Cancer Risk Estimates**

5
6 The uncertainty discussions are generally clear, objective, and scientifically appropriate, but they can be
7 improved and extended. Considerations about uncertainty directly pertaining to the analyses reported
8 can be separated into uncertainty due to the data themselves (particularly from reliance on a single
9 dataset), and uncertainty of the results given the data. The SAB recommends that in order to provide a
10 deeper understanding of the data source, the EPA should obtain and archive the NIOSH data and include
11 several tables or figures with descriptive summaries of the characteristics of the NIOSH cohort. The
12 uncertainty arising from the use of a single data source can be reduced by highlighting how the Swedish
13 data help support the conclusions reached from the NIOSH data.

14
15 The qualitative discussion of uncertainty can be improved by better quantification of the results from the
16 various models (such as reporting unit risk estimates and comparisons in sensitivity analyses). The SAB
17 recommends downweighting epidemiologic results based on external standards (e.g., standardized
18 mortality ratio, standardized incidence ratio) due to the healthy worker effect.

19
20 **Accuracy, Objectivity, and Transparency of the Revised Draft Assessment**

21
22 *Genotoxicity*

23
24 The draft assessment presents an accurate, objective, and transparent summary of published studies on
25 EtO genotoxicity. The SAB agrees that the weight of the scientific evidence from epidemiological
26 studies, laboratory animal studies and *in vitro* studies supports the general conclusion that the
27 carcinogenicity of EtO in laboratory animals and humans is mediated through a mutagenic mode of
28 action (MOA). The SAB finds that several areas of the draft assessment can be improved to enhance the
29 clarity of presentation and to provide a more detailed interpretation of findings within the context of
30 more recent advances in the understanding of the biology of cancer. Specific recommendations include
31 revisions to Table 3.6 to specify the sites involved and the weight assigned to each of the studies;
32 presenting the rationale for decisions made for model selection within the context of MOA
33 considerations; and presenting the synthesis of information supporting a mutagenic MOA in a more
34 systematic and complete manner.

35
36 *Response to the 2007 SAB Comments*

37
38 Appendix H of the draft assessment provides a summary of the 2007 SAB comments and the EPA's
39 response to the comments. Overall the SAB finds that the EPA was highly responsive to the comments
40 and recommendations. The responses are transparent, objective, and for the most part, accurate
41 (exceptions are noted in the current report). There are four main comments and recommendations from
42 the 2007 SAB report that are not implemented in the current draft assessment:

- 43 1. using a non-linear modeling approach for deriving a unit risk;
- 44 2. using the Union Carbide cohort data for unit risk derivation;

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- 1 3. using a single model to fit the occupational and environmental exposure-relevant regions of the
- 2 dose response curve; and
- 3 4. moving the contents of Appendix A to the main body of the assessment.
- 4

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

- 7 1. finds that conditions for including a non-linear assessment per EPA *Guidelines for Carcinogen*
- 8 *Risk Assessment* (EPA, 2005) are not met in the case of EtO, and therefore a non-linear modeling
- 9 approach need not be included;
- 10 2. concurs with the decision not to use the Union Carbide Cohort data for unit risk derivation, but
- 11 suggests that the agency discuss the extent to which this study and others (e.g., the Swedish
- 12 study) corroborate results from the NIOSH study;
- 13 3. suggests that the EPA consider using the same model for both environmental and occupational
- 14 exposures;
- 15 4. agrees with the decision not to move the contents of Appendix A to the main body of the draft
- 16 assessment.
- 17

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

23
24 **Completeness and Clarity of Appendix J – New Studies**

25
26 In general, the literature review of new studies presented in Appendix J appears complete. The logic and
27 progression of the review is clearly supported. The clarity can be improved by distinguishing between
28 statements made by study authors and statements made by the EPA. The SAB concurs that inclusion of
29 the new studies would not substantially alter the findings of the assessment, with the exception of the
30 Swedish study. The Swedish study has detailed exposure data at low doses and documented substantial
31 effects on breast cancer, which has stronger implications than suggested in the draft assessment. The
32 strong breast cancer results at low dose exposures in the Swedish study greatly add to the overall
33 findings. The observation of a 2.5 to 3.5–fold increased risk of breast cancer associated with low
34 cumulative exposure in this study demonstrates strong evidence of carcinogenicity.

35
36 **EPA Response to Public Comments**

37
38 Appendix L presents public comments on the July 2013 draft of the assessment and EPA responses to
39 the public comments. The SAB finds that overall, the EPA has been very responsive to the public
40 comments. The responses are thorough, clear, and appropriate. There were also some public comments
41 on the 2006 draft assessment in Appendix H. The SAB finds that the revisions made to the draft
42 assessment and the EPA response in Appendix L adequately and appropriately address the issues raised
43 in the public comments in Appendix H.

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2. INTRODUCTION

2.1. Background

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

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

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

2.2. Charge to the Science Advisory Board

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

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1 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 18-20,
7 2014, a follow-up teleconference on [DATE], to discuss and deliberate on the charge questions and to
8 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 deal
12 with the exposure-response modeling of the epidemiologic data from the NIOSH study (Steenland et al.,
13 2003, 2004) and development of (1) the inhalation unit risk estimates of cancer risk at low (generally
14 environmental) exposure concentrations and (2) estimates of the cancer risk associated with occupational
15 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 would be expected for the development of breast cancer.” The SAB encourages the EPA to refine the
2 discussion of this uncertainty with a paragraph in the body of the assessment and a summary of an
3 analysis (detailed in an appendix) that examines the sensitivity of estimates of unit risks over the
4 plausible range of latency periods (i.e., 0-20 years). Appendix D (pp. D-24 - D-29) presents detailed
5 SAS® output from a new trial of fitting Cox regression (nested case control) models for incident breast
6 cancer to cumulative exposure and log cumulative exposure with varying lag periods (lags of 0, 5, 10,
7 15, and 20 years). Although there is no discussion of this trial or its evaluation in Appendix D, the
8 results for the models fitted to the log of cumulative exposures show very little to distinguish the fit
9 between the model that imposed a 15-year lag and the model that used no lag in cumulative exposure.
10 This analysis matches the results of the original Steenland et al. (2003) analysis, which found nearly
11 equivalent quality of model fits for log cumulative exposure models with 0- or 15-year lags. The SAB
12 encourages the EPA to formalize the presentation and discussion of the quantitative results for the
13 sensitivity analysis of exposure lags that is currently included in Appendix D, focusing on the sensitivity
14 of the EPA’s recommended models and a strongest competitor(s) to the length of the assumed latency
15 period. The body of the draft assessment should include a short summary of the quantitative results of
16 the sensitivity analysis described in detail in the appendix, accompanied by a qualitative discussion of
17 how the results of the sensitivity analysis should factor into an overall assessment of the biological and
18 statistical uncertainty of the unit risk estimates derived under the alternative models of exposure risk.
19

20 **3.2. Breast Cancer Incidence – Model Selection**

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

26
27 *2a: Please comment on whether the considerations used for model selection and their application in the*
28 *selection of preferred exposure-response models for breast cancer incidence for the purposes of*
29 *estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures*
30 *(Section 4.7) are clearly and transparently described and scientifically appropriate.*

