TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Protecting Texas by Reducing and Preventing Pollution

March 24, 2022

U.S. Environmental Protection Agency
EPA Docket Center
Docket ID No. EPA–HQ–OAR–2018–0746
Mail Code 28221T
1200 Pennsylvania Avenue NW
Washington, DC 20460

Re: Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review; EPA Docket ID No. EPA–HQ–OAR–2018–0746

Dear Sir or Madam:

The Texas Commission on Environmental Quality appreciates the opportunity to respond to the U.S. Environmental Protection Agency's request for comments in the notice published in the February 4, 2022 edition of the Federal Register entitled: "Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review."

If you have any questions concerning the enclosed comments, please contact Allison Jenkins, Toxicology, Risk Assessment, and Research Division, Office of the Executive Director, at 512-239-0656 or allison.jenkins@tceq.texas.gov.

Sincerely,

Toby Baker
Executive Director

Enclosures

Texas Commission on Environmental Quality (TCEQ) Comments on the U.S. Environmental Protection Agency (EPA) Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review February 4, 2022 *Federal Register (87 FR* 6466)

The February 4, 2022 Federal Register (FR) notice entitled "Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review" (2022 MON Reconsideration) addresses five petitions for reconsideration, one of which was submitted by TCEQ on October 12, 2020, and requests public comment on two specific issues. These issues are:

1) The use of EPA's 2016 Integrated Risk Information System (IRIS) value for ethylene oxide (EtO)[1] in assessing cancer risk for the source category (2016 IRIS EtO Assessment); and
2) The use of TCEQ's EtO risk value from the 2020 Final TCEQ Ethylene Oxide Carcinogenic Dose-Response Assessment (2020 TCEQ EtO Assessment)[2] as an alternative risk value to EPA's IRIS value.

TCEQ is committed to protecting human health and the environment and appreciates the opportunity to comment. In its 2022 MON Reconsideration, EPA suggests that the 2020 TCEQ EtO Assessment and the petitions for reconsideration do not provide a scientifically supportable basis for relying on the unit risk estimate (URE) developed by TCEQ to assess the residual risk for sources in EPA's August 12, 2020 "National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review" (2020 MON Final Rule). EPA further states that no new studies or other information have been identified by TCEQ that would call into question the conclusions in the 2016 IRIS EtO Assessment or suggest that TCEQ's URE provides a better estimate of the risk of exposure to EtO. TCEQ disagrees. EPA's 2022 MON Reconsideration ignores mathematical errors in EPA's calculation of key model-fit parameters, as well as new TCEQ dose-response model accuracy and validation analyses, and fails to consider the most recent scientific information regarding the association between EtO exposure and breast cancer, all of which were highlighted in TCEQ's October 12, 2020 Administrative Petition for Reconsideration of the 2020 MON Final Rule (Petition for Reconsideration).

[1] United States Environmental Protection Agency (USEPA). 2016. Evaluation of the inhalation carcinogenicity of ethylene oxide (CASRN 75-21-8): In support of summary information on the Integrated Risk Information System (IRIS). EPA/635/R-16/350Fa. Washington, DC, U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment.

[2] TCEQ Ethylene Oxide Carcinogenic Dose-Response Assessment, Final, May 15, 2020, available at: https://www.tceq.texas.gov/toxicology/ethylene-oxide and in Attachment A.

General Comments

TCEQ disagrees with EPA's assertions in the 2022 MON Reconsideration that TCEQ's EtO assessment is not scientifically supported and should not be relied on to assess the residual risk for sources in the 2020 MON Final Rule. The 2020 TCEQ EtO Assessment (included in these comments as Attachment A) demonstrated that there were two major flaws in EPA's 2016 IRIS value. First, the 2016 IRIS value was derived using improperly calculated model-fit parameters (i.e., Akaike information criteria (AIC) and p-values) that resulted in the selection of a model that significantly overpredicts the number of cancer deaths caused by EtO exposure. Second, EPA's inclusion of EtO-induced breast cancer in its 2016 IRIS EtO Assessment is not supported by the weight of scientific evidence, including recent studies that found no significant association between EtO exposure and breast cancer in humans. These errors resulted in an overly conservative URE that does not accurately reflect the risk of exposure to EtO. Because TCEQ's URE for EtO addresses and resolves both of these errors, TCEQ's URE should be used instead of the 2016 IRIS value to estimate the risk of exposure.

TCEQ's 2020 EtO Assessment used the correct calculations for the AIC and p-value parameters; demonstrated that the TCEQ's chosen EtO cancer dose-response model correctly predicted the number of cancer deaths observed in two cohorts of occupationally exposed workers; and determined that the evidence that EtO causes breast cancer was too weak to include breast cancer as an endpoint in the assessment. TCEQ engaged the University of Cincinnati, Risk Science Center to conduct an external peer review of the TCEQ EtO Assessment with six internationally recognized experts in risk assessment, epidemiology, and statistical modeling. These experts were asked specifically to opine on the above topics (as well as other elements of TCEQ's EtO assessment), and they agreed with the TCEQ's conclusions on the points discussed above.

<u>EPA's 2022 MON Reconsideration does not resolve the two key errors identified by TCEQ in EPA's derivation of the 2016 IRIS value</u>

In its Petition for Reconsideration, TCEQ demonstrated that there were two key flaws in the derivation of the 2016 IRIS EtO Assessment, as well as applicable new information, which would justify using an alternative value for EtO. Specifically, TCEQ identified the following flaws in EPA's assessment:

a. EPA improperly calculated two key model-fit parameters when conducting its 2016 IRIS EtO Assessment: AIC scores and p-values. This mathematical error resulted in EPA's selection of an incorrect and unreliable model that significantly overpredicts lymphoid cancer deaths.
b. EPA's 2016 IRIS EtO Assessment included EtO-induced breast cancer even though the weight of scientific evidence does not support the conclusion

that EtO causes breast cancer in humans, especially when considering more recent published studies and evaluations.

EPA's 2022 MON Reconsideration fails to scientifically rebut either of these errors. In the 2022 MON Reconsideration, EPA states, "…TCEQ did not submit new data for the EPA's consideration that would cause us to use the final TCEQ cancer risk value instead of the IRIS cancer risk value for the MON risk review. Rather, TCEQ has pursued a different approach to analyzing the same National Institute for Occupational Safety and Health (NIOSH) occupation exposure dataset that is the basis of the 2016 IRIS cancer risk value." EPA goes on to state "these petitioners have not identified a basis for changing our approach to the risk assessment" and that the arguments had already been addressed in the "response to the RFC, in the 2020 MON final rule's preamble (85 FR 49084; August 12, 2020), and in the response to public comment document for the 2020 MON final rule" (EPA's May 2020 Summary of Public Comments and Responses for the Risk and Technology Review for Miscellaneous Organic Chemical Manufacturing; found at https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0200) (EPA 2020 RPC).

However, the EPA's 2022 MON Reconsideration and documents referenced therein do not specifically scientifically rebut errors in their model selection process documented by TCEQ (i.e., AIC and p-value calculations being incorrect), or scientifically rebut dose-response model accuracy and validation analyses conducted by TCEQ. Instead, EPA mostly relied on previous responses and an EPA Science Advisory Board (SAB) review process that similarly did not evaluate the accuracy of the AIC and p-value calculations or specifically address these more recent scientific demonstrations by TCEQ. In addition, new model validation analyses and EtO breast cancer studies are presented by TCEQ, which substantively impact EPA's conclusions about EtO risk.

EPA's 2022 MON Reconsideration also incorrectly states that because TCEQ uses the same key dataset, there are no new data being presented. TCEQ presented new analyses of dose-response model accuracy and validation analyses that warrant consideration by EPA. Furthermore, EPA wrongly asserts that TCEQ did not consider women in its EtO assessment. The 2020 TCEQ EtO Assessment includes lymphoid cancer modeling for both men and women; however, TCEQ's final URE value is based only on the male data set from the NIOSH cohort because utilization of the male data set (as opposed to the male and female combined data set) resulted in a more conservative and protective URE, thus benefiting both men and women. TCEQ also considered breast cancer in women as a potential endpoint but ultimately determined that the weight of scientific evidence does not support that EtO causes breast cancer in humans. Thus, EPA's assertion that TCEQ excluded women from its EtO analysis is both misleading and untrue.

TCEQ urges that these errors be submitted to the Scientific Advisory Board for further review

Based on these important concerns, TCEQ requests that EPA employ the SAB to re-evaluate EPA's 2016 IRIS EtO assessment in light of the new scientific information and analyses in the 2020 TCEQ EtO Assessment. Specifically, TCEQ requests that the SAB review the accuracy of EPA's AIC and p-value calculations; EPA's inclusion of EtO-induced breast cancer in formulating its 2016 IRIS value in light of recent studies and the 2020 TCEQ EtO Assessment; as well as EPA's model selection given TCEQ model accuracy and validation analyses and other relevant considerations (e.g., correct AIC and p-value calculations).

