

EPA's Response to Major Interagency Comments on the 2011 Interagency Science Discussion Draft IRIS Carcinogenicity Assessment of Ethylene Oxide

July 2013

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6) where Executive Offices of the President and other federal agencies can comment on draft assessments. The following are EPA's responses to major interagency review comments received during the Interagency Science Discussion step (Step 6) for the draft IRIS carcinogenicity assessment of ethylene oxide (dated July 2011). All interagency comments provided were taken into consideration in revising the draft assessment. After further consideration, EPA has decided to undertake an additional peer review on how the Agency responded to the Science Advisory Board (SAB) panel recommendations on the external peer review draft, on the exposure-response modeling of epidemiologic data, including new analyses since the 2007 external peer review, and on the adequacy, transparency, and clarity of the revised draft.

For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

Topic #1 – Carcinogenic Hazard

OMB commented that in responding to SAB comments EPA should better articulate its scientific justification for agreeing with the majority of the SAB reviewers, who concurred with EPA's conclusion that the weight of the evidence supported the cancer hazard characterization of "carcinogenic to humans", and for disagreeing with the minority of the SAB reviewers, who favored a characterization of "likely to be carcinogenic to humans".

EPA Response: EPA characterized ethylene oxide (EtO) as "carcinogenic to humans." The majority of the SAB Panel concurred with this cancer characterization. A minority of SAB Panel members were of the opinion that the descriptor "likely to be carcinogenic to humans" was more appropriate, as they judged the epidemiological evidence to be weak and the data insufficient to conclude that key precursor events were observed in humans (SAB, 2007, p. 10).

EPA concluded that the evidence for EtO was in accordance with the lines of evidence set forth in EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) for a characterization of "carcinogenic to humans" when the epidemiologic evidence of a causal association between human exposure and cancer is less than convincing. Specifically, (1) there is strong evidence for EtO-induced lymphohematopoietic cancers and some evidence for EtO-induced breast cancer in EtO-exposed workers; (2) there is extensive evidence of EtO-induced carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice; (3) EtO is a direct-acting alkylating agent whose mutagenic and genotoxic capabilities have been well established in a variety of experimental systems, and a mutagenic mode of carcinogenic action has been identified in animals involving the key precursor events of DNA adduct formation and subsequent DNA damage, including point

mutations and chromosomal effects; and (4) there is strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage, such as chromosomal aberrations, sister chromatid exchanges, and micronuclei in EtO-exposed workers.

In response to the interagency comments, EPA has strengthened the summary review of these data in the human evidence section (Section 3.1) and in the cancer hazard characterization section (Section 3.5.1). In addition, the assessment specifically addresses the precursor data for rodents and humans, and, while the databases for humans and rodents contain different types of studies, there is no evidence of an inconsistency. Thus, EPA concluded that the data support a finding of a mutagenic mode of action and are relevant to humans, a finding with which the SAB concurred. The discussion of these data was expanded, specifically in Sections 3.3.3.2, 3.3.3.3, and 3.4.1. Additionally, cross-referencing to these revisions was added in the response to the SAB comment in Appendix H.

Topic #2 – Study Selection

OMB commented that the specific criteria for study selection should be discussed for each study.

EPA Response: For the hazard assessment, all identified epidemiological studies were included in the weight-of-evidence evaluation. An explanation of the criteria used to evaluate the strengths and weaknesses of the epidemiological studies was added at the beginning of Section 3.1. The National Institute of Occupational Safety and Health (NIOSH) study (Steenland et al., 2003, 2004) is given more weight due to the relatively higher quality of and confidence in the study compared to other EtO studies, with respect to a number of important considerations (e.g., large size, comprehensive quantitative exposure assessment, inclusion of females, long follow-up, use of internal comparisons, no identified exposures to other chemicals).

For the development of quantitative unit risk estimates based on human data, there were only two studies that had quantitative exposure estimates and provided the necessary exposure-response information. Of the two cohorts with exposure-response data, the NIOSH cohort was used for the quantitative assessment, as it was considered to be substantially superior to the other cohort with respect to a number of key considerations for quantitative risk estimation (in particular, quality of the exposure estimates, cohort size, inclusion of women, and absence of co-exposures). EPA has revised the assessment to include a summary table of important considerations for study selection in Section 4.1 and an expanded discussion of the exposure assessment for the NIOSH cohort (Appendix A, Section A.2.8).

