



November 14, 2014

Mr. Aaron Y. Yeow
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1200 Pennsylvania Avenue, N. W.
Mail Code: 1400R
Washington, DC 20460

Sent via email to: Yeow.aaron@Epa.gov

Re: Comments on the Revised External Review Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

Dear Mr. Yeow:

The Ethylene Oxide Panel (Panel) of the American Chemistry Council (ACC) appreciates the opportunity to submit the attached summary of its comments on the U.S. Environmental Protection Agency's (EPA) July 2013 draft Integrated Risk Information System (IRIS) assessment titled, "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide." The Panel supports the development of a scientifically robust and high quality IRIS assessment that includes clear and transparent data evaluation criteria and recognizes the importance of incorporating up-to-date scientific knowledge.

EPA has not satisfactorily addressed the recommendations made by the 2007 SAB Panel reviewing the 2006 draft and by the public reviewing both the 2006 and 2013 drafts. For example, the 2007 SAB Panel report states:

The Panel concurred that the NIOSH cohort is the best single epidemiological data set with which to study the relationship of cancer mortality to the full range of occupational exposures to EtO. That said, the Panel encouraged the EPA to broadly consider all of the epidemiological data in developing its final Assessment. In particular, the Panel encourages the EPA to explore uses for the Greenberg et al. (1990) data including leukemia and pancreatic cancer mortality and EtO exposures for 2,174 Union Carbide workers from its two Kanawha Valley, West Virginia facilities.

In its Response to Comments, EPA states "EPA reevaluated all of the epidemiological studies with quantitative exposure-response data and has revised the assessment to include an expanded discussion of study selection, including a summary table of important considerations." However, it does not appear that EPA has incorporated any recommendations that would alter the outcome of the risk assessment. In fact, the overall unit risk factor is the same as the 2006 draft.



Mr. Aaron Y. Yeow
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The Panel stated in its 2013 comments that EPA should substantially revise the document to accurately convey the best available science and weight-of-evidence in compliance with both EPA's Cancer Guidelines and OMB and EPA Information Quality Act Guidelines. Appendices H and L of EPA's 2014 draft addresses ACC's 2013 comments. In these Appendices, EPA provides only a very brief summary of ACC's technical comments. Please find attached the Executive Summary and Introduction from our 2013 comments that summarize our substantial concerns and recommendations on the 2013 draft. The full 2013 comment document can be found on www.regulations.gov (Document ID No. EPA-HQ-ORD-2006-0756-0057).

If you have any questions or require additional information please feel free to contact me by phone (202-249-6714) or by email at bill_gulledge@americanchemistry.com.

Sincerely,

Bill Gulledge

Bill Gulledge
Senior Director, Chemical Products and Technology Division
Manager, Ethylene Oxide Panel





October 11, 2013

Office of Environmental Information (OEI) Docket
Mail Code: 28221T
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW.
Washington, DC 20460

Submitted via <http://www.regulations.gov>

Re: Comments on the Revised External Review Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Docket ID No. EPA-HQ-ORD-2006-0756

Dear Sir or Madam:

The Ethylene Oxide Panel (Panel) of the American Chemistry Council (ACC) appreciates the opportunity to submit comments on the U.S. Environmental Protection Agency's (EPA) draft Integrated Risk Information System (IRIS) assessment titled, "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide" (EPA/635/R-13/128a) and on the draft peer review charge questions. The Panel supports the development of a scientifically robust and high quality IRIS assessment that includes clear and transparent data evaluation criteria and recognizes the importance of incorporating up-to-date scientific knowledge.

The attached comments provide both a summary and detailed analyses of the Panel's major concerns with the July 2013 revision of the Ethylene Oxide (EO) draft IRIS assessment. Please note that the detailed analyses are provided in the appendices and that links from the main text to the relevant appendices are included. The appendices also include references or copies of recent publications relevant to the IRIS assessment review.

The Panel supports the comments submitted by ACC's Center for Advancing Risk Assessment Science and Policy (ARASP) and the ARASP recommendations to augment the draft peer review charge questions. These recommendations include the addition of the following questions:

- Please comment on EPA's evaluation of the background levels of endogenous EO exposures and their potential impact on the unit risk estimate.
- Please comment on EPA's determination that recommendations from the 2007 SAB Peer Review Panel to present both linear and nonlinear modeling in the unit risk calculations in the final EO assessment were not warranted.



- Please comment on the EPA's integration of the available epidemiological and toxicological data to inform the development of the unit risk estimate and cancer classification.
- Please comment not only on the manner in which the two-piece linear spline model is implemented, but also on whether or not it is appropriate for developing unit risk estimates for lifetime exposure based on the available incidence data.

In addition, the Panel recommends that the following charge question be considered:

- Please review EPA's approach of aggregating tumor types to estimate the total cancer risk given the previous National Academy of Sciences recommendations on this practice and the Panel's comments on this draft IRIS assessment.

If you have any questions or require additional information please feel free to contact me by phone (202-249-6714) or by email at bill_gulledge@americanchemistry.com.

Sincerely,

Bill Gulledge

Bill Gulledge

Senior Director, Chemical Products and Technology Division

Manager, Ethylene Oxide Panel

EXECUTIVE SUMMARY

The American Chemistry Council's Ethylene Oxide Panel (ACC) appreciates the opportunity to comment on EPA's Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide in support of Summary Information on the Integrated Risk Information System (IRIS) (Draft IRIS Assessment). ACC strives to ensure appropriate product stewardship, and, as part of its mission, addresses important science and public policy issues related to the chemical industry, including evaluating the Draft IRIS Assessment.

As set forth in these comments, EPA has failed to comply with the Office of Management and Budget's Information Quality Act (IQA) Guidelines, EPA's own IQA Guidelines, the recommendations of the National Academy of Sciences (NAS), as set forth in its 2011 review of EPA's draft IRIS assessment of formaldehyde (NAS 2011), as well as EPA's Guidelines for Carcinogen Risk Assessment (Cancer Guidelines) (EPA 2005). EPA classifies the Draft IRIS Assessment as a "highly influential scientific assessment" and therefore it must adhere to a rigorous standard of quality. EPA has failed to apply a transparent and systematic weight-of-evidence approach in both qualitatively and quantitatively assessing the cancer risks of ethylene oxide (EO) exposures and did not base the Assessment on the best available science. Numerous studies were either not reviewed or only superficially considered by EPA. Finally, because EPA has not made underlying data available to the public, and efforts to retrieve these data have been unsuccessful, the Assessment is not consistent with the OMB and EPA IQA guidelines for influential information as the analytic results are not "capable of being substantially reproduced."

The Draft IRIS Assessment contains environmental and occupational unit risk estimates for EO that are unrealistically high and conflict with human, animal and mechanistic scientific observations. The fact that EO is a weak mutagen and the inconclusive findings from the large number of epidemiology studies are inconsistent with what would be expected from a potent carcinogen. EPA arrived at these unrealistic estimates as a result of errors in its modeling, calculations, and assumptions using the National Institute for Occupational Safety and Health (NIOSH) studies.