Use of EPA's URE in EtO risk assessments leads to unrealistic risk conclusions and has real-world consequences

Implementation in the real world demonstrates the unreasonableness of EPA's scientifically flawed URE, as EPA's EtO ambient air urban background study[3] found that background concentrations of EtO (0.1-0.2 ppb) far exceed EPA's maximum acceptable air concentration (0.01 ppb at 1 in 10,000 excess risk). EPA's value has caused ill-informed actions regarding ethylene oxide, such as shutdowns of medical sterilization facilities because of the (unwarranted) concerns of panicked communities. These sterilizer shutdowns have led to shortages of life-saving medical equipment.[4]

Specific Comments

EPA's Consideration of What Constitutes "New Information" is Too Limited and Excludes Relevant Information

EPA should consider additional sources of new data and analyses when determining the body of the best available scientific information for informing the EtO dose-response assessment. In the 2022 MON Reconsideration, EPA stated that TCEQ did not submit new data, but rather based its EtO evaluation on the same underlying data set as EPA. Although TCEQ did use the same underlying dataset as EPA to calculate its URE, this is only one of the many studies and analyses that inform decisions made in the EtO dose-response analysis. Information about chemical mode of action (MOA), confounders or biases in studies, and new analyses of the same data can crucially inform the ultimate dose-response model and URE. In fact, EPA has used new analyses of existing data sets to make decisions about dose-response for other chemicals. For example, EPA's Office of Pesticide Programs (OPP), when conducting a cancer evaluation for the chemical captan, had hypothesized that the MOA for intestinal tumors in mice was based on mutagenesis. Therefore, OPP used a

[3] EPA reported urban background levels of 0.1-0.2 ppb based on EPA sampling from October 2018 through March 2019 (available at https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-data-summary-national-air-toxics-trends)

[4] FDA. 2019 Statement on concerns with medical device availability due to certain sterilization facility closures. (available at https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures)

non-threshold dose-response model to derive an oral slope factor for the chemical. However, following third-party review and evaluation of existing MOA data, OPP ultimately determined that captan acts through a non-mutagenic threshold MOA, and that it is not likely to be a human carcinogen at environmentally relevant doses (Gordon, 2007; USEPA, 2004).[5] In that case, a change was made based on a new analysis of existing data. If EPA had discarded the new captan analysis just because it was not a new key study, it would not have been applying the best scientific information to its assessment. As with captan, EPA should consider other forms of new data—not just a new key study—to be relevant to applying best available scientific information to the EtO dose-response assessment. The results of new analyses of dose-response model accuracy and validation analyses qualify as new data that should be considered, as well as new studies about the association between EtO and breast cancer.

TCEQ's Model Accuracy and Validation Analyses Provide New Scientific Data

TCEQ's dose-response model accuracy and validation evaluations are additional scientific analyses that provide new data for the selection of the most predictive model for lymphoid cancer mortality caused by EtO. TCEQ presented the results of these analyses in the 2020 TCEQ EtO Assessment that was provided to EPA as part of TCEQ's Petition for Reconsideration. These analyses evaluate how well a model can predict the number of cancer deaths observed in a group of people who were exposed to EtO. Both EPA and TCEQ used the estimated EtO exposures and the observed cancer deaths from the key NIOSH cohort[6] to develop a model that estimates how many cancer deaths would be anticipated from EtO exposure – this is the EtO dose-response model. To validate the dose-response models, TCEQ tested both EPA's and TCEQ's models to see how well they could predict the number of lymphoid cancer deaths in the NIOSH cohort (that was used to build model). A valid model should be able to reproduce the data that went into it.

These analyses demonstrate that EPA's selected dose-response model (i.e., linear two-piece spline model) overestimates lymphoid cancer deaths, the cancer endpoint that primarily drives the URE, in the key NIOSH cohort by a statistically significant amount.[7] TCEQ showed that EPA's selected model statistically significantly over-predicts each quintile of exposed NIOSH workers,

[5] Gordon, E., 2007. Captan: transition from 'B2' to 'not likely'. How pesticide registrants affected the EPA cancer classification update. J. Appl. Toxicol. 27, 519-526.
United States Environmental Protection Agency (USEPA), 2004. Captan; Cancer Reclassification; Amendment of Reregistration Eligibility Decision; Notice of Availability. US Environmental Protection Agency, Washington, DC. Fed. Regist. 69, 68357-60.
[6] The NIOSH cohort refers to the group of more than 17,000 sterilization workers who were occupationally exposed to EtO. NIOSH studied these workers to determine the relationship between EtO and cancer.
[7] 2020 TCEQ EtO Assessment, Appendix 3, Sections A3.1 and A3.2.

including the lowest exposed on which EPA places special emphasis for model selection ("more local fits in the low-exposure range"),[8] even when the maximum likelihood estimate (MLE) is used. This was also the case when a healthy worker effect for lymphoid cancer mortality was assumed for the worker population. These findings mean that EPA's model does not pass the test of whether it can reproduce the data that was used to build the model, and so is not a valid model for use in EtO risk assessment.

EPA addressed questions of model validation assessments in the EPA 2020 RPC, and those responses are referenced in the EPA 2022 MON Reconsideration. However, all the arguments made in the EPA 2020 RPC that the EPA uses to dismiss model validation results were tested in the 2020 TCEQ EtO Assessment. The results of the TCEQ analyses continued to show that EPA's selected dose-response model significantly over-predicted the lymphoid cancer deaths that were observed in the NIOSH cohort. Specifically, EPA made four arguments to explain why the model validation results for the NIOSH cohort were over-predictive:

1. EPA Assertion: EPA's URE is based on the 95th percentile upper confidence limit, and "a more suitable basis for comparison with the observed deaths is the maximum likelihood estimates (MLEs) of the models."[9]
    a. TCEQ Response: All TCEQ's model validation analyses evaluated the predicted number of cancer deaths using EPA's dose-response model MLE. EPA's MLE significantly over-predicted cancer deaths in the evaluated cohorts.[10]
2. EPA Assertion: "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."[11]
    a. TCEQ Response: TCEQ evaluated the model predictions in each exposure quintile and found that in all exposure groups, including the lowest exposure quintile, EPA's dose-response model MLE significantly over-predicted cancer deaths in the NIOSH cohort.[12]
3. EPA Assertion: In reference to the over-prediction of the NIOSH cohort observed cancer deaths using the upper bound results from the risk model, EPA states, "This does not imply, though, that the same upper bound relationship would be high if applied to a different independent data set."[13]

[8] February 4, 2022 87 FR 6466, 6472 (MON Reconsideration).
[9] EPA 2020 RPC, page 96.
[10] 2020 TCEQ EtO Assessment, Section 4.2.3.
[11] EPA 2020 RPC, page 97.
[12] 2020 TCEQ EtO Assessment, Section 4.2.3.
[13] EPA 2020 RPC, page 97.

a. TCEQ Response: TCEQ conducted an additional model validation analysis prompted by the peer review report of the 2020 TCEQ EtO Assessment, using a different independent data set: the Union Carbide Company (UCC) cohort. This analysis demonstrated that EPA's model for the NIOSH dataset is unable to accurately predict lymphoid cancer deaths in the UCC cohort and, in fact, is statistically significantly over-predictive.[14] By contrast, TCEQ's data validation analysis proved that TCEQ's selected dose-response model — the standard Cox proportional hazards model — accurately predicts the number of lymphoid cancer mortalities that occurred in the UCC cohort.