31
32 There is not enough detail provided for the NIOSH exposure data for the SAB to determine the
33 appropriateness of the data. Therefore the SAB response is conditional on the assumption that the
34 NIOSH exposure data are appropriate. The SAB requests that the EPA provide better documentation of
35 the NIOSH data, particularly with respect to exposure. The response to Charge Question 4 provides a
36 discussion of considerations of the adequacy of the results not conditional on the appropriateness of the
37 exposure data.
38

39 Although generally the EPA’s model selection for breast cancer incidence is scientifically appropriate, it
40 could be described more clearly and transparently. The EPA is encouraged to revise the discussion of
41 the Cox model, or more generally, relative risk models, to use terminology that can be directly linked
42 with the published literature. Prentice (1985) provides examples of this terminology and a discussion of

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

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

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

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1 local spline models) on the fitted dose-response in the low-exposure range of the data. Although it is
2 worthwhile observing from the fits (e.g., Figure 4-5) that the log and square root transformations also
3 exhibit a similar behavior to the linear spline at low exposures (namely that the risk increases rapidly at
4 low exposures and then continues to increase at higher exposures, but much less rapidly), the global
5 nature of these estimates makes them less desirable for estimation of unit risks.

6
7 There are clear advantages to relying on parsimonious regression models directly fit to the individual-
8 level cumulative exposure data using spline models to parameterize exposure. It is straightforward to
9 compute unit and excess risk estimates directly from these fitted results. Furthermore, spline models
10 have the advantage of being sensitive to local behavior in the data. They can also be chosen to be
11 parsimonious (an example is a 2-piece linear spline). Models fit to exposure categories are similarly
12 sensitive to local behavior in the data, but they require more parameters to be estimated and are thus less
13 parsimonious than the spline models considered in the assessment. They also impose the implausible
14 assumption that the risk is constant within each exposure category. Furthermore, it is not straightforward
15 to translate the relative risk estimates from a categorical relative risk regression model to unit and excess
16 risk estimates. This requires the less desirable additional step of summarizing the categorical model fit
17 by translating its results into a functional form that can be used in a risk assessment. (See the response to
18 Charge Questions 2b and 3 for further detail.)

19
20 The SAB has some concern about the number of models that were fit to the data because over-reliance
21 on the best-fitting results can lead to statistical artifacts (such as “random high bias” which has been
22 defined in the context of hypothesis testing; e.g., see Fleming (2010)). Many of the model fitting
23 evaluations came from the initial peer-reviewed published reports, although additional models were fit
24 by Dr. Steenland under contractual direction from EPA. At this stage of the EtO risk assessment, the
25 SAB’s concern with the large number of models that have been explored can best be addressed by
26 striving for comprehensive reporting of model results; i.e., sensitivity analyses should be reported for a
27 range of results. These should include sensitivity to the functional form of the model (both the choice of
28 relative risk function and the functional form of exposure within that). Other aspects of the analysis
29 should also be considered such as inclusion of confounding variables, choice of lag, and cohort (full
30 cohort vs. those with interviews). The SAB recommends inclusion of tables documenting the various
31 estimates of the target parameter of interest (which is predominantly the unit risk estimate) from the
32 many models that were considered for the risk assessment. Although not all models are equally
33 reasonable from a risk assessment perspective, full and transparent reporting of the target parameters of
34 interest provides valuable context. Appropriate use of appendices and thoughtfully designed tables in the
35 main report can minimize the potential for confusion that may result from reporting so many estimates.
36 The SAB notes that the EPA already addressed this recommendation to some degree in its draft
37 assessment by including the EC_{01} and LEC_{01} estimates for many models. These are useful but require an
38 additional transformation before the target quantity of interest can be considered.

39
40 In conclusion, the SAB generally concurs with EPA’s selected model for the breast cancer incidence
41 data. However, a somewhat different set of criteria for selecting the most appropriate model would be
42 preferred. A preferred approach would prioritize the most parsimonious model that fits the data well
43 among exposure parameterizations that are not unduly reliant on data in the high exposure range. In
44 other words, spline functions are preferred over global fits that result from transformations of the

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1 exposure. In addition, biologic plausibility and other external information (such as corroborating
2 information from other studies) should be incorporated into the model selection. For example, the
3 incidence rate ratio (IRR) results reported by Mikoczy et al. (2011) could be used to support the selected
4 model. The task of selecting a final model is more challenging when a set of plausible models gives
5 widely disparate unit risk estimates. The response to Charge Question 2c provides further advice on how
6 to prioritize potentially plausible models. Ultimately though, using this preferred approach may result in
7 selection of a model very similar to the one selected by the EPA.

8
9 As a final comment, the draft assessment states that low-dose extrapolation was performed for risk
10 assessment, but the document does not state whether or not the doses considered for the unit risk
11 estimates were outside the range of the NIOSH exposure data. For instance, as given by the conversion
12 shown in footnote “e” of Table 4-13, 5,800 ppm-days corresponds to 0.075 ppm (with the correction to
13 the formula that one divides by 365). The tenth percentile of the breast cancer incidence data
14 corresponds to 157 ppm-days of exposure and 17 incident cases have nonzero exposure at or below this
15 level (using a 15-year lag; see Table D-1a). Using the same formula, this corresponds to 0.00202 ppm.
16 The LEC_{01} from the preferred model is 0.00576 ppm, more than twice 0.00202 ppm, suggesting there is
17 no low-dose extrapolation in these data. Because there is no low-dose extrapolation in these data, there
18 is less uncertainty of the unit risk estimate than would be otherwise present.

19
20 *2b: For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as*
21 *well as a range of estimates from models considered “reasonable” for that purpose (Sections 4.1.2.3*
22 *and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the “reasonable*
23 *models” is clearly and transparently described and scientifically appropriate.*

24
25 The SAB interprets the draft assessment’s description of “reasonable” models for providing unit risk
26 estimates as those that appear in Table 4-13. A few additional models are described in Table 4-12, some
27 of which could also be considered reasonable. The presentation of “reasonable” models considers model
28 fit and some *a priori* (and not clearly articulated) notion about the acceptable shape of the dose-response
29 function in the low-dose region. Because the data do not appear to conform to the *a priori* notion, the
30 draft assessment also considers models based on an untransformed continuous exposure term or a linear
31 regression of the categorical results as reasonable. However, these models do a poorer job reflecting the
32 patterns in the data. Although much of the approach is scientifically appropriate, the SAB does not
33 completely agree with all of the judgments. In order to strengthen the assessment and presentation, some
34 modifications to the approach to comparing models and choosing which models are reasonable are
35 encouraged. The discussion should be revised to provide more clarity and transparency as well as
36 making the disposition easier to follow. In general, discussion of statistical significance should occur in
37 a more nuanced fashion so that important perspective about the results is not lost in the tendency to turn
38 the statistical evidence into a binary categorization of significant vs. not significant. (This can mislead
39 readers into interpreting a pair of results as inconsistent when their p-values, effect estimates, and 95%
40 confidence intervals are very similar but the two p-values happen to be on opposite sides of 0.05.)
41 Consideration of reasonable models should address the quality of fit in the region of interest for risk
42 assessment. Prioritizing sufficiently flexible exposure parameterizations (e.g., not linear) and exposure
43 functions with more local behavior (e.g., splines, linear and cubic) reduces the impact of highly exposed
44 individuals on the risk estimates for lower exposures. Discarding a model because the fitted curve is

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1 “too steep” needs scientific justification. Furthermore, follow-up by the EPA is needed to clearly
2 articulate the criteria for determining that models are reasonable as well as providing transparent
3 definitions for frequently used terms such as “too steep,” “unstable,” “problematic,” and “credible” (p.
4 4-38). The SAB recommends assigning weight to certain types of models based on a modified
5 combination of biologic plausibility and statistical considerations, and using somewhat different
6 considerations for comparing AICs than those currently employed in the draft assessment.
7

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

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

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1 observed dose-response relationship. Specifically the SAB encourages a discussion of the Mikoczy et al.
2 (2011) results using the internal comparison group.