Despite the Science Advisory Board's (SAB) recommendations, EPA based its exposure-response models on a summary of the available data and not on the individual data, employed a non-peer reviewed supra-linear spline model, rejected consideration of the well accepted log-linear rate ratio model, provided insufficient development of the assumption that EO's carcinogenic mode of action (MOA) is via direct, DNA-reactive mutagenicity, and failed to incorporate the recently updated Union Carbide Corporation (UCC) epidemiology data. The exposure assessment of the NIOSH studies suffered from several limitations including the absence of data prior to 1976 and a regression model that fixed the calendar year effect to 1978. The exclusion of UCC data on the basis of exposure assessment limitations is, therefore, not justified. Had EPA followed the NAS (2011) recommendations, and used a transparent, standardized and systematic approach to review the strengths and weaknesses of individual

studies, EPA likely would not have been able to rely upon the NIOSH studies while rejecting the UCC studies.

Given the weak epidemiology evidence and the lack of consistency and a clear exposure-response, the selection of a target organ is problematic. The categories of “lymphoid” and “lymphohematopoietic” are both a non-defensible combining of malignancies that are derived from different cells of origin. In particular, the category of “lymphohematopoietic” has no etiologic, pathologic or clinical meaning. The choice of breast cancer as a target organ is not justified as the evidence is even weaker than that for “lymphoid” tumors.

EPA’s *de minimis* environmental concentrations in the sub parts per trillion (ppt) are orders of magnitude below:

- Risk based concentrations based on potency estimates using the Cox Proportional Hazards model with cumulative exposure;
- EO concentrations in ambient air;
- Endogenous levels of EO in the body; and
- EO concentrations associated with a meaningful increase in DNA adduct burden.

Key deficiencies in the Draft IRIS Assessment include:

- EPA’s proposed direct, DNA-reactive mutagenic MOA is not supported by the most recent scientific evidence and, therefore, does not justify the use of only a linear, non-threshold approach.
 - The Draft IRIS Assessment cites the extensive literature on genotoxicity; however, EPA does not view the findings in terms of dose levels for mutagenicity. By doing so, it fails to recognize that EO is a weak mutagen.
 - EPA overstates the evidence that precursor events (i.e., mutations) resulting from EO are anticipated to occur in human potential target tissues and progress to tumors.
 - EPA fails to use currently available mechanistic data to support its designation of a direct, DNA-reactive mutagenic MOA for rodent carcinogenicity. Other MOAs should be considered.
 - The mere demonstration of mutagenicity for a chemical that causes cancer is not sufficient to conclude that it does so by a direct, DNA-reactive mutagenic MOA; dose-response and temporality relative to carcinogenicity are necessary.

- For a direct, DNA-reactive mutagenic MOA, mutation induced by the chemical must be the first step which initiates a cascade of other key events such as cytotoxicity or cell proliferation that are key to the carcinogenesis process.
- Recent studies designed to test the hypothesis of a direct, DNA-reactive mutagenic MOA for EO have concluded that data do not sufficiently support this MOA. In fact, such an MOA is inconsistent with mutations in the target tissue under EO exposure conditions that induce tumors in the tissue.
- EPA has misinterpreted Marsden et al. (2009) to support linearity of risk at low doses.
- EPA's selection of target organ(s) is biologically and epidemiologically unsupportable. There is no obvious target organ.
 - The epidemiology data for EO provides limited evidence of carcinogenicity, despite 14 cohort studies involving over 33,000 EO workers in five countries.
 - There is no evidence of increases among females for the specific lymphoid cancers used as a target organ and no pattern of consistency across studies for breast cancer or specific types of lymphoid cancers.
 - There is no evidence of a statistically significant positive cumulative exposure-response relationship for any cancer endpoint in the NIOSH study or UCC study.
 - The choice of breast cancer as a target organ for EO dose-response assessment is not justified as evidence is weaker than the evidence for lymphoid tumors.
 - EPA has incorrectly used the categories of "lymphoid" and "lymphohematopoietic" cancer as target organs for quantitative risk assessment and for assessing consistency among epidemiology studies. This is an inappropriate grouping of malignancies that are derived from different cells of origin.
 - Combining unit risk estimates for breast cancer and "lymphoid" cancers is not scientifically justified.
 - The NIOSH breast cancer incidence data are not publicly available; therefore, EPA's analyses of this endpoint cannot be verified.
- Several SAB Panel members recommended that both linear and nonlinear extrapolation models be considered in the EO assessment. However, EPA did not include a nonlinear approach.

- The Draft IRIS Assessment contains several substantial modeling issues; any one of these when corrected would substantially change the proposed risk values.
 - There were significant flaws in EPA’s exposure-response modeling, as discussed in Valdez-Flores and Sielken (2013) and Valdez-Flores et al. (2010).
 - EPA’s method of evaluating different exposure-response models is mathematically incorrect, is based only on a summary of the available data and not the individual data themselves, and erroneously rejects more appropriate models and SAB recommendations.
 - Contrary to SAB recommendations, EPA uses a supralinear, two-spline model for breast cancer incidence.
 - EPA’s exposure-response modeling methodology and choices for the component factors in the calculation of points of departure (PODs) exaggerates the risk by as much as 1500 fold.
 - EPA’s exposure-response modeling techniques over predict the number of cancer mortalities actually observed in the NIOSH cohort study.
 - EPA’s dose-response modeling methodology exaggerates the risks and limits the power of the risk assessment by using only data from one epidemiology study (NIOSH).
- Substantial errors prevent accurate assessment of EPA’s statistical analysis.
 - In addition to the inappropriate combining of lymphoid and breast cancer risks, there are several statistical problems with the way EPA performed this combination.
- EPA inappropriately ignores the uncertainties in the NIOSH retrospective exposure assessment while emphasizing those of the UCC study.
 - The limitations in NIOSH’s exposure assessment largely invalidate EPA’s reliance solely on the NIOSH epidemiology study and the exclusion of the UCC epidemiology study.
 - The power of the dose-response assessment would be increased by adding in the data from the UCC study.
- EPA did not adequately consider background and endogenous levels of EO.

ACC urges EPA to substantially revise the Draft IRIS Assessment to accurately convey the best available science and weight-of-evidence in compliance with existing standards for quality, including the OMB and EPA IQA guidelines, EPA's Cancer Guidelines, and the NAS recommendations.

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INTRODUCTION

The American Chemistry Council's Ethylene Oxide Panel (ACC) appreciates the opportunity to comment on EPA's Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide In Support of Summary Information on the Integrated Risk Information System (IRIS) (Draft IRIS Assessment). ACC strives to ensure appropriate product stewardship, and, as part of its mission, address important science and public policy issues related to the chemical industry, including the EPA's Draft IRIS Assessment.