4. EPA Assertion: In reference to the use of national cancer rates as part of the validation analysis, EPA states, "A 'healthy worker effect', as often seen in occupational epidemiology, will also lead to lower observed tumor rates in a worker study. Accordingly, the EPA disagrees with the claims that agency risk models, when applied to the NIOSH cohort lead to 'statistically significant overpredictions of risk'."[15]

    a. TCEQ Response: A healthy worker effect[16] for lymphoid cancers was not observed in the NIOSH cohort. That is, unexposed NIOSH EtO workers were no less likely to die from lymphoid cancer than the general population, so TCEQ's use of national lymphoid cancer rates in the model validation analysis is appropriate. Specifically, the 95% confidence interval (CI) on the standardized mortality ratio (SMR) for unexposed NIOSH workers includes 1, which indicates that the mortality rate in the unexposed workers and the U.S. population mortality rate are not statistically significantly different. Similar results are obtained for the male NIOSH workers that drive lymphoid cancer risk (i.e., the lymphoid cancer SMR in unexposed NIOSH males is 1.03 (6/5.8) with a 95% CI of 0.38, 2.25). Thus, it is demonstrated by TCEQ that, in fact, there is no healthy worker effect for this critical cancer endpoint in this key cohort, and by corollary that TCEQ methods are appropriate. However, even assuming that there was a healthy worker effect for

[14] 2020 TCEQ EtO Assessment, Appendix 3, Section A3.3.3.
[15] EPA 2020 RPC, page 97.
[16] The healthy worker effect refers to the possibility that a population of workers may be generally healthier and so less likely to develop a given disease of interest compared to the general population. If this is the case, then by comparing worker populations to the general population in the calculation of risk estimates, the effect of the exposure on the workers may be underestimated. This is more common with illnesses such as cardiovascular disease and is less likely to be the case for cancer. To determine if a healthy worker effect is occurring in a study, the cancer rate in the group of people not exposed to the chemical agent (called the control population) is compared to the cancer rate in the general population. If the cancer rates are the same, such as with lymphoid cancer rates in the NIOSH cohort, then there is no evidence of a healthy worker effect for that cancer.

lymphoid cancer mortality in the NIOSH cohort (despite TCEQ's demonstration to the contrary), the results of the dose-response model accuracy analyses do not change significantly.[17] That is, in the model validation analysis, EPA's selected model is again demonstrated to be inaccurate, statistically significantly over-predicting the number of lymphoid cancer mortalities.

Altogether, this evidence demonstrates the unreliability of EPA's chosen dose-response model for predicting cancers in the cohort upon which the model was based, as well as for other populations and exposure scenarios. All the reasons that EPA has proffered to explain the model over-prediction were disproved by TCEQ in the 2020 TCEQ EtO Assessment. Thus, the model selected by EPA is unsuitable for use in assessing risk from EtO. By contrast, TCEQ's selected dose-response model (i.e., standard Cox proportional hazards model) accurately predicts the number of cancer deaths observed in the key NIOSH cohort, both overall and for each exposure quintile (including the lowest exposed), as well as the number of lymphoid cancer deaths that occurred in the validation (i.e., UCC) cohort. In light of these and other TCEQ analyses, EPA should use the final TCEQ cancer risk value instead of the IRIS cancer risk value for the MON risk review.

The 2022 MON Reconsideration fails to rebut or even address the model accuracy and data validation analyses set out in the 2020 TCEQ EtO Assessment. Instead, EPA references only the EPA 2020 RPC to explain why its two-piece spline dose-response model over-predicted lymphoid cancer deaths in the NIOSH cohort. However, that document was released in May 2020, the same month that the 2020 TCEQ EtO Assessment was released. Therefore, it is understandable that EPA would make the arguments detailed above in the EPA 2020 RPC, not knowing that they had all been addressed in TCEQ's model validation analyses. However, for the 2022 MON Reconsideration, EPA had ample time to review TCEQ's scientific analyses, to see the additional model validation analyses that had been conducted, and to further address those points in this 2022 MON Reconsideration determination. EPA did not do so, and in fact, the 2022 MON Reconsideration says nothing at all about the subject of model validation.

<u>EPA's Incorrect AIC and p-value Calculations Contributed to the Selection of an Unreliable Dose-Response Model</u>

EPA's mathematical error in calculating two model fit parameters—the AIC scores and the p-values—resulted in the selection of a model that does not accurately predict lymphoid cancer mortalities from EtO exposure. The 2020 TCEQ EtO Assessment corrects these mathematical errors and selects a model that fits the key data set of the NIOSH cohort just as well, but moreover, much more accurately predicts lymphoid cancer mortalities in the key cohort as well

[17] 2020 TCEQ EtO Assessment, Appendix 3, Section A3.3.2.

as an independent validation data set, the UCC cohort. As a result, TCEQ's URE value, which was derived using a demonstrably predictive dose-response model, more accurately predicts cancer risk from EtO exposure than EPA's 2016 IRIS value.

In TCEQ's Petition for Reconsideration, TCEQ described the mistake made in EPA's calculation of the AIC scores and p-values. The basis of this mistake is that in these calculations, EPA did not account for the model fit statistical optimization process used in determining "knot" values (the point of inflection) between the lower and upper splines. The knot, in fact, should have been counted by EPA as an estimated parameter but was not. As a result, EPA used a "2" in its calculations (for the degrees of freedom) when really a "3" was required because there were three estimated parameters: (1) the knot value, (2) the slope at concentrations higher than the knot, and (3) the slope at concentrations lower than the knot. Because the knot was estimated based on the data (just like the slopes were), it must be taken into account as an additional variable in the equation, but EPA did not do this. Unfortunately, this error significantly impacted the rest of EPA's analysis, leading to:

- Inappropriately decreased p-values for adequate statistical fit for the spline models, incorrectly implying that the linear two-piece spline model with a knot at 1,600 parts per million (ppm) × days for lymphoid cancer fit the data statistically better than other models in Table 4-6 of the 2016 IRIS EtO Assessment;[18] and
- Incorrectly decreased AIC for the spline models, which did not allow for an appropriate comparison of model fit among models for either lymphoid cancer or breast cancer incidence.

EPA's response to these concerns (in the 2022 MON Reconsideration, the EPA 2020 RPC, and the 2021 Response to the Request for Correction (2021 RFC Memo)[19]), relied on the SAB's review and determinations of EPA draft EtO assessments. Specifically, EPA noted that SAB stated "…the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data… In the draft assessment, fixing the knot when estimating linear spline model fits from

[18] e.g., 2016 IRIS EtO Assessment page 4-16 states "Neither of the two-piece spline models with the knot at 1,600 ppm × days had a p-value <0.05; however, both were close to 0.05 (p = 0.07 for each model)…" This demonstrates that a p-value that was close to 0.05 (which would not be the case for the appropriately calculated p-value of 0.15) contributed to EPA's choice of model.

[19] EPA. EPA's Response to American Chemistry Council (ACC)'s Request for Correction to the IRIS Value for Ethylene Oxide (EtO) used in the National Air Toxics Assessment (NATA) in 2018. December 13, 2021. https://www.epa.gov/system/files/documents/2021-12/signed-response-to-william-p.-gulledge-of-acc-re-rfc-18003_09-sept-2021-oira_clean_2-oar-22-000-0344.pdf and the attached memorandum from EPA's ORD. August 25, 2021. https://www.epa.gov/system/files/documents/2021-12/final-eto-rfc-memo-cascio-to-goffman-8-25-2021.pdf

relative risk regressions is one such example. (SAB, 2015, page 12)." However, this statement supports *fixing* of some model parameters (i.e., setting those parameters without using the data). But EPA estimated all three model parameters (two slopes, and the inflection point or knot between them) using the data. Because EPA did not fix any of the parameters, the quote from the SAB discussing the use of fixed parameters does not apply and does not adequately address TCEQ's concerns about the AIC and p-value calculations.

In the 2021 RFC Memo, EPA also stated that "[a]dditionally, the two-step approach to knot selection and model fitting was clearly presented in the draft IRIS assessment materials reviewed by the SAB."[20] Although the SAB may have approved of a two-step approach that involved first using the data to estimate a knot, and then using the data-derived knot to estimate the slopes of the lines below and above the knot, the SAB did not evaluate specifically how EPA calculated its AIC and p-values, and whether the calculations appropriately accounted for the three data-derived parameters. TCEQ sought to verify its assertions regarding the degrees of freedom and estimated parameters values through a formal external expert peer review organized by the University of Cincinnati Risk Science Center, which included review by two independent mathematical and statistical modeling experts. TCEQ then incorporated the recommendations of these experts into its 2020 EtO Assessment. These experts agreed that EPA's calculations for those model fit criteria are incorrect.[21]

Statistical optimization of knot values was utilized for EPA's two-piece spline modeling approach. The 2016 IRIS EtO Assessment indicates that for this approach, the splines were fit to the EtO cancer exposure-response data, and the knot was generally selected by evaluating different knots in increments (e.g., 100, 500, or 1,000 ppm × days) of cumulative exposure and then by choosing the one that resulted in the best (i.e., largest) model likelihood.[22] Thus, from the process described, it is readily apparent that:

- The knot was an iteratively fit model parameter and not simply "preselected";[23] and
- The knot values, *being statistically estimated/optimized based on the NIOSH data*, clearly do not conform to EPA SAB's notion of potentially fixing some model parameters *not estimated from the data* in the interest of parsimony.[24]

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[20] 2021 RFC Memo, page 5.
[21] *See* pp. 30-33 of Final Report for Letter Peer Review of Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document (April 30, 2020).
[22] 2016 IRIS EtO Assessment, pages 4-13, 4-26, 4-36, 4-45.
[23] 2016 IRIS EtO Assessment, page 4-52.
[24] *See* EPA. 2015. Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft-August 2014), August 7, 2015, page 12 (explaining that "in some settings the principle of parsimony may suggest that the

"Preselected" is a somewhat ambiguous term used by EPA that does not adequately characterize and obfuscates how the knot value was statistically fit. This is an important procedural/methodological issue as it appears that under EPA's interpretation, multiple model parameters could be statistically estimated/optimized upstream of a final dose-response model, yet none of the fitted parameters would ultimately count as an estimated (*k*) parameter as they were "preselected" based on prior model-fitting exercises.