3
4 The application of AIC for selecting models is acceptable within some constraints, however this not a
5 preferred way to characterize model fit. AIC is an appropriate tool to select between nested models
6 because it allows tradeoff for parsimony. It is not an appropriate tool for comparing across different
7 models that are fit using different measures, such as comparing a Poisson vs. least squares fit to count
8 data. Similarly one should not use AICs to compare models using different transformations of the
9 outcome variable. There can be a third challenge with comparing AICs from models estimated using
10 different software tools, including different functions within the same statistical package, because many
11 implementations of AIC remove constants in the likelihood from the estimated AIC. AIC can be used to
12 compare the same regression model with the same outcome variable and different predictors. This gives
13 a consistent estimate of the mean-squared prediction error which is one criterion for choosing a model.
14 Finally, the theory behind this criterion can break down with a large number of models. Thus, naïve
15 application of AIC for model selection can be problematic. Differences in AICs could be an artifact of
16 how the calculation was done. This is a possible difference between the linear and exponential relative
17 risk models applied to the breast cancer incidence data, but the information provided to the SAB is
18 insufficient to determine whether or not this is the case.

19
20 In conclusion, the SAB finds that much of the approach to model selection is scientifically appropriate,
21 but encourages some modifications and more transparency in the presentation.

22
23 *2c: For analyses using a two-piece spline model, please comment on whether the method used to*
24 *identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically*
25 *appropriate.*

26
27 The method used to identify the knots involves a sequential search over a range of plausible knots to
28 identify the value at which the likelihood is maximized. This is scientifically appropriate and a practical
29 solution that is transparently described.

30
31 **3.3. Lymphoid Cancer – Model Selection**

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

38
39 The SAB has general concerns that pertain to this Charge Question and these concerns may overlap with
40 others as well. These could be addressed by including a better introduction to the data, before the
41 statistical analysis is described. The NIOSH data source may contain more details, but the present

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1 assessment would greatly benefit by repeating some of this information. As examples it would be
2 helpful to build the following tables:

- 3 • Marginal summaries of workers' ages, exposures, and years of entry to employment
- 4 • Cumulative exposure to EtO by duration of employment
- 5 • Cumulative exposure to EtO by year of entry to employment
- 6 • Cumulative exposure to EtO in each of the risk categories

7
8 Overall, the SAB suggests that the EPA revise the text, including more clearly providing the rationale
9 for the methods that were used. At present, the text contains disjointed remarks made to address the
10 SAB (2007) report, but the narrative does not read as a cohesive document.

11
12 *3a: Please comment on EPA's rationale for its use of the linear regression of the categorical results as*
13 *the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer*
14 *(Section 4.1.1.2).*

15
16 The SAB does not prefer the use of linear regression of categorical risks, but rather prefers the use of
17 individual-level continuous exposure data. The models developed using individual-level continuous
18 exposure data appear to be appropriate even though the draft assessment states that they are unsuitable.
19 The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk
20 rises rapidly with a small amount of exposure and then rises much more gradually for even higher
21 exposures. These are summarized in Figure 4-2. The SAB does not agree with the conclusion that the
22 linear regression of the categorical results is a preferable model over the other, better-fitting models
23 using individual-level exposure data.

24
25 The inclusion of a diverse number of cancers into the classification of lymphoid cancers also suggests
26 that the data represent a heterogeneous collection of related outcomes. Similarly, this is another
27 justification for the use of individual-level data, rather than grouping risk levels into a small number of
28 quintiles. The linear regression of categorical estimates should not be selected unless the individual
29 exposure model results are biologically implausible. The draft assessment does not present evidence of
30 biological implausibility.

31
32 If the final assessment proceeds with a linear regression of categorical risk, then it should also explore
33 the effects of including more categories, rather than quintiles. In the final chosen model, there should be
34 tables identifying the characteristics of individuals in each of the risk categories. For example, what is
35 the median estimated exposure, age, and years of employment in each of the categories? The extent of
36 confounding of exposure with the subjects' age, years of employment, and their age at start of
37 employment are unable to be determined in the draft assessment. It is likely that these are all highly
38 correlated but the draft assessment does not allow identification of these relationships.

39
40 The SAB recommends inclusion of multiple estimates of the unit risk in sensitivity analyses and an
41 updated justification of model selection. If linear regression of categorical results is chosen, then the use
42 of category medians rather than the means are recommended, as they provide a better representation of
43 exposure in each category, particularly the highest exposure category.

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1 *3b: Please comment on whether the considerations used for model selection and their application in the*
2 *selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating*
3 *low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section*
4 *4.7) are clearly and transparently described and scientifically appropriate.*

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

11
12 The spline allows different functions of risk for low and high exposure, relies more on local, rather than
13 global, behavior of the data. It is not advisable to use one model for risk assessment for part of the
14 exposure range and a different model for another part of the exposure range. The report demonstrates
15 that it is difficult to estimate the location of the changepoint (or knot). This is a well-known statistical
16 problem. How sensitive are the risk estimates to the final choice of the changepoint? The answer to this
17 question would allow the determination of whether the spline model is more of a measure of global or
18 local behavior. Biologically, the spline model may not have a mechanistic underpinning, but the fitted
19 model may not be far from the true behavior.

20
21 There seems to be some *a priori* notion that using a rapidly increasing function to model risk assessment
22 is unacceptable. However, all the evidence in the data suggests that there is a very steep dose-response
23 in the low-dose range. This general pattern is supported in multiple analyses and by both local and more
24 global parameterizations of the exposure. It suggests that it should be trusted and used in the risk
25 assessment.

26
27 The lack of statistically significant p-values (p. 4-7) is not evidence of a poor-fitting model. Failure to
28 find a statistically significant relationship between exposure and risk is not an indication of the failure of
29 the model. Neither is the use of AIC a proper measure of a good-fitting model. The AIC only allows
30 comparisons of the statistically significant contribution of additional parameters in a pair of nested
31 models, but does not indicate that either model is appropriate.

