STATE OF MICHIGAN
Rick Snyder, Governor

DEPARTMENT OF ENVIRONMENTAL QUALITY

AIR QUALITY DIVISION
Constitution Hall ● 525 WEST Allegan Street ● P.O. Box 30260 ● Lansing, MICHIGAN 48909-7760
www.michigan.gov/air

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Response to Public Comments for Ethylene Oxide (CAS # 75-21-8)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the basis for the Initial Risk Screening Level (IRSL) and Secondary Risk Screening Level (SRSL) for ethylene oxide. As a result of that review, the AQD has determined that the current IRSL and SRSL are appropriate and defensible and the current screening levels will be retained.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ) Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14th, 2017. AQD must respond to these comments within 180 days; the latest date for response is October 11th, 2017.

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources And Environmental Protection Act, 1994.PA 451, as amended (NREPA)

Comments and Responses:

Comment:

DEQ received comments from three commenters, all acknowledging that the AQD IRSL and SRSL for ethylene oxide (EtO) are based on the U.S. Environmental Protection Agency (EPA) (2016a) IRIS assessment, but also commenting that the EPA assessment was faulty and greatly exaggerated the potential cancer risk of EtO. The comments included very specific issues and arguments to support their views. One commenter submitted a very lengthy and detailed analysis and critique of the EPA's 2013 draft assessment; the commenter noted that EPA provided more explanation in the 2016 final assessment, but that the main components of the 2016 final assessment were nearly identical to the 2013 draft. Commenters stated that the EPA failed to provide a transparent and systematic weight-of-evidence approach and did not base the assessment on the best available science.

Response:

Upon reviewing the submitted comments, DEQ notes that the EPA (2016a) Initial Risk Information System (IRIS) assessment was quite recently finalized (in December, 2016) and reflects a rigorous development and peer review process. Furthermore, EPA (2016b) stated that prior to finalization of the IRIS assessment, EPA updated the assessment to reflect new literature through July 2016, although this newest literature did not substantively impact the conclusions of the assessment. The chronology of EPA's risk assessment development is summarized in IRIS-online[2] as follows:

Jun 1985	EPA published the Health Assessment Document for Ethylene Oxide (EPA/600/8-84/009F).
Sep 2006	EPA released a draft reassessment for a 30-day public comment period. [Federal Register Notice September 22, 2006]
Jan 2007	Peer review meeting of the Science Advisory Board (SAB) (public

[2] Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Final Report). Background. History/Chronology. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730

	meeting).
Dec 2007	EPA's SAB issued a final report on the review of the draft assessment of EtO.
Jul 2011	EPA initiated Final Agency and an Interagency Science Discussion of a revised draft assessment of EtO.
Jun 2012	EPA conducted further Agency review of a revised draft assessment of EtO.
Jul 2013	EPA revised the draft assessment and released for additional public review and comment. The interagency science discussion draft of the assessment and related comments were also made available. [Federal Register Notice Jul 23, 2013]
Dec 2013	EPA hosted an IRIS public science meeting to discuss the draft assessment released for public comment.
Aug 2014	EPA submitted the draft assessment (revised in response to public comments) to the SAB for external peer review. [Federal Register Notice Aug 11, 2014]
Nov 2014	EPA's SAB hosted a panel meeting for the SAB Chemical Assessment Advisory Committee (CAAC), augmented for the review of the draft IRIS assessment of EtO.
Aug 2015	EPA's SAB issued a final report on its review of the draft assessment of

	EtO.
Oct 2016	EPA submitted a revised draft for final Agency Review and Interagency Science Discussion.
Dec 2016	EPA posted the final Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide to the IRIS database.

During EPA IRIS's EtO comment/response process, EPA published the comments received as well as providing responses. In order for AQD to evaluate and develop appropriate responses to the comments, the DEQ evaluated the extent to which EPA's key IRIS documentation (cited below) did or did not adequately address the issues raised:

EPA. 2016a. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. Executive Summary. In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-16/350Fc.

EPA. 2016b. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-16/350Fa. Including:

- Appendix H. Summary of 2007 External Peer Review and Public Comments and Disposition.
- Appendix I. EPA Responses to SAB Comments On 2014 External Review Draft.
- Appendix J. Summary of Major New Studies Since the Literature Cutoff Date.
- Appendix K. Summary of Public Comments Received On the July 2013 Public Comment Draft and EPA Responses.

The following are AQD staff's consolidated summaries of the submitted comments. The responses include summaries and some excerpts (for brevity) from EPA (2016a, 2016b) which are particularly germane to the comments.