In the present case, the knot values were determined through model fitting with NIOSH data (e.g., maximization of the likelihood of the model for best fit to the lymphoid cancer data), and thus are clearly additional estimated parameters (*k*) in the analysis. That is, for the spline models, the additional parameters (*k*) estimated by EPA were: (1) the knot value; (2) the slope at concentrations higher than the knot; and (3) the slope at concentrations lower than the knot (*k*=3). However, the 2016 IRIS EtO Assessment did not account for statistically estimating the optimized knot value.

Because EPA incorrectly calculated the estimated parameters value for (*k*), the degrees of freedom (*df*) were inappropriate for the spline models in EPA's assessment (*i.e., df=k*, the number of additional parameters estimated for this model over the model with zero-slope with cumulative exposure). This error was not inconsequential. As noted above, EPA's calculation inappropriately decreased the p-value for adequate statistical fit, incorrectly implying that the linear two-piece spline model with a knot at 1,600 ppm × days for lymphoid cancer fits the data statistically better than other models in Table 4-6 of the 2016 IRIS EtO Assessment. However, when the correct values are used, the Cox proportional hazards model fits just as well and more accurately predicts the number of lymphoid cancer cases in both the key cohort and the validation cohort, as demonstrated in the 2020 TCEQ EtO Assessment. Consequently, not only is the linear two-piece spline model for lymphoid cancer preferred by the 2016 IRIS Assessment not statistically significant (i.e., the model doesn't explain the variability in the data any better than the null model), but the correct AIC values for the linear two-piece spline model (464.5) and the Cox regression model (464.4) are almost identical. The TCEQ-preferred Cox proportional hazards model is, however, demonstrated to be more accurate and is also more parsimonious, consistent with the SAB recommendation that "the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered."

The MOA of EtO demonstrates that the dose-response should be no-more-than linear; an overall supralinear two-piece spline model is not supportable. In the 2022 MON Reconsideration, EPA also stated that it followed the SAB's advice on model selection, including relying less on AIC scores and prioritizing

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most informative analysis will rely upon fixing some parameters *rather than estimating them from the data*…") (emphasis added) EPA-SAB-15-012.

considerations of biological plausibility.[25] However, EPA did use AIC scores for model selection, as discussed in its decision not to use square-root transformation models.[26] To EPA's point about biological plausibility, TCEQ agrees that biological plausibility is an important consideration for model selection. TCEQ prioritized biological plausibility in the model choice by considering the MOA of EtO, which demonstrates that the dose-response should be no-more-than linear. EPA does not present any information that demonstrates an MOA for EtO that is consistent with the overall supralinear two-piece spline model utilized in this case (and acknowledged to the SAB that "the EPA is not aware of a mechanistic explanation."[27]). Instead, EPA's discussion of biological plausibility details the comparison of its two-piece spline model with a knot at 1600 ppm x days, to the statistical best-fit model that had a knot at 100 ppm x days. The latter model had such a steep low dose slope that exposure to an additional 1 part per trillion (ppt) EtO would increase cancer risk by 100 in 1 million. In comparison to that model, EPA considered the 1600 ppm x days spline model to be more biologically plausible. However, biological plausibility is not established by comparing an option to something that is completely implausible if not impossible (everything is plausible when compared to the impossible), but rather by considering what would be expected based on the underlying biological data and characteristics of the chemical. EPA's selection is both biologically implausible and implausible in real-world application.

Importantly, this calculation error in EPA's assessment, identified and documented by TCEQ, is not scientifically rebutted by EPA in any of its responses, including the 2022 MON Reconsideration. As noted above and in the 2020 TCEQ EtO Assessment, EPA's error resulted in a misinformed statistical evaluation of model fit in the 2016 IRIS EtO Assessment, which does not represent best-available science. For this and other reasons discussed herein (e.g., predictive inaccuracy), EPA's 2016 IRIS value for EtO is unreliable and should not be used.

<u>TCEQ Considered the Risk to Women and Selected the Most Conservative Data Set for Development of its URE</u>

In its 2022 MON Reconsideration, EPA incorrectly states that TCEQ excluded women from its analysis, including all lymphoid cancers in women. This is simply not true. Tables 8 and 11 of the 2020 TCEQ EtO Assessment include lymphoid cancer modeling results for men + women (additionally, TCEQ evaluated women's breast cancer as a potential cancer endpoint, discussed below). Thus, TCEQ analyses for lymphoid cancer clearly and specifically included women. The EtO air concentration corresponding to a 1 in 100,000

[25] February 4, 2022 87 FR 6466, 6472 (MON Reconsideration).
[26] 2016 IRIS EtO Assessment, page 4-17.
[27] 2016 IRIS EtO Assessment, page I-29; *see also* pages I-34 and 4-71.

excess risk level for lymphoid cancer is 5.18 parts per billion (ppb) (age-dependent adjustment factor (ADAF)-unadjusted) based on modeling results for men + women, while it is 4.07 ppb (ADAF-unadjusted) based on men alone. While TCEQ's analyses did include women, erring on the side of health protection for both males and females, the final EtO URE selected was based on the NIOSH (male only) data, which is conservative for application to females (i.e., results in higher excess risk estimates for females compared to a URE based on males and females combined). Simply put, occupationally exposed men appear more susceptible to EtO-induced lymphoid cancer than women, so ultimately using men alone in this analysis results in a more protective standard for both men and women. Following EPA's assertion that TCEQ should base its URE on both the male and female data would have led to TCEQ selecting both a less conservative, less protective URE and air concentration at 1 in 100,000 excess risk. In any event, EPA's allegation that TCEQ excluded women from their analyses is incorrect.

TCEQ chose to use data for the more susceptible sex (as opposed to both sexes combined), which allows for a more conservative (i.e., protective) standard. This is consistent with EPA's own cancer risk assessment methods, which allow for this separation of modeling data by sex, and choosing the most sensitive species and sex is a common method used in toxicity factor development. EPA's Office of Research and Development (ORD) Staff Handbook for Developing IRIS Assessments states that "[o]ne situation in which combining data is often reasonable occurs when responses in different subgroups of one study—such as males and females—do not differ materially for the same outcome."[28] However, the responses in males and females were different enough for Steenland et al. (2004)[29] to justify separate analyses (e.g., see Tables 6 and 7 of that study). As stated on p. 4-7 of the 2016 IRIS EtO Assessment, "[f]or both all lymphohematopoietic and lymphoid cancers, Steenland et al. (2004) found stronger positive exposure-response trends in males and so presented the results for some of the regression models separately by sex." Moreover, Steenland et al. concluded, "Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect are not known."[30] TCEQ would, and EPA should, consider this at least a potential material difference in response that justifies separate analyses.

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[28] EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov. 2020). EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020, page 12-9.

[29] Steenland, K, Stayner, L, Deddens, J. 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med. 61:2-7.

[30] In Steenland et al. (2004), the only dose-response models that were reported to have statistically significant positive slopes for the given exposure metric were: (1) lymphohematopoietic cancer mortality: males, log cumulative exposure model, and 15-year lag; (2) lymphoid cancer mortality: males, log cumulative exposure model, and 15-year lag (Valdez-Flores et al. 2010). Additionally, Table 4 of Valdez-Flores et al. (2010) shows negative slopes for NIOSH females for multiple cancer types (e.g., lymphohematopoietic tissue cancer, lymphoid

Despite EPA's determination that it is reasonable to analyze sex-specific data when one sex may have a materially different response, the 2016 IRIS EtO Assessment limited the analysis of human data to both sexes combined. However, EPA found it appropriate to perform sex-specific analyses for EtO-exposed laboratory animal data (Section 4.2 of EPA IRIS 2016).[31] This is inconsistent with EPA's criticism of TCEQ's conservative, sex-separated approach to human data. Thus, TCEQ was justified in looking at male workers only in addition to males + females combined, with the analysis for male workers resulting in a lower air concentration at 1 in 100,000 excess risk, which was in turn adopted as a more conservative value for the protection of public health for everyone (both males and females) since there were "stronger positive exposure-response trends in males."[32]

Best-Available Science Does Not Support EtO-induced Breast Cancer as an Endpoint

EtO-induced breast cancer should not be included when deriving a cancer risk value for EtO exposure because there is insufficient evidence to show that EtO actually causes human breast cancer. TCEQ outlined the scientific rationale behind this conclusion in its Petition for Reconsideration and discussed it at length in the 2020 TCEQ EtO Assessment. Specifically, TCEQ pointed out that most epidemiology studies did not find statistically significantly elevated breast cancer rates with EtO exposure. TCEQ also noted findings from several new studies (published after 2016) evaluating the EtO-breast cancer relationship, highlighted the differences in carcinogenic responses in species in response to EPA's reliance on mouse studies, and expressed serious concerns about parity bias. Nonetheless, EPA proposes to continue its reliance on the 2016 IRIS value which was derived using breast cancer as an endpoint for EtO exposure.