32
33 Instead, there are model diagnostics that could be explored to validate the adequacy of the fit. The risk
34 equation (Equation 4-2) is assumed to be constant for age, but this assumption can be checked by
35 including a regression term for age in the Cox regression model. In addition, there are definitions of
36 residuals for proportional hazards models of individual-level data that can be plotted to identify unusual
37 observations. These are used to locate unusual values of the explanatory variables in the Cox regression.
38 These might identify, for example, a number of very young workers with lymphoid cancer.

39
40 The draft assessment should identify and cite guidance for the use of low-dose/low-exposure
41 extrapolation in risk assessment and indicate how consistent the draft assessment is with the guidance.

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1 *3c: EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for*
2 *the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the*
3 *approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for*
4 *using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).*
5

6 The approach used for deriving risk estimates for lymphoid cancer incidence and the rationale for using
7 this approach are explained transparently and are scientifically appropriate.
8

9 However, if the draft assessment were also intended for a broad audience, the approach could be more
10 transparently described. It could be helpful to go through some more crudely estimated alternatives so
11 general readers can understand clearly all the different aspects of obtaining the unit risk and excess risk
12 estimates without having to rely on the more complex life table analyses. It is suggested that extra
13 lifetime risk be presented in terms of the number of lymphoid cancers that are due to the exposure to
14 EtO in the cohort. The risk estimates (Table 4-5, for example) would benefit by expressing these in
15 scientific notation, rather than a list of leading zeros.
16

17 This exercise will help interpreting the steep slope discussed in Charge Question 3b. Specifically, for the
18 spline model, what is the risk associated with higher levels of exposure? Expressed in easily understood
19 terms, this answer might suggest that exposure does indeed rise quickly at low doses but reaches either a
20 high or low plateau. This conclusion would make the results more easily understood.
21

22 **3.4. Uncertainty in the Cancer Risk Estimates**

23 *Charge Question 4: Please comment on whether the qualitative discussions of uncertainty (Sections*
24 *4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.*
25

26 The uncertainty discussions are generally clear, objective, and scientifically appropriate but they can be
27 improved and extended. Considerations about uncertainty directly pertaining to the analyses reported
28 can be separated into 1) uncertainty due to the data themselves (particularly from reliance on a single
29 dataset), and 2) uncertainty of the results given the data. Suggestions are provided on how to enhance
30 the presentation and to encompass additional considerations from the SAB.
31

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

33 The SAB supports the use of the NIOSH ethylene oxide worker cohort described in Steenland et al.
34 (2003, 2004) as the primary data source for the modeling of cancer risk from ethylene oxide exposures.
35 This is consistent with the support for the data source in the previous SAB (2007) review. The support
36 of the NIOSH data is founded on study documentation of the original exposure measurements,
37 procedures for exposure estimation (Hornung et al., 1994) and historical modeling (prediction) of
38 exposures that occurred before the time period in which actual exposure measurements were
39 systematically collected. All such model-based reconstructions of exposure data are subject to variable
40 and potentially systematic sources of error (i.e. bias). No statistical treatment of data is expected to be
41 unaffected by such errors and, as noted in the responses to the previous Charge Questions, any complete
42 statistical treatment should transparently describe both the results of the analysis and the implications of

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1 any uncertainty in the data inputs or the assumed statistical model. The previous SAB (2007) review
2 identified several areas of data and modeling uncertainty that should be addressed further. Appendices D
3 and H of the current draft assessment provide a comprehensive response to most of the key questions of
4 data or model uncertainty that were raised in the SAB (2007) review (see the response to Charge
5 Question 5b). For example, a key question raised concerns about the extent to which the introduction of
6 15- and 20-year lags in cumulative exposure measures (to account for latency) would make the modeled
7 exposure measures heavily dependent on historical time predictions from the Hornung et al. (1994)
8 regression model.

9
10 Appendix H provides a comprehensive response on the issue of estimation of exposures prior to 1975 (in
11 the absence of any sampling data prior to 1975). It addresses the implication of the original exposure
12 prediction model assumption (Hornung et al., 1994) that calendar time effects (year) which were
13 significant after 1978 but were absent prior to 1978 - allowing the predictions to pre-1978 exposures to
14 be a function of the 1978 time effect (Figure 1 in Hornung et al., 1994) and additive effects of other
15 predictors in the model of log exposure (exposure category, product type, product age, engineering
16 controls, air volume of work area, etc.).

17
18 Based on the draft assessment, supporting materials, and discussion in the public meeting, the SAB
19 understands that:

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

29
30 Recognizing these four points, the SAB recommends that the EPA consolidate the current discussion of
31 exposure uncertainty that appears in various sections of Appendices D and H and also to include in the
32 body of the draft assessment a qualitative discussion of the statistical uncertainty that is associated with
33 the model-based predictions of annual exposures. Furthermore, the SAB recommends that in order to
34 provide a deeper understanding of the data source, the EPA should obtain and archive the NIOSH
35 modeled exposure data set and include in the revised report several tables or figures with descriptive
36 summaries of the characteristics of the NIOSH cohort and the distributions of predicted exposures in the
37 NIOSH data set. Although not a true means of assessing the precision or accuracy of the historical
38 prediction of exposures from the regression model, these descriptive summaries will provide insight on
39 historical trends and patterns of variability in the model-generated measures of annual EtO exposure for
40 workers in the study cohort.

41
42 Key characteristics of the NIOSH cases and controls that should be analyzable from the study data set
43 and could be summarized in descriptive tables or figures include the following distributions:

- 44 • Gender distribution over time

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- 1 • Year of entry to the EtO workforce
- 2 • Age of entry to the EtO workforce
- 3 • Duration of employment in the EtO cohort
- 4 • Age and year of departure/retirement from the EtO cohort

5
6 A useful descriptive summary of the exposure characteristics for cases and controls could include the
7 following:

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

14
15 Given the approach of using a nested case-control design in the NIOSH cohort analyses as an
16 approximation to the proportional hazards model with a time-dependent covariate, the SAB recognizes
17 that without the analysis datasets that were used, precise reproduction of the “controls” in the analyses is
18 challenging. An alternative solution is to mimic the nested case-control sampling and select controls
19 from the remaining at risk cohort each time a new case occurs.

20
21 The SAB is also concerned that the public had exposure data from the NIOSH cohort that the EPA did
22 not have. For instance, a few selected graphs were presented by the public that indicated exposure
23 predictions for 4 jobs in two of the fourteen plants showed lower exposures in some or all years prior to
24 1975. The SAB was provided only a few carefully selected examples, and thus was unable to assess the
25 extent of these surprising data. This is an uncertainty that can easily be ruled out. Upon reviewing the
26 model equation in Hornung et al. (1994), the SAB finds the surprising historical behavior to be unlikely
27 and could be explained by changes in processes in specific plants, rather than some failure of the model
28 to capture historically larger exposures. The EPA should ensure that they obtain all relevant data
29 released from NIOSH to members of the public.

30
31 Although the SAB concurs with the EPA’s decision to rely solely on the NIOSH dataset for the risk
32 assessment, the use of only one dataset is a source of uncertainty. This uncertainty can be reduced by
33 highlighting how the Swedish data (Mikoczy et al., 2011) help support the conclusions reached from the
34 NIOSH data.