As set forth in these comments, EPA has failed to comply with the Office of Management and Budget's Information Quality Act (IQA) Guidelines, EPA's own IQA Guidelines, the recommendations of the National Academy of Sciences (NAS), as set forth in its 2011 review of EPA's draft IRIS assessment of formaldehyde (NAS 2011), as well as EPA's Guidelines for Carcinogen Risk Assessment (Cancer Guidelines) (EPA 2005). EPA classifies the Draft IRIS Assessment as a "highly influential scientific assessment" and therefore it must adhere to a rigorous standard of quality. Throughout the Draft IRIS Assessment, for example, EPA has failed to apply a transparent and systematic weight-of-evidence approach in both qualitatively and quantitatively assessing the cancer risks of ethylene oxide (EO) exposures. Moreover, the Draft IRIS Assessment is not based on the best available science. Numerous studies were either not reviewed or only superficially considered by EPA. Finally, because EPA has not made underlying data available to the public, and efforts to retrieve these data have been unsuccessful, the assessment is not consistent with the OMB and EPA IQA guidelines for influential information as the analytic results are not "capable of being substantially reproduced."

EPA's proposed environmental and occupational unit risk estimates for EO are unrealistically high and conflict with human, animal and mechanistic scientific observations. The fact that EO is a weak mutagen and the inconclusive findings from the large number of epidemiology studies are inconsistent with what would be expected from a potent carcinogen. The Agency arrived at these unrealistic estimates as a result of errors in its modeling, calculations and assumptions using the National Institute for Occupational Safety and Health (NIOSH) studies.

ACC urges EPA to substantially revise the Draft IRIS Assessment to accurately convey the best available science and weight-of-evidence in compliance with existing standards for quality, including the OMB and EPA IQA guidelines, EPA's Cancer Guidelines, and the NAS recommendations.

I. EPA and OMB Information Quality Guidelines Apply to the Draft IRIS Assessment

Congress enacted the Information Quality Act (IQA), Pub. L. No. 106-554, 114 Stat. 2763A-153 to 2763A-154, to "ensur[e] and maximiz[e] the quality, objectivity, utility and integrity of information ... disseminated by Federal agencies" such as the EPA. The IQA required the Office of Management and Budget (OMB) to issue government-wide guidance, which each federal agency was to follow in its issuance of its own guidelines.

In February 2002, OMB issued its guidelines, and EPA issued its agency-specific guidelines (EPA IQA Guidelines) later that year.¹ The purpose of the EPA IQA Guidelines is to apply the OMB Guidelines to the agency's particular circumstances, and to "establish administrative mechanisms allowing affected persons to seek and obtain correction of information ... disseminated by the agency that does not comply with the [OMB] guidelines...." EPA's Draft IRIS Assessment must meet OMB's guidelines as well as the Agency's own guidelines.

A. The Draft IRIS Assessment is influential information and must adhere to a rigorous standard of quality

The Draft IRIS Assessment is "influential" scientific risk assessment information as set forth in EPA IQA Guidelines² because it is a "[m]ajor work product undergoing peer review," and "will have ... a clear and substantial impact (i.e., potential change or effect) on important public policies or private sector decisions."³ Moreover, EPA classifies the Draft IRIS Assessment as a "highly influential scientific assessment." The Draft IRIS Assessment, therefore, must adhere to a rigorous standard of quality, including meeting the higher standard of reproducibility.⁴ The substance of the information must be "accurate, reliable, and unbiased."⁵ EPA must use the best available science and supporting studies, as well as "a 'weight-of-evidence' approach that considers all relevant information and its quality."⁶

EPA must present the information in a "comprehensive, informative, and understandable" manner, specifying:

- Each population addressed by any estimate of applicable human health risk;
- The expected risk or central estimate of human health risk for the specific populations affected;

¹ 67 Fed. Reg. 8452 (Feb. 22, 2002); see EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*, available at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf.

² Pub. L. No. 106-554. The Information Quality Act was developed as a supplement to the Paperwork Reduction Act, 44 U.S.C. §3501 et seq., which requires OMB, among other things, to "develop and oversee the implementation of policies, principles, standards, and guidelines to ... apply to Federal agency dissemination of public information."

³ EPA IQA Guidelines at 19 (internal citations omitted); OMB Guidelines For Ensuring and Maximizing the Quality Objectivity Utility and Integrity of Information Disseminated by Government Agencies. 67 Fed. Reg. 8452, 8455 (Feb. 22, 2002) (OMB IQA Guidelines).

⁴ Quality includes objectivity, utility, and integrity.

⁵ EPA IQA Guidelines at 22; OMB IQA Guidelines at 8453.

⁶ EPA IQA Guidelines at 21. "In this approach, a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered." *Id.* at 26. The definition of best available science mirrors that articulated in *Chlorine Chemistry Council v. EPA*, 206 F.3d 1286 (D.C. Cir. 2000), referring to "the availability at the time an assessment is made." EPA IQA Guidelines at 23.

- Each appropriate upper-bound or lower-bound estimate of risk;
- Each substantial uncertainty identified in the process of the assessment of risk and studies that would assist in resolving the uncertainty; and
- Peer-reviewed studies known to support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.⁷

As set forth below and in the attached Appendices, however, EPA has failed to comply with the explicit information quality requirements.

B. EPA’s Cancer Guidelines are critical to ensuring and maximizing the quality of the Draft IRIS Assessment

EPA’s Cancer Guidelines emphasize “a critical analysis of all the available information that is relevant to assessing the carcinogenic risk,” rather than rely on default options as the starting point (EPA 2005, at 1-6 to 1-7). This analysis should include a complete analysis all tumor types, followed by an overall synthesis that includes a characterization of the risk estimates across tumor types, the strength of the mode of action information of each tumor type, and the anticipated relevance of each tumor type.

EPA’s Cancer Guidelines stress the importance of relying upon, “common sense, reasonable applications of assumptions and policy, and transparency ... to avoid unrealistically high estimates” (EPA 2005, at 5-2). “Otherwise, risk management decisions may be made on varying levels of conservatism, leading to misplaced risk priorities and potentially higher overall risks” (EPA 2005, at 5-2 to 5-3). In developing the Draft IRIS Assessment, however, EPA did not adhere to its Cancer Guidelines.

II. EPA should include a nonlinear approach for the EO assessment.

A. EPA should follow the recommendation of members of the SAB to include a nonlinear approach.

When the EPA Science Advisory Board (SAB) reviewed EPA’s previous draft assessment of the carcinogenicity of EO, “[w]ith appropriate discussion of the statistical and biological uncertainties, several Panel members strongly advocated that both linear and nonlinear calculations be considered in the final EtO Risk Assessment” (EPA 2007, at 4). In the Draft IRIS Assessment, however, EPA states that it “considered this suggestion but judged that the support for a nonlinear approach was inadequate” (EPA 2013, at 4-43).

⁷ EPA IQA Guidelines at 22-23; OMB IQA Guidelines at 8458.

The Cancer Guidelines state:

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. Special attention is important when the data support a nonlinear mode of action but there is also a suggestion of mutagenicity. Depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches. (EPA 2005, at 3-22) (emphasis in original).

The Cancer Guidelines refer to chemicals with direct mutagenic activity as “generally considered to be linear” (EPA 2005, at 3-21). However, this does not mean that EPA must use a linear approach if the science does not support it.⁸ By contrast, EO genetic toxicity data indicate the EO assessment should at least consider both linear and nonlinear modes-of-action, in accordance with the Cancer Guidelines. Moreover, as discussed in Section II.B., below, EO should be considered a weak mutagenic substance, further justifying the inclusion of both linear and nonlinear modes of action.