The 2022 MON Reconsideration failed to address the new studies presented by TCEQ. For instance, EPA did not acknowledge the work by Vincent et al. (2019)[33] or the draft EtO Toxicological Profile from the Agency for Toxic Substances and

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tumors, non-Hodgkin's lymphoma, leukemia, lymphocytic leukemia) whereas the slopes for NIOSH males are positive.
Valdez-Flores, C, Sielken Jr, R, Teta, J. 2010 Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data. Regulatory Toxicology and Pharmacology. 56:312-320.

[31] EPA IRIS (2016) p. 4-76 [emphasis added] "The overall approach in this derivation is to find a unit risk for each of the bioassays—*keeping data on males and females separate*—from data on the incidence of all tumor types and then to use the maximum of these values as the summary measure of the unit risk from animal studies (*i.e., the unit risk represents the most sensitive species and sex*)."

[32] 2016 IRIS EtO Assessment, page 4-7.

[33] Vincent, MJ, Kozal, JS, Thompson, WJ, et al. 2019. Ethylene oxide: cancer evidence integration and dose-response implications. Dose-Response: An International Journal October-December 1-17.

Disease Registry (ATSDR),[34] which demonstrate that the weight of scientific evidence does not support the conclusion that EtO causes breast cancer. The Marsh et al. (2019)[35] study was addressed in the EPA 2020 RPC starting on page 85. EPA dismissed the results of that study with the argument that the meta-analysis conducted by the study authors evaluated mortality rather than incidence of breast cancer and that EPA selected only two of the five studies selected by Marsh et al. (2019). This is incorrect, however, because the Marsh et al. (2019) paper included studies that evaluated both breast cancer mortality and incidence, and both were included in the meta-analysis. Both incidence and mortality studies are relevant in determining whether EtO causes breast cancer, so it is appropriate for Marsh et al. (2019), as well as TCEQ and EPA, to evaluate both.

The EPA also inappropriately cited the 2007 SAB review to justify the inclusion of breast cancer as an endpoint. Regarding the inclusion of breast cancer in EPA's URE, the response to public comment 31 in the EPA 2020 RPC states, "the EPA determined that the available evidence is sufficient to consider breast cancer a potential hazard from ethylene oxide exposure" and that "the 2007 SAB panel did not object to the derivation of unit risk estimates based on the available breast cancer evidence." However, since 2007 a number of peer reviewed studies have been published, including three after 2016 (two of which were meta-analyses) that found no association between EtO and breast cancer.[36] In addition, the latest report on carcinogens from the National Toxicology Program (NTP 2021) reports that IARC concluded that there is limited evidence for a causal relationship between EtO and breast cancer in humans.[37] This is consistent with EPA's own assessment, which states that "there is little strength in the associations…"[38] and even the best epidemiological data EPA can cite does not demonstrate causation for breast cancer; it merely does not preclude it.

Additional evidence of the lack of relationship between EtO exposure and breast cancer is provided by ATSDR's 2020 draft EtO Toxicological Profile (Figure 2-6 of that report is reproduced below). All the studies evaluating EtO associations with breast cancer show a null or non-statistically significant association. EPA did not address this finding either.

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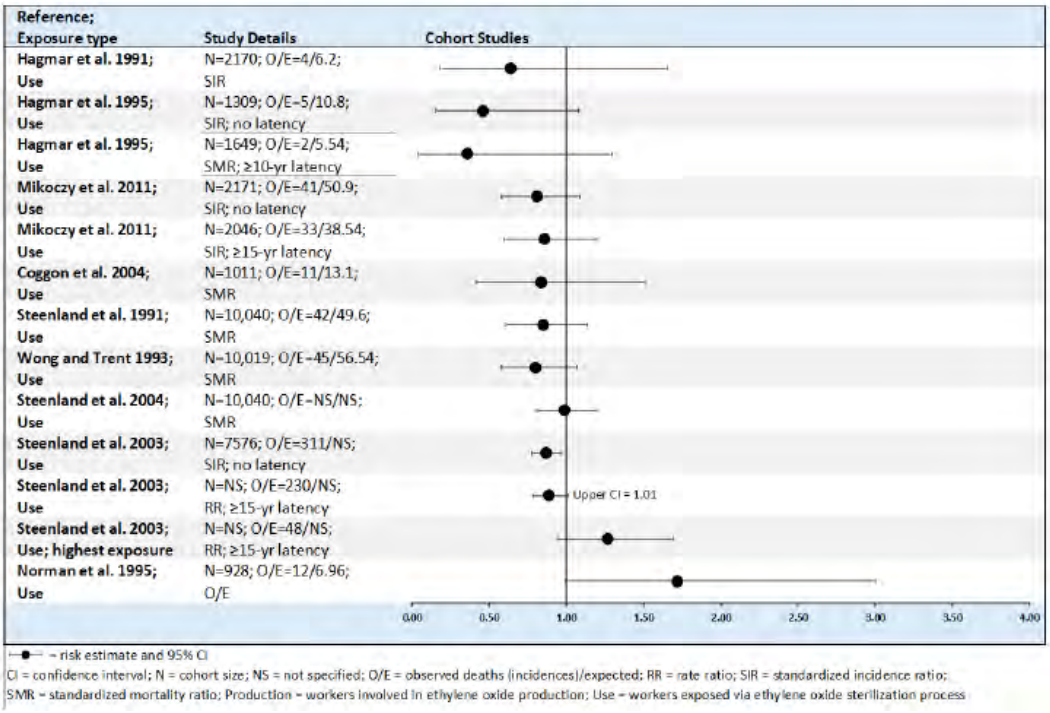
[34] ATSDR Toxicological Profile for Ethylene Oxide Draft for Public Comment, dated September 2020, available at: https://www.atsdr.cdc.gov/ToxProfiles/tp137.pdf.
[35] Marsh, GM, Keeton, KA, Riordan, AS, et al. 2019. Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health. 92(7):919-939.
[36] Marsh et al. 2019; Vincent et al. 2019; Jain, RB. 2020. Associations between observed concentrations of ethylene oxide in whole blood and smoking, exposure to environmental tobacco smoke, and cancers including breast cancer: data for US children, adolescents, and adults. Environmental Science and Pollution Research.
[37] NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition; Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.
[38] 2016 IRIS EtO Assessment, page 3-69.

Figure 2-6. Summary of Epidemiological Studies Evaluating Associations between Inhaled Ethylene Oxide and Breast Cancer



Although EPA uses the study by Mikoczy et al. (2011)[39] as support for the breast cancer endpoint, that study only found an association between breast cancer and EtO when comparing to the lowest cumulative exposure group, not when comparing to rates of breast cancer in the general population. EPA justified this internal comparison by citing the healthy worker effect, which stipulates that workers are healthier and get diseases at lower rates than the general population. However, the Kirkeleit et al. (2013)[40] study found that breast cancer incidence in over 83,000 female workers was similar to the incidence in the general population (i.e., SIR of 1.02 (0.95, 1.09)), which strongly supports the conclusion that the breast cancer SIR of 0.52 for the lowest cumulative exposure group in Mikoczy et al. (2011) is an anomalous study finding that should not be used for internal analyses. This SIR was not based on a reference (unexposed) population only, but rather on workers who were both unexposed and who were exposed to lower levels of EtO.

[39] Mikoczy, Z, Tinnerberg, H, Björk, J, Albin, M. 2011. Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide updated cohort study findings 1972-2006. Int. J. Environ. Res. Public Health. 8:2009-2019.
[40] Kirkeleit, J, Riise, T, Bjørge, T, Christiani, DC. 2013. The healthy worker effect in cancer incidence studies. Am J Epidemiol. 2013; 177(11): 1218-1224.