35
36 Uncertainty of the results given the data

37 The SAB recommends better quantification of the results from the models that were fit as a way of
38 improving the qualitative discussion of uncertainty. In particular, as has been noted in previous Charge
39 Question responses, the unit risks should be reported and compared in sensitivity analyses for a rich set
40 of models. This can include analyses that differ according to the various outcomes, subcohorts, link
41 functions, functional forms of the exposure (i.e. exposure parameterizations), exposure metrics,
42 exposure lags (see response to Charge Question 1), confounder adjustments, and standard error
43 estimation approaches (Wald vs. profile likelihood). This will provide context for the unit risk behavior

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1 across the range of plausible models. The SAB also encourages consideration of focusing the reporting
2 of sensitivity analyses on the target parameters of interest (unit risk, excess risk).

3
4 If feasible, consideration of additional analyses using alternative exposure metrics is suggested. The
5 December 4, 2014 EPA memo (U.S. EPA, 2014) notes that four exposure metrics were already
6 considered. If additional metrics are available, it would also be valuable to consider these as well.

7
8 Additional considerations related to qualitative uncertainty assessment

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

- 12 1. The dose-response model indicated by the NIOSH cohort that suggests risk increases sharply for
13 low exposures and then increases further but less steeply for higher exposures. The biologic
14 plausibility of this functional form is uncertain, and evidence that there are mechanistic
15 explanations that support this form will inform the risk assessment.
- 16 2. The analysis of NIOSH data relies on cumulative exposure as the dose metric. Given the status
17 of the exposure data, it is unlikely that other more refined exposure information can be used to
18 better understand the mechanisms of ethylene oxide exposure in cancer initiation. Furthermore, it
19 is often difficult to determine mechanisms from epidemiological data, particularly when these
20 data are limited.
- 21 3. The SAB recommends downweighting all epidemiological results that are based on external
22 standards (e.g. standardized mortality ratio, standardized incidence ratio). The presence of the
23 healthy worker effect cannot be denied in these occupational data and the use of an external
24 standard for comparison does not avoid healthy worker types of biases.

25
26 **3.5. Accuracy, Objectivity, and Transparency of the Revised Draft Assessment**

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

30
31 *5a: Section 3.3.3 and Appendix C (genotoxicity)*

32
33 Section 3.33 and Appendix C of the draft assessment present an accurate, objective and transparent
34 summary of the results of research studies published up to July 2013 on EtO genotoxicity. The SAB
35 agrees that the weight of the scientific evidence from epidemiological studies, laboratory animal studies
36 and in vitro studies supports the general conclusion that the carcinogenicity of EtO in laboratory animals
37 and humans is mediated through a mutagenic mode of action (MOA). Indeed, the genotoxicity database
38 has firmly established that EtO is a direct-acting agent, as evidenced by the formation of DNA adducts
39 and highly reproducible, positive effects in a variety of in vitro and in vivo mutation and clastogenesis
40 assays.

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

5
6 Recommendations

- 7 • Table 3.6 should be revised to specify the sites involved and the relative importance (weight)
8 assigned to each of the individual studies presented. In addition, a new table should be added to
9 show the dose-response relationships for the formation of DNA adducts and the in vivo
10 genotoxic effects in humans and comparative model systems.
- 11 • The rationale for decisions made regarding model selection for calculations of unit risk should be
12 presented in this section, and elsewhere, within the context of MOA considerations and the initial
13 key biological events involved in mutagenesis and carcinogenesis. The evidence for mutagenic
14 MOA can be used to explain the behavior of the data in low dose regions and the subsequent
15 extrapolation for risk assessment.
- 16 • Although the description of the database was found to be adequate, the synthesis of the
17 information used to support a mutagenic MOA should be presented in a more systematic and
18 complete manner. Section 3.4 should be reorganized around a broader evidence base for a
19 mutagenic MOA to more clearly establish the framework for defining mutagenic MOA. Key
20 elements of this framework, as informed by a recent review by Eastmond (2012) should include:
 - 21 ○ Characterization of Molecular Alterations: Does the chemical interact with protein and/or
22 DNA, undergo redox cycles, or modulate cell cycle/rates of cell replication, apoptosis,
23 signaling pathways? What are the doses required to induce these changes? In the case of
24 EtO, the primary effect appears to be direct interaction with DNA to produce a variety of
25 DNA adducts. Other effects occur include, protein adducts and likely oxidative stress.
 - 26 ○ Characterization of mutagenic or clastogenic effects: Which biological systems and what
27 are the doses required for adduct formation? In the case of EtO, genotoxic effects occur at
28 doses well below those required to induce cytotoxicity or tumorigenesis. It would be
29 helpful to clarify whether specific DNA adducts are associated with genotoxic effects,
30 but the absence of these data does not negate a mutagenic MOA for EtO.
- 31 • In the absence of further mechanistic information, evidence for DNA interactions coupled with
32 consistency in the occurrence of mutagenic/clastogenic effects provides a sound basis for
33 applying a mutagenic MOA to risk assessment. Additional data that may be informative in
34 revising the draft to support a mutagenic MOA includes:
 - 35 ○ Genotoxic Effects in Cancer Target Organs: These effects can include DNA adducts
36 (weight increased if they are known to be promutagenic DNA adducts), mutational and
37 clastogenic effects in the target organ. In the case of EtO there is evidence for mutational
38 effects in several target tissues. For example, EtO-induced breast tumor tissue from
39 mouse cancer bioassays has shown altered mutational spectra (Houle et al. 2006), as well
40 as altered mutational spectra in lung and other target tissue tumors (Hong et al. 2007).
41 The fact that EtO-induced mutational spectra changes occur in tumor suppressor genes
42 and oncogenes provides additional weight for a mutagenic MOA. Regarding lymphoid
43 tumors, there is evidence from several studies for genotoxic effects of EtO in bone

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1 marrow and peripheral blood lymphocytes. On a more general basis, if target organ data
2 do not exist, consideration should be given as to whether toxicokinetic or physico-
3 chemical factors exist that would prevent access to the cancer target organ. This does not
4 appear to be the case for EtO.