EPA should follow the recommendation that both linear and nonlinear calculations be considered in the EO assessment.

B. EPA’s proposed direct, DNA-reactive mutagenic mode of action is not supported by the most recent scientific evidence and, therefore, does not justify only a linear, non-threshold approach.

As discussed in detail in [Appendix A](#), the Draft IRIS Assessment cites the extensive literature on genotoxicity; however, EPA does not view the findings in terms of dose levels for mutagenicity, but more from a “yes” and “no” perspective. By doing so, the Agency fails to recognize that EO is a weak mutagen.

For example, EO is a stage specific mutagen (weakest classification) in *Drosophila* male germ cell mutagenicity testing; it was the weakest among 41 alkylating agents evaluated for mutagenic

⁸ The Cancer Guidelines state: “These cancer guidelines are intended as guidance only. They do not establish any substantive “rules” under the Administrative Procedure Act or any other law and have no binding effect on EPA or any regulated entity, but instead represent a non-binding statement of policy. EPA believes that the cancer guidelines represent a sound and up-to-date approach to cancer risk assessment, and the cancer guidelines enhance the application of the best available science in EPA’s risk assessments. However, EPA cancer risk assessments may be conducted differently than envisioned in the cancer guidelines for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment. The science of risk assessment continues to develop rapidly, and specific components of the cancer guidelines may become outdated or may otherwise require modification in individual settings” (EPA 2005, at 1-2 to 1-3).

and carcinogenic potency. EO's genetic activity profile, as shown in the IARC (1994) report reproduced in the Draft IRIS Assessment and in Waters et al. (1999), indicates Lowest Effective Doses for positive results between 1.0 and 10.0 µg/ml or mg/kg (23 to 230 µM; equivalent to >150 ppm by inhalation). Mutagenicity study of plasmids has indicated that mutation in this system is a high-exposure phenomenon.

EPA includes sister chromatid exchanges, DNA strand-breaks and unscheduled DNA synthesis in its consideration of mutagenic potency and mutagenic MOA; however, these are all DNA damage but not mutagenic endpoints. Moreover, EPA incorrectly overstates that there is strong evidence that precursor events (i.e. mutations) resulting from an EO exposure are anticipated to occur in human potential target tissues and progress to tumors. ([See Appendix A.](#))

EPA fails to use currently available mechanistic data to support its designation of a direct, DNA-reactive mutagenic MOA for EO's rodent carcinogenicity. The mere demonstration of mutagenicity for a chemical that causes cancer is not sufficient to conclude that it does so by a direct, DNA-reactive mutagenic MOA; dose-response and temporality relative to carcinogenicity are necessary. For a direct, DNA-reactive mutagenic MOA, mutation induced by the chemical must be the first step which initiates a cascade of other key events, such as cytotoxicity or cell proliferation, that are essential to the carcinogenesis process. ([See Appendix A.](#))

Recent studies designed to test the hypothesis of a direct, DNA-reactive mutagenic MOA for EO have concluded that data do not sufficiently support this MOA. In particular, EPA has misinterpreted Marsden et al. (2009) to support linearity of risk at low doses. ([See Appendix A.](#))

The Draft IRIS Assessment states:

Using sensitive detection techniques and an approach designed to separately quantify both endogenous N7-HEG adducts and "exogenous" N7-HEG adducts induced by EtO treatment in rats, Marsden et al. (2009) reported increases in exogenous adducts in DNA of spleen and liver consistent with a linear dose-response relationship ($P < 0.05$) down to the lowest dose administered (0.0001 mg/k) injected i.p. daily for 3 days) (EPA 2013, at 3-29 to 3-30).

This statement, however, applies only to exogenously derived N7-HEG adducts. Figure 2 in Marsden et al. (2009) shows that the total level of N7-HEG adducts (endogenous + exogenous) only becomes significantly greater than the level of endogenous adducts alone at the highest doses of EO administered.

[Appendix D](#) provides the details of a statistical review of the results in Marsden et al. (2009). For all study endpoints (liver, spleen, and stomach), there are no statistically significant differences between the response level in the control group and the response level in the lower dose groups (for the lowest 3 doses for liver, the lowest 2 doses for spleen, and the lowest dose for stomach). Furthermore, in the Draft IRIS Assessment, EPA does not address the authors'

major conclusion: “In summary, by using a dual-isotope approach combining HPLC-AMS with LC-MS/MS analysis, we have provided evidence supporting a linear dose-response relationship for the major EO DNA adduct after exposure to low occupationally relevant doses. More importantly, we have proven that the extent of damage arising from this route is insignificant compared with the background level of N7-HEG naturally present” (Marsden et al. 2009, at 3058). Therefore, Marsden et al. (2009) does not support linearity of risk at low EO doses.

As explained in [Appendix A](#), EPA’s assertion that no other MOAs would be applicable is incorrect and other MOAs should be considered. Recent studies have concluded that direct, DNA mutagenesis does not appear to be the driver for cancer and have also provided evidence in support of a complex MOA (Haber et al. 2012; Parsons et al. 2013). These studies:

- Could not eliminate a direct effect as a component;
- Provided evidence for selective amplification of pre-existing cells with *Ras* mutations rather than direct, induction of *de novo ras* mutations; and
- Provided evidence for oxidative stress with oxidative DNA damage.

Therefore, a direct, DNA-reactive mutagenic MOA is inconsistent with mutations in the target tissue under EO exposure conditions that induce tumors in the tissue.

Marsden et al. (2009) also demonstrates that, even at the highest exposure doses of EO employed in the study, the increases in N7-HEG adducts derive from endogenous EO are not the result of direct action of the exogenously administered EO. The N7-HEG adducts are an indirect effect of the administered EO, which indicates an indirect mutagenic MOA at these doses. As outlined in the Cancer Guidelines, an indirect mutagenic MOA is not supportive of a linear, non-threshold low-dose extrapolation. ([See Appendix A.](#))

In summary, [Appendix A](#) describes at least two plausible MOAs, including indirect mutagenicity due to oxidative stress and indirect mutagenesis via cell proliferation. Neither of these indirect mechanisms of mutagenesis supports the use of a default linear extrapolation. Based on the foregoing, EPA should include a non-linear approach in the Draft IRIS Assessment.

III. EPA should re-examine its selection of target organ(s) to support the risk assessment.

A. EPA’s selection of target organ(s) is biologically and epidemiologically unsupportable.

As discussed in [Appendix B](#), the epidemiology data for EO provide limited evidence of carcinogenicity, despite 14 cohort studies involving over 33,000 EO workers in five countries. There is no evidence of increases among females for the specific lymphoid cancers used as a target organ and no pattern of consistency across studies for breast cancer or specific types of

lymphoid cancers. In addition, as discussed in [Appendix G](#) and [Appendix S](#), there is no evidence of a statistically significant positive cumulative exposure-response relationship for any cancer endpoint in the NIOSH study or UCC study ([See Appendix S](#)).