Comment:
EPA's cancer unit risk estimate is based on the NIOSH epidemiology study results. EPA should have included in the quantitative risk assessment the Union Carbide Corporation

(UCC) industry study data as well as the NIOSH data, and individual data rather than group summarized data. Individual data from the NIOSH study is not available to the public for review. Modeling performed in EPA's assessment of the NIOSH study did not utilize individual data and instead inappropriately grouped populations. The NIOSH study considered in the IRIS assessment is based on the inadequate body of evidence from human studies that includes historical exposure levels to EtO that are significantly higher than current exposure limits. The NIOSH study limitations largely invalidate the decision to rely on it and EPA failed to justify the exclusion of the industry cohort study.

Response:
EPA (2016a) regards the NIOSH study as a high-quality study based on attributes including availability of individual worker exposure estimates from a high-quality exposure assessment, cohort study design, large size, inclusion of males and females, adequate follow-up, absence of any known confounding exposures, and use of internal comparisons. EPA (2016a) states that, "The unit risk estimate is intended to provide a reasonable upper bound on cancer risk from inhalation exposure….The primary sources of uncertainty in the unit risk estimates derived from the human data include the retrospective exposure assessment conducted for the epidemiology study….Retrospective exposure estimation is an inevitable source of uncertainty in this type of epidemiology study; however, the NIOSH investigators put extensive effort into addressing this issue by developing a state-of-the-art regression model to estimate unknown historical exposure levels using variables, such as sterilizer size, for which historical data were available."

EPA (2016b) described the published findings of the UCC studies, which are a series of retrospective mortality studies of about 2000 male workers who were assigned to operations that produced EtO. EPA (2016b) noted several limitations of the UCC studies, including problems of ascertaining and categorizing participants as to exposure, lack of quantitative estimates of exposure, multiple exposures to many different chemicals to which observed cancers could be attributed, and low statistical power. In contrast, the NIOSH studies were viewed by EPA (2016b) as superior. "This [NIOSH] study is the most useful of the epidemiologic studies in terms of carrying out a quantitative dose-response assessment. It possesses more attributes than the others for performing risk analysis (e.g., good-quality estimates of individual exposure, lack of exposure to other chemicals, and a large and diverse cohort of workers)." (EPA, 2016b). EPA's Science Advisory Board (SAB) concurred with EPA's decision to use the NIOSH study data, and to not use the UCC cohort data, to derive the unit risk estimates (EPA, 2016b, Appendix I.)

EPA (2016, Appendix H, p. H-26) stated, “The EPA agrees that it may be generally preferable to develop risk models on the basis of direct analysis of individual exposure and cancer outcome data.” EPA (2016b) stated that they, “…explored additional analyses using the individual data rather than relying on the published group data”, for both the lymphohematopoietic and breast cancer data. EPA (2016b) stated that the selected breast cancer model used the individual-level exposure data. EPA (2016b, Appendix H, p. H-11) stated that modeling did provide a reasonable fit to the individual-level exposure data for the breast cancer incidence data, but not for the lymphoid cancer data. Thus, EPA retained the approach of basing the preferred unit risk estimates for lymphoid cancer on a linear regression using the categorical data. EPA (2016b, Appendix H, p. H-32-33) adds that, “The categorical and summary statistics used by the EPA are constructed from the individual data in the NIOSH study….However, it was the judgment of the EPA that these models generated estimates of risk in the low-dose region that were excessively sensitive to changes in exposure level, and therefore, would not be suitable as the basis for low-dose unit risk values. This is what led the EPA to use the regression methodology with the published grouped data…..In the revised assessment, linear low-dose estimates based on the two-piece spline model and using the Langholz-Richardson linear approach were used for breast cancer incidence risk estimates.”

EPA (2016b, Appendix K) also responded to comments on the use of individual data and defended their chosen approach of using linear regression of the categorical data for lymphoid cancer and for the breast cancer *mortality* data.

Although commenters note that the NIOSH study’s detailed breast cancer incidence data are not available to the public, EPA (2016b, Appendix K) notes that the EPA’s Information Quality Act guidelines allow for confidentiality constraints. The EPA assessment otherwise appears to be very transparent. DEQ agrees with EPA’s approach.

Comment:
EPA should not have assumed for the NIOSH study that 1978 exposure levels represented exposure levels for earlier years.