EPA also uses the finding that EtO induces mammary tumors in rodents as support for their conclusion that EtO causes breast cancer in humans (mammary cancer is the name used for breast cancer in rodents). However, interspecies differences in carcinogenic responses are common (e.g., tumor types, sensitivity), even between different rodent species, with greater differences between rodents and humans. EtO caused mammary tumors in mice but not rats; thus the animal data supporting EtO-induced mammary tumorigenesis are actually mixed. To specifically address the question of whether carcinogens cause tumors at the same sites in different species, a 2019 IARC study[41] analyzed tumor site concordance using a data set of 111 agents classified as carcinogenic to humans. Sixty agents had both a human tumor site and an animal tumor site identified and were used to evaluate concordance across 39 tumor sites in animals and humans.[42] Reported results show that mammary cancer is more frequently/commonly induced in laboratory animal species than breast cancer is in humans. More telling is that while there is 47% overlap between agents that cause lymphoid and hematopoietic cancers in humans and animals, there is only a 20% overlap between agents that have been shown to cause breast cancer in humans and mammary tumors in animals.[43] IARC (2019) made the following consensus statement: "At present, the state of the science does not support tumour site concordance as a general principle." This IARC consensus, especially combined with the mixed rodent results and the insufficient human data (which is the reason why EPA must rely on animal carcinogenicity data at all), provides no support for EtO-induced breast cancer in humans.

Additionally, per a 2020 TCEQ EtO Assessment external peer review expert, the role of parity (i.e., the number of children a woman has) adds particular complexity in studying occupational exposures and breast cancer.[44] Parity is strongly related to risk of breast cancer (i.e., higher parity predicts lower risk) and is also strongly related to remaining in the work force to accrue greater exposure (i.e., more live births predict cessation of employment). Without careful control in the analysis, this would result in a spurious positive association—the women with no or few children have elevated risk of breast cancer and work for longer periods of time, thus accruing greater cumulative exposure. Only one of the breast cancer studies, the Steenland et al. (2003)[45] breast cancer incidence study, controlled for parity in the analysis, but due to

[41] International Agency for Research on Cancer (IARC). 2019. Tumour site concordance and mechanisms in carcinogenesis. IARC Scientific Publication No. 165, Lyon, France: International Agency for Research on Cancer.
[42] *See* IARC 2019, Figures 21.1 and 21.2.
[43] IARC 2019, Table 21.7.
[44] *See* p. 25 of Final Report for Letter Peer Review of Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document (April 30, 2020).
[45] Steenland, K, Whelan, E, Deddens, J, Stayner, L, Ward, E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes and Control. 14:531-539.

the lack of details (i.e., how this was done, particularly in relation to the exposure lag periods), it is not clear that parity was effectively handled. Moreover, the finding that duration of exposure was more strongly associated with breast cancer incidence than cumulative exposure (duration multiplied by EtO concentration) is consistent with parity bias (i.e., working longer predicts higher risk). The other breast cancer studies did not appear to control for parity at all. In fact, the finding in the Mikoczy et al. (2011) study that the lowest exposure group had a significantly lower risk of breast cancer, could be explained by parity bias. The total employment time for the individuals in the lowest exposure group was approximately five to eight years shorter than the employment time for the higher exposure groups. If parity contributed to shorter employment duration in women, this could have increased the percentage of women who had children in the low exposure group compared to the percentage of women with children in the general population, leading to an artificially lower breast cancer incidence. In the absence of parity information, this potential bias is not controlled for in the study. EPA did not address TCEQ's concerns about parity bias in the 2022 MON Reconsideration, nor was it discussed in EPA's referenced documents, the 2021 RFC Memo and the EPA 2020 RPC.

Altogether, the breast cancer studies: 1) may be biased based on parity; 2) they mostly do not show statistically significant results (demonstrated by the 2020 ATSDR draft Toxicological Profile for EtO and by several recent meta-analyses); and 3) IARC determined in 2019 that there was no evidence that mammary tumors in rodents will predict breast cancer in humans. Given all relevant considerations, if convened today the SAB may find, as TCEQ did more recently, that the evidence is too weak to support including breast cancer in the EtO URE. This would be consistent with an external expert peer reviewer of TCEQ's assessment who stated, "Given inherent limitations noted in the NIOSH studies of both breast cancer incidence and mortality, suggestive but not compelling results limited to specific analytic approaches, and the absence of confirmatory data, an informed, unbiased evaluator could well come to the judgment that TCEQ did, i.e., not considering breast cancer in the overall EtO assessment."[46]

[46] *See* p. 25 of Final Report for Letter Peer Review of Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document (April 30, 2020).

Attachment A

TCEQ Ethylene Oxide Carcinogenic Dose-Response Assessment CAS Registry Number: 75-21-8

Development Support Document Final, May 15, 2020

Ethylene Oxide
Carcinogenic Dose-Response Assessment

CAS Registry Number: 75-21-8

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Development Support Document

Final, May 15, 2020

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

DSD History

Effective Date	Reason
August 16, 2017	Public request for toxicity information
June 28, 2019	DSD proposed for public comment
February 18, 2020	Revised DSD and responses to public comments on 2019 draft DSD posted
February – April 2020	External peer review by experts in the field
May 15, 2020	DSD posted as final

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
ADAF	age-dependent adjustment factor
AIC	Akaike Information Criteria
AMCV	air monitoring comparison value
ATSDR	Agency for Toxic Substances and Disease Registry
°C	degrees Celsius
CI	confidence interval
DNA	deoxyribonucleic acid
DSD	development support document
EC	effective concentration
ED	effective dose
ESL	effects screening level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based effects screening level for nonthreshold dose response cancer effect
EtO	ethylene oxide
HAWC	Health Assessment Workspace Collaboration
Hb	hemoglobin
HEV	hemoglobin N-(2-hydroxyethyl)-valine
IARC	International Agency for Research on Cancer
LCL	lower confidence limit
LEC	lower limit on the effective concentration
LHC	lymphohematopoietic cancers
LHN	lymphohematopoietic neoplasms
Lymphoid cancer	Includes leukemia (and specifically myeloid and lymphocytic leukemia), non-Hodgkin's lymphoma, and multiple myeloma
MW	molecular weight
µg	microgram
µg/L	micrograms per liter

Acronyms and Abbreviations	Definitions
µg/m^3	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
MLE	maximum likelihood estimate
mm Hg	millimeters of mercury
MOA	mode of action
n	number
N/A	not applicable
NATA	National Air Toxics Assessment
NEI	National Emissions Inventory
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NHL	non-Hodgkin's lymphoma
PECO	Population Exposure Comparator/Controls Outcome(s)
POD	point of departure
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
ROB	risk of bias
RPF	relative potency factor
RR	risk ratio
SAB	Science Advisory Board
SAS	Statistical Analysis System
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error

Acronyms and Abbreviations	Definitions
SEER	United States Surveillance, Epidemiology, and End Results (SEER) Program
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TCEQ	Texas Commission on Environmental Quality
TRARD	Toxicology, Risk Assessment, and Research Division
UCC	Union Carbide Corporation
URF	unit risk factor
USEPA	United States Environmental Protection Agency
USFDA	United States Food & Drug Administration
WHO	World Health Organization
WV	West Virginia

Chapter 1 Executive Summary and Summary Tables

Executive Summary

- Ethylene oxide (EtO) is a chemical with many industrial applications and is particularly useful as a sterilant for medical devices. Urban background monitored levels of EtO in the United States are in the range of 0.1-0.2 ppb. EtO is also produced endogenously and the amount of EtO naturally present in the human body is equivalent to continuous exposure of ≈0.56-4.5 ppb in air (Kirman and Hays 2017).
- Because EtO is emitted in Texas and has been determined by other agencies to be a carcinogen, the TCEQ undertook a carcinogenic dose-response assessment and derivation of a unit risk factor (URF) and an effects screening level (ESL) for this chemical for use in TCEQ's remediation and air permitting programs, respectively.
- Review of the EtO literature supports direct mutagenicity as the putative carcinogenic mode of action (MOA) and suggests that the exogenous EtO cancer dose-response should be no more than linear overall.
- The TCEQ conducted a hazard assessment for the carcinogenic potential of EtO in humans, which included a review of the available human and animal carcinogenicity studies as well as the MOA analysis. Based on insufficient human data, but with sufficient animal data and a putative mutagenic MOA (noted above), the TCEQ determined that EtO is *likely to be carcinogenic to humans*.
- Further, the TCEQ determined that the weight of evidence suggests a potential association between EtO and human lymphohematopoietic tumors but does not suggest an association with human breast cancer. The TCEQ's breast cancer determination is based on: (1) the weak primary epidemiological evidence for EtO-induced breast cancer (Section 3.3.1.1.1.1); and (2) recent meta-analyses evaluating the strength of the overall weight of evidence for EtO-induced breast cancer (Marsh et al. 2019, Vincent et al. 2019) that showed a lack of association between EtO and breast cancer.
- Based on the *likely to be carcinogenic to humans* determination, the TCEQ conducted a carcinogenic dose-response assessment to derive a chronic inhalation toxicity factor for EtO. Human data are preferred for toxicity factor development under TCEQ guidelines (TCEQ 2015) and the TCEQ conducted a systematic review to identify human studies that could inform the derivation of a cancer URF for inhalation exposures to EtO.
- The systematic review identified two high-exposure occupational cohorts (i.e., the Union Carbide Corporation (UCC) and National Institute for Occupational Safety and Health (NIOSH) cohorts) that the TCEQ used to inform the EtO dose-response assessment. These and other studies had high EtO exposures and there were no

available human data that provided information about the shape of the dose-response curve at low (i.e., environmentally-relevant) EtO concentrations.