The choice of breast cancer as a target organ for EO dose-response assessment is not justified as evidence is weaker than the evidence for lymphoid tumors. [See Appendix E](#). EPA recognizes that magnitudes of increased risks for breast cancer were not large and implies that the evidence is weaker than that for lymphoid tumors (EPA 2013, at 3-19). Despite these issues, EPA proceeds to introduce breast cancer as a target organ. The data are not sufficiently robust to support any quantitative modeling as the weight of evidence for this tumor would only support a descriptor of “suggestive evidence of carcinogenic potential,” as per the EPA Cancer Guidelines (EPA 2005).

The uncertainties described by Steenland et al. (2003) related to the breast cancer incidence study are dismissed as unimportant by EPA. Steenland et al. (2003) state:

A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and *hence greater cumulative exposure*. Unfortunately, we did not have residential history, limiting our ability to explore this possibility (emphasis added).

Steenland et al. (2003) recognized this limitation, admitted they were unable to fully address it and listed it as one of his uncertainties:

Moreover, the NIOSH breast cancer findings have no relevance to today’s workers or to low level environmental exposures because they relate to a historical period when worker exposures were relatively high. NIOSH’s findings, which were through 1998, were seen with a 15-year lag for incidence analysis and 20-year lag for mortality analysis (i.e., exclude cases from the exposed category if their only exposure is within 15 (20) years of diagnosis). Therefore, all relevant exposure to EO occurred prior to 1983 for the incident cases and prior to 1978 for the mortality cases. The NIOSH results relate to the period between 1943 and the 1980s, prior to the substantial decline in worker exposures. NIOSH has recognized this decrease in worker exposure:

Persons exposed to very high levels of EtO may be at an increased risk of developing blood cancers among men and breast cancers among women. Since 1985, when the new OSHA EtO standard went into effect, worker EtO exposures have been significantly lowered, which has reduced the risk of disease (NIOSH 2004).

Furthermore, as discussed in [Appendix E](#), EPA gives greater weight to studies of weak design (Norman et al. 1995, Kardos et al. 2003) than of stronger design (Coggon et al. 2004) in order to bolster its argument of consistency with other epidemiology studies on breast cancer. Inadequate attention is given to the mortality analysis overall, which does not suffer from under-ascertainment and shows death rates from this disease to be virtually identical to the comparison population (0.99, 95%CI: 0.81-1.20).

Internal comparisons of categorical rate ratios for breast cancer can be misleading when the referent group has unusual disease rates, such as the deficit of breast cancer in the NIOSH mortality referent population, creating, in comparison, an elevation in the highest exposure group. Because the data for the referent group are random and not known *a priori* any exposure-response model fit to rate ratios should estimate the intercept, rather than fixing it equal to 1 (Valdez-Flores and Sielken 2013). See [Appendix E](#) and [Appendix F](#).

B. EPA has incorrectly used the categories of “lymphoid” and “lymphohematopoietic” cancer as target organs for quantitative risk assessment and for assessing consistency among epidemiology studies.

As discussed in [Appendix C](#), EPA has inappropriately grouped organs that are derived from different cells of origin. Hematopoietic and lymphoid neoplasms represent many different diseases that can be distinguished on the basis of cell of origin, genetic characteristics, pathogenesis and etiology. For example, non-Hodgkin’s lymphoma (NHL) represents over 20 distinct diseases that can be distinguished from each other according to these criteria. In contrast to lymphoid neoplasms, myeloid neoplasms originate either in a pluripotent stem cell or myeloid progenitor cells, with genetic abnormalities used to distinguish these diseases.

In the draft IRIS assessment of formaldehyde, EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of lymphohematopoietic (LHP) cancers—“all LHP cancers,” “all leukemias,” and “myeloid leukemias.” The NAS committee that reviewed the draft assessment did not support the grouping of “all LHP cancers” because it combines many diverse cancers that are not closely related in etiology, cells of origin, and other characteristics (NAS 2011). The committee recommended that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.

Consistent with the NAS (2011) recommendations, in the draft assessment of EO, EPA should not combine all tumors of lymphoid and myeloid together, but instead rely on the biological classifications now in routine use by hematologists. The Agency should consider the three categories in the lymphoid group individually. The three cancers in the “lymphoid” category have been examined for males and females and the NIOSH and UCC studies looked at these cancers separately and combined using Cox proportional hazard models with cumulative exposure (See [Appendix G](#) and [Appendix S](#)).

No endpoint shows a statistically significant positive slope. The slopes for lymphocytic leukemia and NHL are negative for UCC males and NIOSH females and the slope for multiple myeloma is negative for all gender and study groupings. While there is no clear choice for a target organ, if NHL were selected, the exposure concentration corresponding to a 1-in-a-million added environmental cancer risk could be between 270 to 3,000 fold greater than EPA's proposed value of 0.3 ppt ([See Appendix S](#)). Consistent with the state of the science, including the World Health Organization (WHO) classification (Swerdlow et al. 2008) and NAS (2011), EPA must evaluate each LHP cancer separately, rather than combining them before conducting modeling. We recommend that EPA rely only on the quantitative value for NHL.

C. Combining unit risk estimates for breast cancer and “lymphoid” cancers is scientifically unjustified.

As discussed above, the “lymphoid” category includes a large number of diverse cancers. There is no known agent other than radiation that increases the risk of breast cancer and the malignancies within the lymphoid category. This approach is inconsistent with the NIOSH studies where women showed some association with breast cancer in the highest exposure category, but had no increase in “lymphoid” tumors. Restricting exposure to a 1-in-a-million risk for the category with the greatest unit risk would result in less than a 1-in-a-million risk for the other disease category, making combining the two unit risks unnecessarily conservative.

There is no cogent biological rationale to conclude that lymphoid neoplasms, comprised of either B- or T- lymphocytes at any level of maturity, share common origins with carcinoma of the breast or any somatic cell. The differential embryology of these various tissues is outlined in [Appendix C](#).

D. The NIOSH breast cancer incidence data are not publically available; therefore, EPA's analyses of this endpoint cannot be verified and/or challenged.

EPA uses the NIOSH study as the basis for derivation of unit risk estimates. EPA states, “The NIOSH EtO cohort data can be obtained from the Industry wide Studies Branch of NIOSH” (EPA 2013, at 4-2). These data, however, are not readily available, and it does not appear that EPA obtained and used the individual data in analyzing the epidemiology database.

In an attempt to conduct an independent review of the individual data, in July 2009, ACC submitted a Freedom of Information Act (FOIA) request to the Industry wide Studies Branch of NIOSH for the NIOSH cohort data. NIOSH denied ACC's request stating that the responsive records were exempted from disclosure under Exemptions 3 and 6 of FOIA. NIOSH contended that the records:

are protected pursuant to assurances of confidentiality under Section 308(d) of the Public Health Service Act, 42 U.S.C. Section 242m(d). Our agency is precluded

from making any disclosures of information collected under an assurance of confidentiality except under the express conditions stated in the statutorily authorized assurance. Specifically, that section does not permit the agency to release the information collated under such assurances if the particular establishment or person supplying the information or described in it is identifiable unless the establishment or person has consented to this release. We considered your suggestion for de-identifying the data, and determined even with these measures there is the potential that many members of the study cohort could be identifiable.

See Letter from Lynn Armstrong, CDC/ATSDR FOIA Officer, to Kristy Morrison, ACC, dated December 17, 2009 (Appendix U).