Response:
In discussing the exposure assessment uncertainty as one of the sources of uncertainty in the cancer risk assessment, EPA (2016b) stated that, “Thus, although measurement data were not available for most of the time that the cohort was exposed (exposures started in 1938 for some workers), exposure levels for those early time periods could be estimated from the regression model based on variables for which historical data were

available (e.g., plant- and year-specific sterilizer volume), which served as a surrogate measure for the amount of EtO used. Another variable, calendar year, served as a surrogate for general improvements in work practices after the human health effects of EtO became a matter of concern in the late 1970s. This variable captured decreases in exposure after the late 1970s that were unaccounted for by the other variables. For the years before 1978, when human health effects of EtO were not a large concern, it was assumed that the other variables more fully accounted for exposure levels and the calendar year was fixed at the 1978 level. While this assumption is impossible to corroborate, it is reasonable, and the calendar year variable provides a means of dealing with general work practice improvements that are otherwise difficult to quantify….Nevertheless, errors in retrospective exposure assessments are inevitable, and exposure estimation is a primary source of uncertainty in unit risk estimates. Thus, the unit risk estimates based on the NIOSH study could over-predict or over-predict the true risks to an unknown extent." This EPA explanation for the chosen approach appears to be rational.

Comment:
EPA should not have grouped the lymphomas, and also combined the lymphomas and breast cancer, for development of the unit risk estimate. The categories of "lymphoid" and "lymphohematopoietic" are both a non-defensible combining of malignancies that are derived from different cells of origin. The choice of breast cancer as a target organ is not justified as the evidence is even weaker than that for "lymphoid" tumors. One commenter recommended that EPA should rely only on the quantitative data for non-Hodgkins lymphoma (NHL).

Response:
EPA (2016b) explained that, according to the 2005 EPA Guidelines for Carcinogen Risk Assessment, cancer risk estimates are intended to reflect total cancer risk, not site-specific cancer risk. To derive a total cancer risk estimate, EPA assumed that the cancer types are independent. EPA (2016b, Appendix H, p. H-17-18, 34) stated that, "As recommended by the panel, the primary risk estimates in the revised assessment are based on the analysis of the lymphohematopoietic cancer subtype of lymphoid cancers which was the subtype with the strongest evidence of an EtO association in the NIOSH data set. Analysis based on total lymphohematopoietic cancers is also included for completeness and comparison purposes." EPA (2016b, Appendix I) states that EPA's SAB agreed with EPA's response to comments that lymphohematopoietic and lymphoid cancers should not be grouped because they are derived from different cells of origin; EPA's response, "…clearly states the rationale for grouping these together and notes that the SAB (2007) report agreed with the logic of that grouping for comparison purposes. This response is clear and appropriate." EPA (2016b, Appendix K) states

that, “The EPA did appropriately combine lymphoid cancers, as the “lymphoid” cancer category is a grouping of cancers with a common lymphohematopoietic cell lineage (multiple myeloma and most lymphocytic leukemias and non-Hodgkins lymphomas develop from B-lymphocytes). The 2007 SAB panel supported the use of this grouping. The larger lymphohematopoietic cancer grouping is provided solely for comparison because many of the epidemiologic studies do not present data for a lymphoid cancer grouping.” SAB also concurred with EPA’s derivation of unit risk estimates by combining breast cancer and lymphoid cancer after initially modeling them separately (EPA, 2016b, Appendix I). EPA’s approach appears to be rational and appropriate.

Comment:
EtO is a mutagen, but only a weak mutagen. The fact that EtO 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 provided insufficient development of the assumption that EO’s carcinogenic MOA is via direct, DNA-reactive mutagenicity.

Response:
EPA (2016a) addressed this issue as follows: “Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and as there are no chemical-specific data from which to assess early-life susceptibility, increased early-life susceptibility should be assumed, according to EPA’s Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens….When using the adult-based unit risk estimates to estimate extra cancer risks for a given exposure scenario, the standard ADAFs should be applied, in accordance with the EPA’s Supplemental Guidance.” EPA (2016b) reported that, “EtO-induced genotoxicity is observed after shorter exposure durations and at lower exposure concentrations than those associated with tumor induction in both rodents and occupationally exposed humans…..The available data are strongly supportive of a mutagenic mode of action involving gene mutations and chromosomal aberrations (translocations, deletions, or inversions) that critically alter the function of oncogenes or tumor suppressor genes….There are no compelling or additional hypothesized modes of action for EtO carcinogenicity….Oxidative stress has been hypothesized as a mode of action, but there is little evidentiary support for this hypothesis and the role of oxidative stress in EtO-induced carcinogenicity is speculative at this time.” EPA (2016b, Appendix H, p. H-26) agreed that EtO may be described as a relatively weak mutagen when compared to some substances but not when compared to other environmental mutagens; they did not consider the mutagenicity and carcinogenicity findings to be in conflict with the potency estimates. EPA and their SAB (EPA, 2016b, Appendix I) agreed that data do

not adequately support alternative hypotheses that the carcinogenicity mode of action involves oxidative stress and cell proliferation.