- 5 ○ Non-linearities: Are there non-linearities that would suggest that the mutagenic MOA
6 does not continue to be operative at low or high dose levels? In the case of EtO, the DNA
7 adduct dose response extends to very low doses, well below the cancer effect level
8 (Marsden et al., 2009).
- 9 ○ Temporal Relationships: Do DNA adducts and genotoxic effects precede the
10 carcinogenic effect? In the case of EtO, as cited in the draft assessment, short-term and
11 subchronic studies find evidence of genotoxic effects.
- 12 ○ Alternative Mechanisms: Are there other effects that might account for the oncogenic
13 effects, at what doses do they occur, and how robust are these findings? In the case of
14 EtO, cytotoxicity, oxidative stress, alterations of signaling pathways may occur, but
15 evidence is lacking that these effects would become a primary effect at low doses.
- 16 ○ Summarization of the Cancer MOA: This summary of the key events should describe
17 how the key events combine to yield a mutagenic basis for cancer causation. As
18 presented in the draft assessment, key events appear to be: (a) DNA adduct formation; (b)
19 mutation/clastogenesis; (c) clonal expansion of altered cells; (d) tumor formation.
20

21 Suggestions

- 22 • Inclusion of additional experimental details about the separation of endogenous from exogenous
23 adducts as reported by Marsden et al. (2009) would help provide biological perspective for issues
24 related to risk assessment considerations, especially linearity versus non-linearity of dose-
25 response relationships.
- 26 • The genotoxicity section would be improved by consideration of the role that differences in
27 DNA repair capacity between different target cells in different tissues plays in relative
28 vulnerability to mutagenesis. For example, genes known to regulate vulnerability of breast
29 cancer in women, such as BRAC1, BRAC2 and XRCC1, are known to regulate DNA repair
30 pathways in breast tissue (Shi et al., 2004; Hu et al., 2002). This line of thinking can help to
31 inform the biological bases to better understand the shape of the dose response in the low dose
32 region of the NIOSH dataset.
- 33 • In light of the above discussion, the organization of the text can also be revised to include
34 information about known differences in mutagenic and carcinogenic pathways for EtO at
35 different tumor sites, as well as the degree to which biochemical differences at the cellular or
36 tissue level differentially impact MOA. Furthermore, references made in page 3-29 to the levels
37 of different adducts are presented without making a clear and necessary distinction between the
38 putative or assigned biological impact for N-7 versus O-6 DNA adducts.
39

40 *5b: Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to*
41 *the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer*
42 *hazard characterization (p. H-3).*
43

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

9
10 There are some recommendations or suggestions that are not implemented in the current draft
11 assessment, including:

- 12 1. use a non-linear modeling approach for deriving a unit risk;
- 13 2. use of the Union Carbide cohort data for unit risk derivation;
- 14 3. use a single model to fit the occupational and environmental exposure-relevant regions of the
15 dose response curve; and
- 16 4. moving the contents of Appendix A to the main body of the assessment.

17
18 Feedback regarding these decisions are provided in the detailed response to this charge question and in
19 responses to other charge questions. This feedback can be summarized as follows:

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

33
34 This charge question asks specifically about responses to comments on endogenous EtO (p. H-4), a
35 nonlinear approach (P. H-13 to H-17), and the cancer hazard characterization. Each of these topics is
36 addressed in the detailed response to the charge question, but can be summarized as follows: (1) The
37 SAB supports the expanded discussion of endogenous EtO provided in the draft assessment and has
38 suggestions for further improvement; (2) As noted above, the SAB agrees with the decision not to
39 include a unit risk value for EtO based upon nonlinear extrapolation, but recommends a more balanced
40 and objective discussion of the subject; and (3) the SAB recognizes and agrees with revisions to
41 strengthen support for a classification of EtO as "carcinogenic in humans."
42

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1 A more extensive discussion of EPA’s responses to the comments and recommendations in SAB (2007)
2 report follows. Comments and recommendations from the SAB (2007) report are summarized, followed
3 by a summary of the EPA’s responses and the SAB evaluation of the responses.
4

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

6 A majority of the SAB judged that the weight of the mutagenicity, animal and epidemiology
7 evidence included in the EPA 2006 assessment supported the characterization of EtO as
8 “Carcinogenic to Humans.” Although the SAB agreed with the use of internal comparisons for
9 estimating cancer risks, and with characterization of the epidemiology data as “less than
10 completely conclusive”, there was a divergence of opinion on the strength of the epidemiology
11 evidence, with a minority of members considering it too weak so that, in light of insufficient data
12 on precursor events in humans, the hazard descriptor “Likely to be Carcinogenic to Humans”
13 would be more appropriate. The SAB recommended strengthening the assessment by improving
14 the introduction to the hazard identification section, including the addition of an initial summary;
15 enhancing the description and clarifying the criteria for quality descriptors of the epidemiology
16 data, and moving materials presented in Appendix A of the assessment into the body of the
17 assessment. The SAB also requested clarification of the apparent incongruence between the
18 descriptor of the magnitude of the unit risk estimate as “weak” in light of estimated magnitude.
19

20 Summary of EPA Response

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

30 The introductory paragraph summarizing the contents of Chapter 3 that was added improves the
31 readability of the assessment. Another related recommendation was to add “a more inclusive
32 summary figure and/or table at the beginning of Chapter 3.0”. The EPA did not address this
33 comment specifically. The EPA also did not move material from Appendix A into the main body
34 of the assessment.
35

36 The SAB realizes that the recommendation to add the summary figure/table at the beginning of Chapter
37 3 was perhaps not clear. The recommendation was meant to include a brief summary of the key findings
38 of the Hazard Assessment at the beginning of the chapter in some form. This is consistent with the new
39 format for IRIS assessments, which includes a grey box at the beginning of this chapter (and the rest of
40 the chapters in the assessment) highlighting the main conclusions of the Hazard Identification section. A
41 similar addition should be considered for Chapter 4 of the current draft assessment.
42

43 The SAB agrees with the decision to not transfer *in toto* materials from Appendix A – Critical Review of
44 the Epidemiological Evidence to the main body of the assessment. The addition of the two brief

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1 summary tables on the hematopoietic and breast cancer studies is a good alternative for strengthening
2 the chapter. This choice is consistent with the National Research Council (2011) recommendations that
3 the main body of the assessment focus on the critical data, rationales, and analyses used to support the
4 unit risk derivation and that, as much as feasibly possible, detailed description of key and other studies
5 or analyses be summarized in appendices with appropriate cross-referencing in the main body of the
6 assessment. If anything, the current document could benefit from transferring more materials to
7 appendices, although it is acknowledged that the current draft assessment is not intended to conform
8 completely to the new format for IRIS assessments.

9
10 EPA also clarified its designation of the unit risk estimate as “weak” in the prior draft assessment, and
11 section 3.5.1 of the current draft assessment provides a good evaluation of the strength of the weight of
12 the evidence in term of Hill’s criteria for causality.

13
14 Summary of SAB (2007) Comments on Charge Question 1b – Additional Studies/Reports

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

21
22 Summary of EPA Response

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

37
38 Based on the discussion presented in the assessment and considering the weight of the evidence from
39 human and animal studies, the SAB finds EPA’s conclusion on endogenous exposure to EtO to be
40 supported. Nonetheless (and also in light of the analyses presented on pages H-15 to H-17 and further
41 insights derived from the SAB recommendations in the response to Charge Question 5a – Section 3.5 of
42 this report), it appears that recognizing this source of metabolic EtO and briefly expanding on its
43 relevance to the assessment would complete the description of sources of endogenous EtO and their

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1 relative importance for adduct formation. This could be readily done in detail in Appendix C with the
2 expanded, but succinct description added to Chapter 3.0 and cross-referenced to the appendix.

3
4 The EPA added 24 of the 34 additional references recommended by the panel. There was no explanation
5 as the reasons for not including 10 of the references suggested for inclusion.

6
7 Summary of SAB (2007) Comments on Charge Question 1c – MOA Conclusions

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

11
12 Summary of EPA Response

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

16
17 The SAB finds that the EPA has been responsive in providing an expanded and more balanced
18 discussion of human and animal studies of precursor events that support a mutagenic MOA. However,
19 the supportive evidence for a mutagenic MOA needs further enhancement and discussion as indicated in
20 the SAB response to Charge Question 5a (Section 3.5 of this report).