In July 2013, ACC requested access to the data pursuant to a “Data Use Agreement” between ACC and NIOSH. As part of the Agreement, ACC, and its consultants, agreed that they would not “attempt to link nor permit others to attempt to link the data sets with individually identifiable records from any other data sets” or “attempt to use the data sets nor permit others to use them to learn the identity of any individual person(s) or establishment(s) included in any set.” Despite, this Agreement, NIOSH again denied ACC’s request for data on confidentiality grounds, stating “Even with redacting direct identifiers from the data, it is possible to indirectly identify individuals in the cohort through other variable.” *See* Email from Brian Curwin, Ph.D., Deputy Branch Chief, Industry wide Studies Branch, to Bill Gullledge, ACC, dated August 28, 2013 (Appendix U).

As these data cannot be obtained and/or reviewed, EPA has failed to ensure that the reproducibility standard in the EPA and OMB IQA guidelines has been met.

IV. EPA should correct several substantial modeling issues which would result in substantial changes to the Draft IRIS Assessment.

A. There are substantial flaws in EPA’s exposure-response modeling as discussed in Valdez-Flores and Sielken (2013) and Valdez-Flores et al. (2010).

As discussed in [Appendix F](#) and [Appendix S](#), there are three major flaws in EPA’s approach to exposure-response modeling. EPA’s method of evaluating different exposure-response models is (1) mathematically incorrect, (2) is based only on a summary of the available data and not the individual data themselves, and (3) erroneously rejects more appropriate models and SAB recommendations. EPA did not comply with the SAB’s recommendation “to use a direct analysis of the individual exposure and cancer outcome data” in their modeling of breast cancer mortality or lymphoid cancer (EPA 2007, at 4). Most of EPA’s modeling and quantitative risk estimates are based on categorical rate ratio values from analyses of the NIOSH data, rather than direct analyses of the available individual exposure and cancer outcome data for the 17,530 workers in the NIOSH study. EPA’s exposure-response model based on summary rate ratios

also is restricted to estimate a rate ratio of 1 at zero cumulative exposure and excludes the highest-exposed workers are excluded. In addition, EPA's evaluation of the goodness-of-fit of its fitted exposure-response models is inappropriately based on categorical rate-ratio graphical summaries used in the Draft IRIS Assessment.

Second, as discussed in [Appendix J](#), contrary to SAB recommendations, EPA uses a supralinear, two-spline model for breast cancer incidence. EPA's judgment that the exposure-response relationship for breast cancer incidence is supralinear is based on visual inspection of a summary of the available data and not on statistical evaluation of the individual data themselves.

Moreover, EPA's new two-spline rate ratio model has not been peer-reviewed. As EPA states in the Cancer Guidelines:

Use of the cancer guidelines in future risk assessments will be based on decisions by EPA that the approaches are suitable and appropriate in the context of those particular risk assessments. *These judgments will be tested through peer review, and risk assessments will be modified to use different approaches if appropriate.* (EPA 2005, at 1-2) (emphasis added).

EPA's two-piece spline for breast cancer incidence is supralinear (i.e., its slope in the low-exposure region is greater than its overall slope). EPA does not justify that a supralinear exposure-response relationship is biologically appropriate for EO. Furthermore, the two-spline rate ratio model does not fit the individual data statistically significantly better than the fit to the log-linear rate ratio model (Cox Proportional Hazard Model). Contrary to SAB's recommendations against using "two different models for two different parts of the dose response curve" (EPA 2007, at 5), EPA's modeling for occupational risks is an inconsistent mixture of different modeling approaches. OMB questioned the use of this spline model during the interagency review of the Draft IRIS Assessment (OMB 2011). OMB noted "that it is not typical for EPA to rely on a two-piece linear spline model (which is not necessarily a biologically based model) and we question if this is consistent with the Cancer Guidelines recommendations. If this is a new modeling approach for an IRIS assessment, shouldn't its use for this purpose be peer reviewed first?"

Finally, as discussed in [Appendix G](#), [Appendix H](#) and [Appendix S](#), EPA's exposure-response modeling methodology and choices EPA for the component factors in the calculation of PODs exaggerates the risk by as much as 1500 fold. Valdez-Flores et al. (2010) ([See Appendix S](#)) state that "Cox model estimates of the concentrations corresponding to a 1-in-a-million extra environmental cancer risk are all greater than approximately 1 ppb and are more than 1500-fold greater than the 0.4 ppt estimate in the 2006 EPA draft IRIS risk assessment." Using the numerical values in the Draft IRIS Assessment, the impact of the exposure-response model for a specific health endpoint rather than a more appropriate model fit directly to the individual data ranges between approximately 10 and 100-fold. In addition, the choices EPA made in its method of calculating risk estimates from the slope in the exposure-response model – including choice of

incidence or mortality background hazard rates, using an 85-year exposure period instead of a 70-year exposure period, using LEC₀₁ instead of the EC₀₁, and using NIOSH data only instead of NIOSH and UCC data – have multiplicative impacts.

These further impacts can increase the risk estimates by approximately another 10-fold. The formulas underlying EPA’s life-table method of calculating extra risks are incorrect for incidence background hazard rates ([See Appendix R](#)). Another choice in the method of calculating risk estimates is the method of implementing an age-dependent adjustment factor (ADAF), which is inconsistent with the Cancer Guidelines ([See Appendix T](#)). If the impacts were independent of each other and multiplicative, then the combination of the 10 to 100-fold impact due to EPA’s choice of exposure-response model and the further 10-fold impact due to EPA’s choices in the method of calculating risk estimates would result in an impact of 100 to 1000-fold.

B. EPA’s exposure-response modeling techniques over predict the number of cancer mortalities actually observed in the NIOSH cohort study.

As discussed in [Appendix I](#), for breast cancer, 102 deaths were observed in the NIOSH study, which is 1 fewer than expected (103) based on US background cancer mortality rates. Using EPA’s exposure response model for breast cancer mortality and EPA’s 95% upper confidence limit, the predicted number of breast cancer mortalities in the study is 153, which is 50 more than expected and 51 more than the actual observed. For lymphoid cancer, 53 deaths were observed in the NIOSH study, which is 3 more than expected (50) based on US background cancer mortality rates. Using EPA’s exposure response model for lymphoid cancer mortality and EPA’s 95% upper confidence limit, the predicted number of lymphoid cancer mortalities in the study is 130, which is 80 more than expected and 77 more than the actual observed.

For breast cancer mortality, lymphohematopoietic cancer mortality, and lymphoid cancer mortality, EPA’s models over predict the observed number of cancer mortalities in the NIOSH cohort.

In almost all cases the over prediction is statistically significant. The 95% confidence intervals on the predicted number of cancer mortalities rarely contain the observed number of cancer mortalities. These over predictions occur despite the fact they assume that the slope in the exposure-response model is zero (flat) in the “plateau” region corresponding to higher exposures.

C. EPA’s flawed dose-response modeling methodology exaggerates the risks and limits the power of the risk assessment by using only data from one epidemiology study (NIOSH).

