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

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

Goal:

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

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

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

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

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

Background:

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

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

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

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

[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.

risk estimates). Sensitivity analyses were performed comparing various model forms and data selection choices, and uncertainties in the quantitative estimates are discussed.

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

Charge Questions:

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

Questions 1-4:

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

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

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

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

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

(Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.

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

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

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

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

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

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

Questions 5-6:

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

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

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

References

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