Topic #3 – Endogenous EtO Production

In their review of the external review draft assessment, the SAB recommended a more comprehensive discussion of the production of DNA adducts from endogenous EtO and more discussion addressing (i) why the current evidence of background levels of 2-hydroxyethylation of DNA does not constitute a threshold and (ii) whether the magnitude and variability in endogenous EtO-induced damage may overwhelm any contribution from exogenous EtO

exposure (other than some acute high-dose exposure). OMB commented that it was not clear that EPA had fully addressed the SAB concerns about endogenous EtO production.

EPA Response: In response to the SAB recommendations, the discussion of endogenous metabolic production of EtO and its significance and contribution to the formation of background adducts in rodents and humans was expanded (Sections 3.3.2 and 3.3.3.1 and Section C.6 of Appendix C, with the latter section devoted specifically to endogenous EtO production). The two subpoints, (i) and (ii), noted by SAB were addressed at the end of Section 4.5. EPA acknowledges that the existence of these high and variable background levels of endogenous EtO-induced DNA damage may make it difficult to observe statistically significant increases in risk from low levels of exogenous exposure, although there is no evidence suggesting that low levels of exogenous EtO exposure do not contribute to carcinogenic risk. Additionally, in a recent study of rats dosed with EtO, Marsden et al. (2009), using sensitive detection techniques and an approach designed to separately quantify endogenous and exogenous N7-(2-hydroxyethyl)guanine adducts, observed increases in exogenous adducts in DNA of the spleen and liver consistent with a linear dose-response relationship. This relationship was observed down to the lowest dose administered, which was a very low dose compared to the LOAELs in the EtO carcinogenicity bioassays. In response to interagency comments, EPA has further expanded its response to the SAB comment in Appendix H and added cross-referencing.

Topic #4 – Modeling of the Human Cancer Data

The SAB, in its review of the external draft assessment, recommended EPA model individual (continuous) data rather than categorical (grouped) data. OMB expressed concerns that EPA had retained a modeling approach based on grouped data that the SAB had discouraged.

EPA Response: EPA followed the SAB recommendations to undertake new modeling work to develop models for the individual (continuous) EtO data which could serve as the basis for the point of departure (POD) estimates, rather than relying on models using published results based on categorical (grouped) data. EPA investigated alternative models to reflect the exposure-response relationships of the full continuous datasets for lymphoid cancers and breast cancer. In addressing breast cancer incidence, EPA was successful in developing an alternative model which is now utilized to estimate the POD for this endpoint. However, alternative modeling approaches did not provide quantitatively stable estimates of risk for the lymphoid cancers. Thus, EPA retained the categorical modeling approach for these data. The evaluation of the different models for the lymphoid cancer data is discussed in detail in Section 4.1.1.2 of the revised EtO assessment and in EPA's response to SAB comments on charge question 2.b in Appendix H. Additionally, EPA is undertaking an additional peer review of the exposure-response modeling of epidemiologic data.

Topic #5 – Presentation of a Nonlinear Approach for Low-Dose Extrapolation

OMB commented that EPA should follow the recommendations of the several SAB Panel members who advocated presenting both a linear and nonlinear approach for low-dose extrapolation.

EPA Response: A few of the SAB panel members recommended presenting a nonlinear approach in addition to the linear extrapolation approach. The reasons for using the nonlinear approach were presented in Appendix C of the SAB report and were largely that (1) DNA adducts may show a nonlinear response when identical adducts are formed endogenously and (2) mutations do not have linear relationships with exposure but exhibit an “inflection point”.

In brief, EtO is a DNA-reactive, mutagenic, multi-site carcinogen in humans and laboratory species; as such, it has the hallmarks of a compound for which low-dose linear extrapolation is strongly supported by EPA’s *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). By comparison, the *Guidelines* recommend that “A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses.”

For EtO, there is sufficient evidence of a mutagenic/genotoxic mode of action (MOA), without evidence of additional or alternative MOAs being operative (Section 3.4.1). Furthermore, recent data from Marsden et al. (2009) support a linear exposure-response relationship for EtO exposure and DNA adducts ($p < 0.05$) and demonstrate increases of DNA adducts from exogenous EtO exposure above those from endogenous EtO for very low exposures to exogenous EtO. Appendix C of the SAB report presents two EtO-specific mutation datasets in support of the thought that mutations do not have linear relationships with exposure but exhibit an “inflection point”. EPA analyzed these datasets, summarized in EPA’s response to SAB comments on charge question 2.b in Appendix H, and found that they are consistent with low-dose linearity. Thus, the available evidence supports the use of a linear extrapolation approach (discussed in detail in the revised assessment, Sections 3.3.3.1 and 4.5), and the inclusion of a nonlinear approach was not warranted.