When using standard models on individual data and increasing the power by analyzing the combination of the NIOSH and UCC studies, the 1-in-a-million extra environmental cancer risk is more than 1500-fold greater than the 0.3 ppt estimate in the Draft IRIS Assessment. Valdez-Flores et al. (2010) ([See Appendix S](#)) reported that when the most recent epidemiological data on

individual workers in the NIOSH and updated UCC occupational studies are used to characterize the potential excess cancer risks of environmental exposure to EO, the risk value determined is three orders of magnitude different. In their study, no evidence of a positive cumulative exposure-response relationship was found. In addition, fitted Cox proportional hazards models with cumulative EO exposure do not have statistically significant positive slopes. The lack of increasing trends was corroborated by categorical analyses.

V. EPA should correct the substantial errors that prevent an accurate assessment of EPA’s statistical analysis.

As discussed in [Appendix K](#), in addition to the inappropriate combining of lymphoid and breast cancer risks, there are several statistical issues with the way EPA performed this combination including:

1. Incorrect accounting for competing risks;
2. Different background populations at risk;
3. Using a mortality-based exposure-response model for lymphoid to calculate incidence risks; and
4. Using results from two very different exposure-response models.

VI. EPA ignores the uncertainties in the NIOSH retrospective exposure assessment while emphasizing those of the UCC study.

A. The limitations in NIOSH’s exposure assessment largely invalidate EPA’s reliance solely on the NIOSH epidemiology study and the exclusion of the UCC epidemiology study.

As discussed in [Appendix M](#), NIOSH had no exposure data prior to 1976 and very little from 1976-1978, when most of the worker exposures occurred. The NIOSH validation procedure was limited to post-1978 data. NIOSH’s final exposure model did not include all of the available data. In developing its exposure regression, NIOSH used data from 36 different companies including several plants not in the NIOSH study. In addition to assuming no effect of calendar year prior to 1978, it was assumed that all other variables in the regression model estimated using post-1978 data had the same effect before 1978 when calendar year was not allowed to vary. Workplace exposure limits were substantially higher prior to 1978. Fixing the effect in the regression model of calendar year at 1978 for approximately 35 prior years for the most important workers (including the longest and highest exposed) in the exposure assessment created bias.

NIOSH’s estimated exposure values before 1978 are unrealistic. Because of the effects of the terms in the regression model, other than “Calendar Year,” the maximum estimated EO concentrations for years before 1978 decrease as you go back in time to earlier years. (This is the opposite of what is expected and the findings of the UCC study). The NIOSH study included

workers who started working with EO as early as 1943. Even though the workplace exposure limit was set at 100 ppm in the mid-1940s, the average exposure concentrations prior to 1978, estimated by the NIOSH exposure model, are less than the average exposure concentrations in 1978 (see Table 1). However, the workplace time-weighted average exposure limits (ACGIH TLVs) were as high as 100 ppm up to 1957. Moreover, EO is a gas at room temperature or has a very high vapor pressure (1095 mmHg at 20 Celsius) and workers complained about the odor of EO. (Note: odor detection threshold for ethylene oxide has been reported to be 260 ppm and 700 ppm in different references and the level of distinct odor awareness for ethylene oxide has been calculated to be 1,625 ppm. Refer to odor threshold in [Appendix L](#) for more details.)

Table 1 – EO Workplace Exposure Limits

<u>Date</u>	<u>Group</u>	<u>Workplace exposure limit</u>
1946-1947	ACGIH MAC-TWA	100 ppm
1948-1956	ACGIH TLV-TWA	100 ppm
1957	ACGIH TLV-TWA	100 ppm to 50 ppm
1971	OSHA	50 ppm
1981	ACGIH TLV-TWA	50 ppm to 10 ppm
1984	ACGIH TLV-TWA	10 ppm to 1 ppm
1984	OSHA	50 ppm to 1 ppm

In addition, with respect to the uncertainty in fixing the calendar effect to 1978, Stayner et al. (1993) stated “[i]t is not possible to test the influence of short-term exposure peaks experienced during the course of a day” and “[t]he mean and median exposure estimates differed substantially, indication that the distributions of these measures were highly skewed. The range of the exposure measures spanned several orders of magnitude.”

B. Inclusion of the UCC data would add substantially to the power of the dose-response analyses.

The number of deaths due to the three cancers included in NIOSH’s “lymphoid” category indicates that the number of observed responses for males is similar in the UCC study to those for males in the NIOSH study (Valdez-Flores et al., 2010) ([See Appendix S](#)). UCC would add 12 deaths to the 18 male NHL deaths in the NIOSH study; 3 deaths to the 4 deaths due to multiple myeloma and 2 deaths to the 5 deaths due to lymphocytic leukemia. These are increases of 67%; 75% and 40% or over 60 % overall. The UCC contribution to the male data is substantial, despite the much larger NIOSH population, for two reasons. First, UCC workers

have much longer average follow up (37 yr. vs. 25 yr.). Second, UCC workers have substantially more deceased study subjects (51% vs. 19%). Both studies suffer from uncertainties in exposure estimation in the pre-1978 period and both have reasonably good estimates based on industrial hygiene data post- 1978.

At the very least, results should be presented both with and without the UCC data. See [Appendix G](#), [Appendix I](#) (especially the section on lymphohematopoietic cancer mortality), and [Appendix S](#).

VII. EPA should ensure that the potency estimate for EO is consistent with the relative toxic and mutagenic potencies for EO.