Comment:
EPA used a faulty extrapolation model approach. The assessment did not fully consider the use of both linear and nonlinear modeling approaches as recommended by SAB in 2007.

Response:
EPA (2016a) concluded that linear low-dose extrapolation is supported by the conclusion that a mutagenic mode of action is operative in EtO carcinogenicity. “In addition, the two-piece spline models used in this assessment to model the supralinear exposure-response relationships are considered to provide a reasonable basis for the derivation of unit risk estimates.” (EPA, 2016a). As noted by EPA (2016b), “The exposure-response models used to fit the epidemiological data are empirical “curve-fitting” models.” EPA (2016b) stated that, “However, the best-fitting dose-response model for both male lymphoid cancers and male all hematopoietic cancer was for dose expressed in terms of log cumulative exposure, indicating supralinearity of the low-dose data. Supralinearity of the dose-response data was also indicated by the categorical exposure results…..the NIOSH data suggest a supralinear dose-response relationship in the observable range.” “Spline models have been used previously for exposure-response analyses of epidemiological data. These models are generally useful for exposure-response data such as the EtO lymphoid cancer data, for which RR initially increases with increasing exposure but then tends to plateau, or attenuate, at higher exposures. Such plateauing exposure-response relationships have been seen with other occupational carcinogens and may occur for various reasons, including the depletion of susceptible subpopulations at high exposures, mismeasurement of high exposures, or a healthy worker survivor effect. No other traditional exposure-response models for continuous exposure data that might suitably fit the observed exposure-response pattern were apparent.” (EPA, 2016b). Further, EPA (2016b, p. 4-95) disagreed with proposals that linear low-dose modeling would conservatively model endogenous exposures and endogenous adduct levels. EPA (2016b, Appendix I) indicates that EPA’s SAB concurred with EPA’s use of the two-piece spline model for estimating breast cancer incidence. For the estimation of lymphoid cancer incidence, the SAB recommended the use of continuous individual-level data over the use of categorical results, so long as the model results are biologically plausible. In response, EPA changed its model selection for lymphoid cancer to a model based on individual-level exposure data (EPA, 2016b, Appendix I). EPA responded to comments that the supralinear spline model was non-peer-reviewed by stating that the model was published in a peer-reviewed journal in 2011 and would receive additional peer review

by the SAB; EPA's SAB found that this response was clear and appropriate (EPA, 2016b, Appendix I, Appendix K). To a comment that EPA should present both linear and nonlinear extrapolation approaches, EPA and SAB responded that there was insufficient information to support use of a nonlinear extrapolation approach (EPA, 2016b, Appendix I).

Comment:
EPA's risk estimates conflict with ambient air data. EtO concentrations in ambient US air (2003-2005) are estimated to be 0.08 to 0.2 ppb. This conflicts with EPA's final unit risk estimates. The EPA unit risk values suggest 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. These risk estimates are unrealistically high.

Response:
EPA (2016b) reported that 2005 estimated average US ambient air levels are 0.0062 ug/m^3 from all sources including concentrations near known air emissions sources, and 0.0044 ug/m^3 excluding concentrations near known sources. EPA (2016b, Appendix K) stated that the unit risk estimates and lifetime exposure to background EtO ambient air levels from all sources is associated with roughly 1 lymphoid cancer case for every 220,000 people and 1 breast cancer case for every 120,000 women; they further stated that the calculations provided by comments based on an exposure concentration of 1 ppb (1.8 ug/m^3) are unrealistic.

Comment:
EPA's risk estimates conflict with data on endogenous EtO levels and conflict with background cancer rate data.

Response:
EPA (2016b) stated, "Furthermore, while the contributions to DNA damage from low exogenous EtO exposures may appear "negligible" (Marsden et al., 2009) compared to those from endogenous EtO exposure, low levels of exogenous EtO may nonetheless be responsible for additional risk (above background risk) above *de minimis* risk levels, which are generally 10^{-6} to 10^{-4} for cancer. 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 (2016b, Appendix H, p. H-37) reiterated that, "The EPA's risk estimates are for risk above background. The issue of endogenous levels is addressed in the revised assessment."

Comment:
EPA's risk estimates overstate risk by orders of magnitude.