21
22 Summary of SAB (2007) Comments on Charge Question 1d – Hazard Characterization

23 Discussion

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

29
30 Summary of EPA Response

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

34
35 The EPA's enhancements to the relevant sections of the draft assessment have improved the assessment,
36 but the sections relevant to MOA need further support. Please refer to the response to Charge Question
37 5a (Section 3.5 of this report) for further detail.

38
39 Summary of SAB (2007) Comments on Charge Question 2a – Epidemiological Data

40 The SAB concurred with the EPA that the NIOSH retrospective cohort studies provide the most
41 robust set of data for estimating the magnitude of carcinogenic risk to humans environmentally
42 exposed to EtO. However, they also recommended that the EPA consider the full range of
43 available epidemiology studies, with special emphasis on the Union Carbide retrospective
44 cohort. They also recommended that the EPA explore the potential for instabilities resulting from

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1 the interaction between the chosen time metric in the dose-response model and the treatment of
2 time in the log cumulative with 15-year lag exposure model estimates.

3
4 Summary of EPA Response

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

12
13 The selection of the NIOSH cohort and the decision not to combine these data with the Union Carbide
14 cohort is better and more transparently justified in the revised draft assessment and the SAB concurs
15 with this decision. However, the SAB considers that a more detailed description of the NIOSH cohort is
16 needed as it relates to the derivation of exposure metrics, as indicated in the SAB response to Charge
17 Question 2 (Section 3.2 of this report) for the current draft assessment.

18
19 It is not known if Dr. Steenland received only the comment as presented in the Executive Summary the
20 SAB (2007) report, or the more detailed discussion in pages 20-22 of the SAB (2007) report. The SAB
21 considers that, although consultation with Dr. Steenland on the technical aspects of this recommendation
22 is appropriate because of his intimate knowledge of the exposure model developed for the NIOSH EtO
23 cohort studies, the EPA should have provided its own response to the SAB (2007) recommendation. Dr.
24 Steenland indicates that he was not completely sure about the meaning of the recommendation and
25 proceeded to present a set of reasonable arguments as to why the bias introduced by using this metric
26 would not alter the analysis appreciably. It is also important to note that the exposure estimates likely to
27 be of lower reliability (because there were no exposure measurement data that could be included in the
28 exposure model prior to 1979) are also likely to be higher than the more recent exposures and, therefore,
29 would play a less important role in the current derivation of the POD. The response, however, has not
30 completely clarified the issue of potential estimate instabilities introduced by interactions between time-
31 varying predictor variables and the log cumulative exposure with a 15-year lag exposure estimate. This
32 issue is addressed in the SAB response to Charge Question 2 (Section 3.2 of this report) for the current
33 draft assessment.

34
35 Summary of SAB (2007) Comments on Charge Question 2b - Modeling

36 The SAB provided very extensive comments and recommendations in response to this charge
37 question. The panel was unanimous in recommending that: (1) the EPA not use the categorical
38 results but instead develop risk models using the original individual exposure and cancer data of
39 the NIOSH cohort, and (2) analysis should be made by lymphohematopoietic (LH) cancer
40 subtype. The SAB did not reach consensus on the appropriateness of linear or non-linear model
41 fit of the data within the observed range and for calculation of the POD, so it was recommended
42 that the EPA explore the use of a range of models (with a preference for biologically-based
43 models). Likewise, the SAB agreed that the EPA did not provide a clear justification for basing

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1 LH risk estimates on males only and recommended that gender differences should be explored
2 (there were different opinions on the procedural aspects of incorporating gender differences).

3
4 The EPA was highly responsive in addressing concerns about the use of categorical data for POD
5 derivation, including obtaining the individual data for the NIOSH cohort and subcontracting with Dr.
6 Steenland, the principal investigator of the NIOSH studies, to perform multiple analyses with these data
7 (including use of individual and categorical exposure estimates) using alternative modeling approaches.
8 In addition, there was also an attempt to expand on the error analysis of the NIOSH cohort exposure
9 estimation (this could not be accomplished because the data files used in that assessment were no longer
10 available). Results from the extensive additional analysis are detailed and well described in the current
11 draft assessment, both in Chapter 4 and in Appendix D, together with the rationale for supporting the
12 decisions by EPA in model selection. Problems with the implementation of the recommendations are
13 described clearly. Outcomes from alternative models are summarized both in tables and graphical form,
14 with justification for the preferred models. It is important to emphasize that Dr. Steenland's involvement
15 in the additional analyses is a strength of the revised draft not only because of his intimate familiarity
16 with the NIOSH cohort studies but his expertise in exposure modeling and occupational epidemiology.
17 The revised assessment for breast cancer risk incidence is based on continuous exposure data. The
18 analysis for LH cancer subtype is based on the NIOSH cohort lymphoid cancer results (results for all LH
19 cancers are also presented) for both genders (no statistically significant differences gender differences
20 were found). Results for individual and categorical data models are presented (EPA preferred the non-
21 categorical model).

22
23 Although there are still significant concerns with the final selection of modeling approaches for
24 derivation of unit risk in the current draft assessment (see the responses to Charge Questions 1-4,
25 Sections 3.1-3.4 of this report), the EPA should be commended for the effort and the commitment of
26 resources to address the comments and recommendations SAB (2007) report. Likewise, the EPA
27 considered the SAB's extensive comments on the rationale for non-linear low dose extrapolation
28 including additional analysis of experimental animal data on mutations by EtO (pages H-15 to H-19 of
29 Appendix H), concluding that the evidence did not indicate low dose non-linear extrapolation or
30 threshold dose-response patterns. Thus, the rationale (including more expansion on EPA guidance) for
31 using low dose linear extrapolation is improved and stronger in the current assessment, but some
32 concerns remain (see responses to Charge Questions 1-3 and 6, Sections 3.1-3.3 and Section 3.6 of this
33 report).

34
35 Concerns about the suitability of life table methodology for determination of LEC_{01} have been
36 addressed. The EPA provides a convincing rationale (especially since alternative approaches are not
37 available) for using the BEIR IV algorithm. The response to the request to present the range unit risk
38 estimates for the upper and lower 95% confidence limits of the EC_{01} is also reasonable.

39
40 EPA also responded in detail to the comments provided in Appendix A of the SAB (2007) report. Many
41 of the comments referred to the use of categorical exposure metrics and regression on group data that are
42 also the subject of the current SAB review and are reflected in the responses to Charge Questions 1-3
43 (Sections 3.1-3.3 of this report).

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

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

5
6 Summary of EPA Response

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

8
9 The SAB finds this to be responsive to the SAB (2007) comment.

10
11 Summary of SAB (2007) Comments on Charge Question 2d – Different Models for
12 Occupational and Environmental Exposures

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

16
17 Summary of EPA Response

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

21
22 The SAB suggests that the EPA consider using the same model for both environmental and occupational
23 exposures. (Please refer to the response to Charge Question 3 – Section 3.3 of this report).