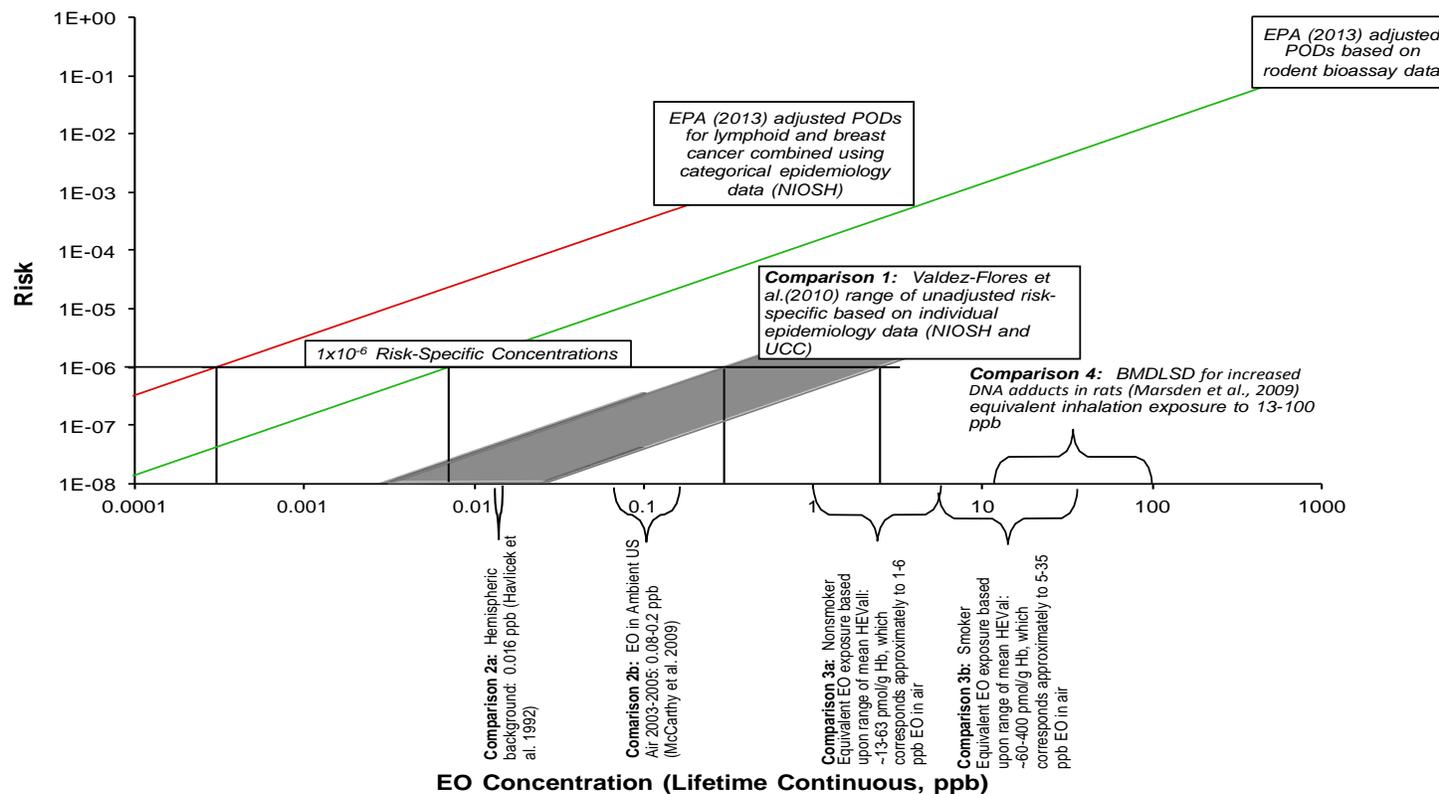
The Draft IRIS Assessment uses flawed modeling methods to derive very high estimates of EO cancer potency and lifetime unit risk. Based on epidemiology data for lymphoid cancers and breast cancer, the EPA unit risk values range from 0.00093 – 0.0018 per ug/m³ or 0.0017-0.0033 per ppb, suggesting that 1 in 1300 to 1 in 300 persons exposed to 1 ppb for 85 years will develop lymphoid or breast cancer due to that exposure (USEPA 2013).

As discussed in [Appendix N](#), EPA's final unit risk estimates are unrealistically high, conflicting with human, animal, and mechanistic scientific observations. One in a million risk environmental concentrations are in the ppt range, orders of magnitude below:

- Risk based concentrations based on potency estimates from Valdez-Flores et al. (2010);
- EO concentrations in ambient air;
- Endogenous levels of EO in the body; and
- EO concentrations associated with a meaningful increase in DNA adduct burden.

These comparisons are illustrated in Figure 1.

Figure 1. Risk Comparisons Using EPA (2013) Unit Risk Values



Based on a comparison of unit risk values, EO would be identified the most potent of the small epoxide or pre-epoxide chemical listed in US EPA’s IRIS database. ([See Appendix N.](#)) These cancer potency estimates are in sharp contrast to the relatively weak genotoxic potency reported for EO. ([See Appendix A.](#)) EPA’s application of inappropriate potency estimates and use of incorrect modeling techniques to calculate risk-based concentrations result in concentrations that are below EO concentrations associated with a meaningful increase in DNA adduct burden (based on benchmark dose modeling of the Marsden et al. (2009) data).

These cancer potency estimates are also inconsistent with the absence of a strong cancer response in epidemiology studies of exposed workers, the primary reason IARC and EPA itself consider the epidemiology evidence “limited.” ([See Appendix B.](#)) Using EPA’s exposure-response models result in statistically significant over predictions of the observed cancer mortalities in the NIOSH cohort study, even after assuming no increase in the exposure-response at high exposures. ([See Appendix I.](#))

EPA hypothesizes that there is a link between endogenous EO exposures and background cancer rates, but this is not supported by available information. Endogenous exposure to EO does not appear to be an important determinant of background cancer rates when compared across species. ([See Appendix O](#)). In the Draft IRIS Assessment, EPA states:

while the contributions to DNA damage from low exogenous EtO exposures may be relatively small compared to those from endogenous EtO exposure, low levels of exogenous EtO may nonetheless be responsible for levels of risk (above background risk). This is not inconsistent with the much higher levels of background cancer risk, to which endogenous EtO may contribute, for the two cancer types observed in the human studies – lymphoid cancers have a background lifetime incidence risk on the order of 3%, while the background lifetime incidence risk for breast cancer is on the order of 15% (EPA 2013, at 4-75).

A link between endogenous EO exposures and background cancer rates is not supported by available information. For example, Swenberg et al. (2011) reported that humans have “nearly 10-fold higher amounts of endogenous 7HEG than are found in rats and mice.” However, despite the higher endogenous levels, humans do not experience 10-fold higher background rates for lymphoid and breast cancers than do rodents. Graphical comparisons of endogenous DNA adducts (in liver) and background cancer rates for mice (based on NTP historical controls), rats (based on NTP historical controls), and humans (based on NCI’s Surveillance Epidemiology and End Results (SEER)) suggest that endogenous adduct levels of EO are not an important predictor of background cancer rates across species. For risk assessment purposes, an assumption that these factors are independent is reasonable.

Finally, as discussed in [Appendix P](#), EPA should follow its Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites (EPA 2002), which recognizes there is little to no benefit to implementing risk reduction strategies that result in levels of agents at or below background levels in a media of interest. Therefore for exposures below 2-10 ppb EO in air, endogenous EO exposures are expected to predominate over exogenous exposures. For this reason, there is not expected to be any reduction in potential risk by regulating/reducing EO exposures below this range.

VIII. EPA should not derive occupation exposure limits for EO.

It is inappropriate for EPA to recommend occupational exposure limits as part of an IRIS assessment. Instead, the Occupational Safety and Health Administration (OSHA) should derive these values.

Moreover, EPA’s estimates of occupational risks are unrealistically high and based on inappropriate and non-peer-reviewed methods. EPA’s modeling for occupational risks is an inconsistent mixture of different modeling approaches. The SAB panel stated that “most of the

Panel did not agree with the estimation based on two different models for two different parts of the dose response curve.... The use of different data to estimate different dose response models curves should be avoided unless there is both strong biological and statistical justification for doing so. The Panel believed this justification was not made in the Agency's draft report” (EPA 2007, at 5).

In addition, lymphoid risks are based on categorical data for lower exposure rather than individual data. Although EPA based its calculations on individual data at higher exposure levels, at lower exposure levels, the calculations are based on log cumulative exposure rather than cumulative exposure. The portion of EPA’s estimates of occupational risks due to breast cancer incidence is based on EPA’s “preferred” two-piece linear spline model, a non-peer-reviewed model.

* * *

Based on the foregoing, ACC urges EPA to substantially revise the Draft IRIS Assessment to accurately convey the best available science and weight-of-evidence in compliance with both EPA’s Cancer Guidelines and OMB and EPA IQA Guidelines.

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