Response:
EPA (2016a) states that, "The unit risk estimate is intended to provide a reasonable upper bound on cancer risk from inhalation exposure…The primary sources of uncertainty in the unit risk estimates derived from the human data include the retrospective exposure assessment conducted for the epidemiology study, the exposure-response modeling of the epidemiological data, and the low-dose extrapolation. Despite uncertainties in the unit risk estimate, confidence in the estimate is relatively high." EPA (2016a) noted, "Confidence in the unit risk estimate is particularly high for the breast cancer component….The actual unit risk might be higher or lower….There is somewhat less, although still relatively high in general, confidence in the lymphoid cancer component of the unit risk estimate because it is based on fewer events (53 lymphoid cancer deaths); incidence risk was estimated from mortality data; and the exposure-response relationship is exceedingly supralinear, complicating the exposure-response modeling and model selection to a greater extent than for breast cancer incidence. The actual unit risk may be higher or lower than that from the selected model, and there were no clear upper or lower bounds for the apparent exposure-response relationship provided by other models….While there is less confidence in the lymphoid cancer estimate, the lymphoid cancer risk estimate is considered a reasonable estimate from the available data, and overall, there is relatively high confidence in the total cancer unit risk estimate". It is noted that lymphoid cancer incidence provided 87% of the final unit risk estimate; breast cancer incidence provided 23% (EPA, 2016b).

EPA (2016b, Appendix H, p. H-37) states that, "The unit risk estimates are derived from, and are consistent with, the results of the NIOSH epidemiology study, as long as they are used in the low-exposure range, as intended. Because the exposure-response relationships for the cancers of interest in the NIOSH study are generally supralinear, the unit risk estimates will overpredict the NIOSH results if applied to the region of the exposure-response relationships where the responses plateau. The potency estimates derived in the assessment are constructed for use with low levels consistent with environmental exposure and are not appropriate for use with exposures in occupational settings, as stated explicitly in the document."

Comment:
AQD should not rely solely on the EPA 2016 IRIS risk assessment. AQD should continue to use the old IRSL, or develop an updated IRSL based on the full body of evidence. The old IRSL is protective of public health and no further benefits would be

obtained by reducing the IRSL value based on the flawed conclusions of the EPA (2016 IRIS) assessment.

Response:
AQD's previous IRSL was based on the results from a rat bioassay. EPA (2016a) concluded that besides being carcinogenic in rats and mice, there is strong evidence of EtO and an increased risk of cancer of the lymphohematopoietic system and of breast cancer in females. Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, EtO is characterized as "carcinogenic to humans" by the inhalation route based on the total weight of evidence (EPA, 2016a). Overall, confidence in the hazard characterization of EtO as "carcinogenic to humans" is high (EPA, 2016a). EPA (2016b) performed a comprehensive evaluation of the body of evidence in deriving a unit risk estimate based on the human carcinogenicity data. DEQ and EPA prefer the use of human data over animal bioassay data for estimating the potential health risk to humans. "The agency takes the position that human data, if adequate data are available, provide a more appropriate basis than rodent data for estimating population risks primarily because uncertainties in extrapolating qualitative risks from rodents to humans are avoided. Although there is a sizeable difference between the rodent-based and the human-based estimates, the human data are from a large, high-quality study, with EtO exposure estimates for the individual workers and little reported exposure to chemicals other than EtO. Therefore, the estimates based on the human data are the preferred estimates for this assessment." (EPA, 2016a).

Summary and Conclusions:
The MDEQ AQD based the IRSL and SRSL on EPA's inhalation unit risk (IUR) for EtO. The EtO comments received by MDEQ AQD were evaluated by staff primarily by reviewing the EPA (2016a, 2016b including Appendices H-K) assessment that resulted in the IRIS inhalation unit risk factor. Staff review of the EPA documentation found that EPA's assessment was thorough and rational, followed a weight-of-evidence approach, and utilized the best available science, and that the EPA assessment underwent a rigorous public and peer review process prior to finalization. EPA's SAB found that EPA's responses to public comments were, "…thorough, clear, and appropriate." (EPA, 2016b, Appendix I). Staff did not find issues raised by commenters that had not been appropriately addressed by EPA (2016a, 2016b). Staff did not find a basis to deviate from the EPA unit risk factor in favor of an alternative approach that would be more appropriate and defensible. Therefore, AQD will retain the current IRSL and SRSL screening levels for use in air emission permitting evaluations to help ensure public health protection.

The primary AQD reviewer for these comments was Robert Sills, AQD Toxics Unit Supervisor. The secondary (peer) reviewer was Mike Depa, AQD Senior Toxicologist.