- Cox regression is the preferred modeling methodology for health endpoints from cohort epidemiology studies under TCEQ guidelines (TCEQ 2015). The TCEQ evaluated fit of other dose-response models to the key individual NIOSH lymphoid cancer data, but none of these models demonstrated a superior fit compared to the standard Cox proportional hazards model. In addition, the standard Cox proportional hazards model was indistinguishable from linear over the dose range in the NIOSH study, which is consistent with a carcinogenic MOA due to a direct-acting mutagen.
- Moreover, the standard Cox proportional hazards model was statistically demonstrated to predict with reasonable accuracy the number of lymphoid cancer deaths observed in the key NIOSH cohort, which remained true in a sensitivity analysis that assumed a healthy worker effect for lymphoid cancer mortality in the NIOSH cohort. Finally, in a validation analysis, the standard Cox model based on the NIOSH dose-response assessment was statistically shown to be reasonably accurate at predicting the number of lymphoid cancer mortalities observed in the UCC cohort.
- The TCEQ selected the standard Cox proportional hazards model for lymphoid cancer mortality in males in the NIOSH cohort as the critical cancer endpoint using a 15-year EtO exposure lag (results for NIOSH males were more conservative than males and females combined). Application of USEPA age-dependent adjustment factors (ADAFs) resulted in an **ADAF-adjusted URF of 4.1E-06 per ppb (2.3E-06 per µg/m^3)** and an **ADAF-adjusted $^{chronic}ESL_{nonthreshold(c)}$ of 2.4 ppb (4.3 µg/m^3)** at an excess cancer risk level of 1 in 100,000 (policy-based per TCEQ 2015).
- The scientific validity and health protectiveness of the TCEQ's modeling and decisions are supported by the following considerations:
    - Lymphoid Cancer Risk from Cohort Studies – Human data alone are acknowledged by TCEQ and USEPA to be insufficient to classify EtO as *carcinogenic to humans*. Additionally, the standard Cox proportional hazards model of lymphoid cancer mortality did not show a relationship with EtO exposure that was statistically significantly different from zero. Therefore, by assuming a significant positive slope in the EtO-cancer association, the TCEQ is making a conservative decision to assume that EtO caused lymphoid cancer in the exposed workers of the NIOSH cohort. To further use an upper confidence limit on the slope is reasonable and conservative in the interest of protecting the public from the potential carcinogenic hazard of EtO.
    - Model Fit with the NIOSH Data – To verify that the standard Cox proportional hazards model based on the NIOSH cohort adequately predicts the original data, the model was used to predict the number of lymphoid cancer deaths based on

the individual exposure estimates for the NIOSH cohort. Both the maximum likelihood estimate and upper bound on the Cox model were reasonably accurate at predicting the total number of lymphoid cancer mortalities in the NIOSH cohort and the number in every exposure quintile. For example, while 53 lymphoid cancer deaths were observed in this cohort of 17,530 workers, the upper bound of the Cox proportional hazard model predicted 59 (95% confidence interval (CI) of 45, 78) lymphoid cancer deaths. Similarly, the Cox model neither significantly over- nor under-estimated lymphoid cancer deaths for any exposure quintile, but rather remained reasonably accurate.

- NIOSH Model Fit with the UCC Data – In a validation analysis, the Cox proportional hazards model based on the NIOSH dose-response assessment was reasonably accurate at predicting the number of lymphoid cancer deaths observed in the UCC cohort. That is, the maximum likelihood estimate (MLE) and upper bound of the Cox model for the NIOSH cohort predicted 28 (95% CI of 19, 43) and 32 (95% CI of 22, 50) lymphoid cancer mortalities for the UCC cohort, respectively, compared to the 25 actually observed in the UCC cohort. These results support the robustness of the standard Cox proportional hazards model fit to the NIOSH data for predicting lymphoid cancer deaths for other populations and exposure scenarios.

- The most recent USEPA URF for EtO was finalized in 2016 (USEPA 2016). Comparisons of the USEPA (2016) and TCEQ EtO URF are discussed in Appendix 6. The EtO hazard identification and dose-response assessment described in this document consider new data and/or analyses from the scientific literature that were not available in 2016 (e.g., Vincent et al. 2019, Marsh et al. 2019, IARC 2019, Kirman and Hays 2017) as well as new TCEQ analyses, including dose-response model predictions of the underlying NIOSH lymphoid cancer data, evaluation of the potential for healthy worker effects for EtO-specific cancer endpoints, Cox proportional hazards modeling results for multiple exposure lag durations, and validation analysis of models based on the NIOSH data using UCC data.

- Thus, the TCEQ determined that use of the standard Cox proportional hazards model to derive a URF for inhalation EtO cancer risk is strongly supported by relevant considerations (e.g., TCEQ guidance, the carcinogenic MOA, standard model fit criteria combined with accurate model predictions of the key underlying cancer data, sensitivity and validation analyses). **Accordingly, the TCEQ's ADAF-adjusted URF for EtO has a sound scientific basis and will be adopted for review of air concentration data and for use in air permit reviews.**

Table 1 provides a summary of the risk-based value from a carcinogenic evaluation of EtO for use in air permitting and air monitoring. Please refer to Section 1.6.2 of the *TCEQ Guidelines to*

Develop Toxicity Factors (TCEQ 2015) for an explanation of the various values used for review of ambient air monitoring data and air permitting. Table 2 provides summary information and the physical/chemical properties of EtO.

Table 1: Chronic Health-Based Screening Values for EtO

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
$^{chronic}ESL_{nonthreshold(c)}$ [a]	**70 yr**	**4.3**	**2.4**	**P,M,R**	**A,S,D**	**--**	**Lymphoid cancer in occupationally exposed workers**	**--**

Bold values used for air permit reviews; values have been rounded to two significant digits.

[a] Based on the ADAF-adjusted URF of 4.1E-06 per ppb or 2.3E-06 per µg/m^3 and a no significant risk level of 1 in 100,000 excess cancer risk.

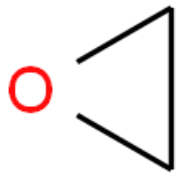
Usage:

P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:

A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2: Chemical and Physical Properties

Parameter	Value	Reference
Molecular Formula	C_2H_4O	ATSDR 1990
Chemical Structure		ChemSpider 2019
CAS Registry Number	75-21-8	ATSDR 1990
Molecular Weight	44.05 g/mol	ATSDR 1990
Physical State at 25°C	Gas	ATSDR 1990
Color/Form	Colorless gas	ATSDR 1990
Odor	Sweet, olefinic	ATSDR 1990
Synonyms	Ethylene oxide; oxirane; epoxyethane	ATSDR 1990
Solubility in water	1×10^6 mg/L	ATSDR 1990
Log K_{ow}	-0.22	ATSDR 1990
Vapor Pressure	1.095×10^3 mmHg	ATSDR 1990
Melting Point	-111°C	ATSDR 1990
Boiling Point	11°C	ATSDR 1990
Conversion Factors	1 ppm = 1.83 mg/m^3 1 mg/m^3 = 0.55 ppm	ATSDR 1990

Chapter 2 Introduction and Problem Formulation

2.1 Introduction

The Texas Commission on Environmental Quality (TCEQ) derives toxicity factors, which are chemical-specific short- and long-term health- and/or welfare-based concentrations or doses that are set to protect human health and welfare in the general public, including sensitive subgroups. These toxicity factors include the following health- and/or welfare-based values: acute and chronic inhalation Effects Screening Levels (ESLs); acute and chronic inhalation Reference Values (ReVs); chronic inhalation unit risk factor (URF) values; and chronic oral Reference Dose (RfD) and slope factor (SFo) values. The processes for developing these toxicity factors are outlined in the TCEQ's Guidelines to Develop Toxicity Factors (TCEQ 2015).