EPA has given careful consideration to the range of perspectives provided in the report, and a response to the issues raised, including the results of EPA’s analysis of the EtO mutagenicity datasets presented in Appendix C of the SAB Report, can be found in EPA’s expanded response to the SAB comments on charge question 2.b in Appendix H of the revised assessment.

Topic #6 – Derivation of Risk Estimates for Lymphoid Cancer Incidence

The SAB Panel noted assumptions in the approach used to derive incidence estimates from mortality data and discouraged use of the approach. OMB expressed concerns that EPA had retained an approach for deriving cancer incidence estimates from mortality data that the SAB had discouraged.

EPA Response: EPA developed estimates of the risk of cancer incidence, not mortality, as the cancers associated with EtO exposure (lymphohematopoietic, in particular lymphoid, and breast cancers) have substantial survival rates, and incidence estimates are preferred for unit risk estimates. The breast cancer incidence estimates are not at issue here because they are based on data from an incidence study. With respect to the lymphoid cancers, for which only mortality data were available, the SAB commented that the approach used would apply to the case where there is a proportional rate of incidence/mortality across the cancer types that are included in the

lymphoid cancer grouping. EPA considered the issue of proportionality with respect to the EtO results and determined that the approach used is not expected to result in an overestimation of the incidence risk estimates (see Section 4.1.1.3 of the revised assessment for discussion), whereas, deriving mortality estimates as the sole cancer risk estimates for lymphoid cancer would substantially underestimate cancer risk. EPA included the mortality-based estimates for comparison, and the lymphoid cancer incidence unit risk estimate is about 120% higher than (i.e., 2.2 times) the mortality-based estimate, which is considered reasonable given the high survival rates for lymphoid cancers. Thus, in the absence of a more suitable approach to estimate risks of lymphoid cancer incidence, EPA retained the approach used in the external review draft, which provides a reasonable estimate of incidence risks.

EPA expanded the discussion of the uncertainties and assumptions outlined by the SAB regarding this approach (Section 4.1.1.3); adding more detail regarding why the assumptions are not considered critical and describing why the approach is reasonable, noting that the quantitative impacts of the uncertainties are minor. EPA has also augmented the response to the SAB comment on this issue under “7. Statistical issues” related to charge question 2.b in Appendix H.

Topic #7 – Presentation of a Lower Bound Estimate of Unit Risk

OMB expressed concerns that EPA did not follow SAB recommendations to provide unit risk estimates based on the upper 95% confidence limit on the EC₀₁ (the effective concentration corresponding to a 1% extra cancer risk).

EPA Response: The SAB Panel encouraged the EPA “to present unit risk estimates based on the range of EC₀₁ values corresponding to the lower 95% confidence limit, the point estimate, and the upper 95% confidence limit”. However, as a consequence of the 2-step approach used by EPA to generate cancer potency estimates from a POD rather than directly from the statistical model used to estimate the POD, potency estimates below the response level corresponding to the POD are no longer associated with the statistical model. While linear extrapolation from a POD that is the 95% (one-sided) lower bound on the central estimate of the exposure concentration associated with the selected (benchmark) response level (e.g., the LEC₀₁) might be generally expected to yield a reasonable upper bound on cancer risk for that dataset (though not strictly a statistical “95%” upper bound), estimates involving a linear extrapolation from the *upper* bound on that central estimate are not generally meaningful and can be misleading if they are mistaken for lower bounds on potency, as the actual exposure-response relationship may exhibit some sublinearity below the response level corresponding to the POD.

In the revised assessment, EPA presents 95% (one-sided) lower bounds and central estimates of the EC_{01s} as well as standard errors for the regression coefficients used in the modeling, which provide information about the variability of the modeled slope estimate. EPA’s *Guidelines for Carcinogen Risk Assessment* also recommend the calculation of a 95% upper bound on the central estimate (in this case the EC₀₁) related to the POD “to the extent practicable” (U.S. EPA, 2005, p. 1-14). For the linear regression model used as the basis for the lymphoid cancer unit risk estimate, it was not practicable to provide such a value, as it was quantitatively undefined.

However, in response to the interagency comments, such a value has been added for the selected breast cancer incidence model.

Abbreviations and Acronyms

EC ₀₁	Effective concentration corresponding to a 1% extra risk
EPA	U.S. Environmental Protection Agency
EtO	Ethylene oxide
IRIS	Integrated Risk Information System
LEC ₀₁	Lower (one-sided) 95% confidence bound on the EC ₀₁
LOAEL	Lowest observed adverse effect level
MOA	Mode of action
NIOSH	National Institute of Occupational Safety and Health
OMB	Office of Management and Budget
POD	Point of departure
SAB	U.S. EPA Science Advisory Board

References

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