24
25 Summary of SAB (2007) Comments on Charge Question 2e – Rodent Data

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

29 Summary of EPA Response

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

33
34 The SAB agrees with EPA's response.

35
36 Summary of SAB (2007) Comments on Charge Question 3 - Uncertainty

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

39
40 Summary of EPA Response

41 The EPA did not have a response.

42
43 SAB comments on uncertainty in the current draft assessment are reflected in the response to Charge
44 Question 4 (Section 3.4 of this report).

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3.6. Completeness and Clarity of Appendix J – New Studies

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

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

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

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

Other specific suggestions include:

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

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3.7. EPA Response to Public Comments

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

Appendix L presents the EPA responses to public comments on the July 2013 draft assessment. The section begins with a brief and clear summary of the comments received. Appendix L lists the source of the comments and notes that excluding the three requests to extend the public comment period, a total of 16 comments were received. Because there was some repetition, some comments are grouped together, making 14 be the total number of unique comments to which the EPA responded.

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

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

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

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

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1 *Comment #4:* The comment states that the evidence for breast cancer is too weak. The response notes
2 that the document acknowledges that the breast cancer database is more limited than that for other
3 cancers. Further, the response notes that the SAB (2007) report accepted the derivation of a unit risk
4 factor based on that database. This response is clear and appropriate. Additionally, the EPA could also
5 discuss the animal model data (NTP, 1987; Parsons et al., 2013) and Swedish occupational data
6 (Mikoczy et al., 2011) to provide further support for breast cancer as a potential hazard from EtO
7 exposure.
8

9 *Comment #5:* The comment notes that EtO is a weak mutagen. Both the response and the draft
10 assessment never claim that EtO is a strong mutagen. The "weakness" of EtO as a mutagen as compared
11 to many anti-cancer compounds and other reactive epoxides is clearly stated. In their response, the EPA
12 provides further justification by noting that there is seldom a good correlation between mutagenic and
13 carcinogenic potencies. This response is clear and appropriate.
14

15 *Comment #6:* The comment states that a mutagenic MOA is not supported by the most recent scientific
16 evidence; other MOAs, specifically oxidative stress and cell proliferation, should be considered. There
17 are two major issues here with regard to the MOA. First, the database concerning the MOA is rather
18 complex, which the draft assessment and the EPA response acknowledge. Second, and most
19 significantly, the Parsons et al. (2013) study cited in the comment is considered to be flawed and does
20 not adequately argue that other MOAs besides direct mutagenesis are involved. The response clearly
21 states that there is no support for the conclusions in Parsons et al. (2013). In the response, the EPA cites
22 another recent study (Nagy et al., 2013) that does not support oxidative stress. The response also
23 provides a detailed discussion of the problems of inferring too much from K-ras mutation data. Even
24 less data exist to support a proliferative MOA. The EPA response methodically presents the reasoning
25 behind this conclusion.
26

27 *Comment #7:* The comment criticizes the EPA for failing to incorporate the Union Carbide Corporation
28 (UCC) data into the dose-response assessment. It goes on to state that the NIOSH exposure assessment
29 also suffered from limitations. The EPA response is concise and clear. This issue is discussed in detail in
30 the draft assessment and was supported by the SAB (2007) report. The NIOSH study meets the criteria
31 of being a high-quality study much more strongly than the UCC data. This response is well-supported
32 and appropriate. The SAB concurs with the EPA decision to not combine UCC EtO exposure data with
33 those from the NIOSH study.
34

35 *Comment #8:* This comment criticizes the EPA for using summary data rather than the individual data in
36 the modeling of breast cancer mortality and lymphoid cancer despite the SAB (2007) recommendations.
37 Two key points are made in the response. First, the rationale for the modeling procedures used and their
38 consistency with the previous recommendations in the SAB (2007) report are noted. Second, the
39 response notes that the current document adds additional models based on continuous exposure data and
40 has added them to the assessment for comparison purposes. This response is appropriate. However, the
41 SAB suggests that the model should only apply to low-dose exposures and that a range of doses over
42 which the model applies should be specified.
43

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

5
6 *Comment #10:* A comment was made regarding other concerns about the modeling procedures used and
7 how they lead to over-prediction of cancer deaths in the NIOSH study. In response to concerns raised by
8 the two publications cited in the comment, the EPA provided additional discussion in Appendix J to
9 specifically address concerns raised with respect to the Valdez-Flores and Sielken (2013) studies. The
10 response further suggested that the referenced citations did not provide convincing evidence of flaws in
11 the modeling. Further, the EPA notes that the potential degree of over-prediction is far less than that
12 claimed in the comment and the two papers. This response is appropriate.

13
14 *Comment #11:* A comment was made from three sources that the EPA should present both linear and
15 nonlinear extrapolation approaches. This subject is discussed at great length in the draft assessment and
16 in Appendix H. The response further notes that the SAB (2007) report agreed that there was presently
17 insufficient evidence to support use of a nonlinear extrapolation approach. This response is appropriate.

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

29
30 *Comment #13:* A comment was made from three sources that the EPA should reexamine its risk
31 determination given background and endogenous levels of EtO and that the EPA's risk estimates are
32 unrealistically high. The EPA response explains how background rates for the cancers of interest have
33 been taken into account in the risk determination. They also note that in one of the comments an
34 unrealistic exposure concentration was used in arguing their point. This response is appropriate.

35
36 *Comment #14:* Two sources commented that the EPA should not be deriving occupational exposure
37 limits for EtO. The EPA response makes two clarifications. First, the EPA's Office of Pesticide
38 Programs (OPP) is indeed responsible for deriving occupational exposure limits. Second, and more
39 importantly, the response notes that such a derivation was not conducted in the present risk
40 determination. Rather, the response notes that with the models used for the EtO cancer data, the unit risk
41 estimate is not appropriate for the full range of occupational exposure scenarios of interest to OPP. For
42 the purposes of OPP, the assessment provides sample risk estimates for exposure scenarios of interest to
43 OPP for its own risk assessment of sterilization uses of EtO.

44

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

3
4 In addition to evaluating the EPA response (Charge Question 7) to public comments received on the July
5 2013 draft assessment, the EPA also presented their responses to public comments received on the 2006
6 draft assessment (EPA, 2006) in Appendix H. Some of the comments were addressed by changes made
7 in the current assessment. For example, one criticism was that the 2006 draft assessment (EPA, 2006)
8 had an improper reliance on data from only one sex. The current draft assessment uses data from both
9 sexes. Another example was the EPA response to Comment #7 regarding the modeling procedures.
10 Although the EPA response to the comment on the 2006 draft assessment (EPA, 2006) was very brief
11 and lacked sufficient detail, these issues are extensively addressed in the current draft assessment and
12 the accompanying appendices. Several other comments were redundant with public comments made on
13 the 2013 draft assessment. Examples include comments on EtO mutagenicity, lack of use of the UCC
14 database, and the use of summary data versus individual data. In summary, the previous EPA responses
15 in Appendix H as well as the changes that were instituted in the current draft assessment adequately and
16 appropriately respond to the public comments on the 2006 draft assessment (U.S. EPA, 2006).

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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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29
30
31