Inhalation ESLs are chemical-specific air concentrations set to protect human health and/or welfare. Exposure to an air concentration at or below the ESL is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions. ESLs are used in the air permitting process to assess the protectiveness of substance-specific emission rate limits for facilities undergoing air permit reviews. More specifically, evaluations of modeled worst-case ground-level air concentrations are conducted to determine the potential for adverse effects to occur due to the operation of a proposed facility. ESLs are screening levels, not ambient air standards. If a predicted airborne level of a chemical exceeds its ESL, adverse health or welfare effects would not necessarily be expected to occur, but a more in-depth review would be triggered. Long-term ESLs are associated with a lifetime exposure duration which is commonly assumed to be 70 years (TCEQ 2015). As alluded to above, for application in air permitting, long-term ESLs are used to evaluate modeled worst-case annual average concentrations, consistent with ton per year emission rate limits in air permits.

Health-based ESLs are based on the most sensitive adverse health effect relevant to humans for the type of assessment (i.e., noncarcinogenic or carcinogenic effect) and given duration (e.g., acute, chronic). Derivation of a ReV (generally for noncarcinogenic effects) or a URF (for carcinogenic effects) begins with a toxicity assessment involving a hazard identification and a dose-response assessment based on the chemical's mode of action. The resulting ReV and URF values are then used to calculate ESLs that correspond to no significant risk levels (e.g., the policy-based 1 in 100,000 excess risk level in TCEQ 2015).

This development support document (DSD) is a technical assessment developed and written by the TCEQ to describe the derivation of a chronic inhalation URF for ethylene oxide (EtO). The purpose of toxicity factor DSDs is to document the toxicity factor development process, including the scientific rationale for key decisions, and provide a summary of the key toxicity studies and information/data used to derive inhalation or oral toxicity factors. The following

general analytical approach is used to derive toxicity factors for chemicals: review essential data (i.e., especially dose-response) including physical/chemical properties and select key studies; conduct a mode of action (MOA) analysis; choose the appropriate dose metric; determine the POD for the key study(ies); conduct appropriate dosimetric modeling; select critical effect; and extrapolate from the adjusted POD to lower exposures based on the MOA analysis. Relevant to this assessment, the TCEQ uses the flow chart shown in Figure 1 to guide long-term ESL development for carcinogens (TCEQ 2015).

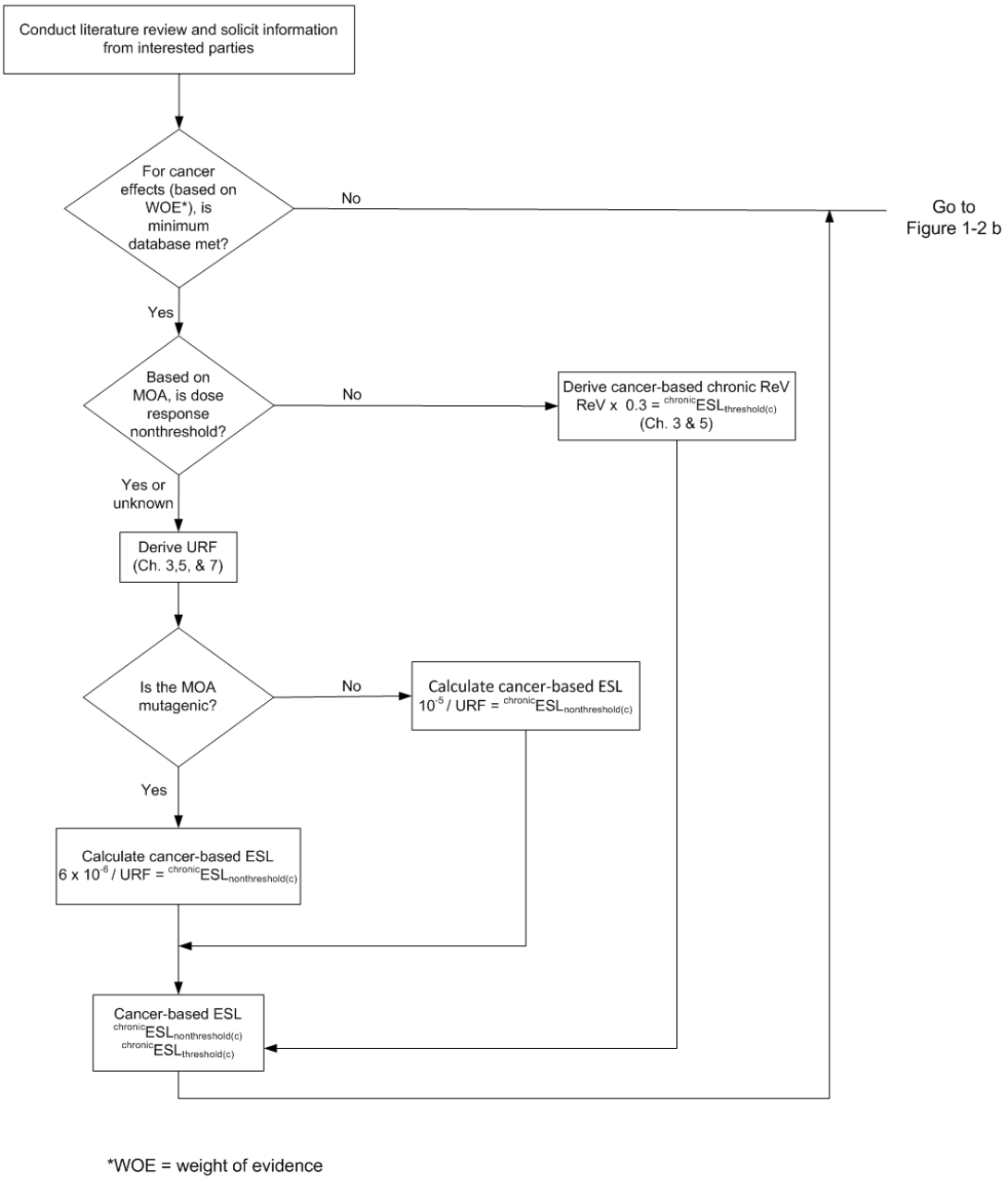


Figure 1: Based on Figure 1-2a Long-Term ESL development for air permitting (TCEQ 2015).

2.2 EtO Background and Problem Formulation

2.2.1 EtO Sources and Uses

Physical/chemical properties of EtO are summarized in Table 2.

EtO is used as a chemical intermediate in the manufacture of ethylene glycol (antifreeze), polyester, detergents, polyurethane foam, solvents, medicine, adhesives, and other products. The conversion of EtO to ethylene glycols represents a major use for EtO in the US (IARC 2012). Relatively small amounts of EtO are used in sterilization of surgical equipment and plastic, as a fumigant, and as a sterilant for food (spices) and cosmetics (IARC 2012).

Sources of EtO emissions into the air include, but are not limited to, industrial emissions or venting with other gases. Other sources of EtO air emissions include sterilizers of medical equipment and its release from commodity-fumigated materials. In 2018, EtO was being produced in the US by 9 companies at 15 facilities in 11 locations. In the US, EtO is primarily produced in Texas and Louisiana ("Ethylene Oxide Frequently Asked Questions," 2018). Based on the USEPA's 2017 National Emissions Inventory (NEI; https://www.epa.gov/air-emissions-inventories/2017-national-emissions-inventory-nei-data), Texas industry emits approximately 40% of the EtO in the US. The general population may be exposed to EtO through breathing ambient air containing EtO, smoking tobacco products, and breathing secondhand cigarette smoke ("Ethylene Oxide. 75-21-8"). Certain occupational groups (e.g., workers in EtO manufacturing or workers that use EtO to produce solvents, antifreeze, textiles, detergents, and polyurethane foam, sterilization technicians, and agricultural workers involved in fumigation) may be exposed in the workplace (IARC 2012).

EtO is also produced endogenously in the body due to oxidation of ethylene, which is generated by intestinal bacteria, and lipid peroxidation of unsaturated fats, methionine, and hemoglobin (Kirman and Hays 2017).

2.2.2 EtO Monitoring and Modeling

After the release of USEPA's 2014 National Air Toxics Assessment (NATA), the USEPA began to evaluate facilities that emit EtO. The 2014 NATA estimated that EtO substantially contributes to potential elevated cancer risks in some census tracts across the US (https://www.epa.gov/national-air-toxics-assessment/nata-frequent-questions#results); this risk is largely driven by the USEPA's recently derived URF (USEPA 2016). Because of concerns related to cancer risk from EtO emissions raised by the NATA, two EtO sterilizing facilities closed in 2019 and two suspended operations (based on available information). The US Food & Drug Administration (USFDA) has warned the public about potential medical device shortages from EtO sterilizer facility closures (https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures). According to the USFDA, EtO is the likely sterilant for medical devices made from certain polymers (plastic or resin), metals, or glass, or that have multiple layers of packaging or hard-to-reach places (e.g., catheters). Approximately fifty percent of all sterile medical devices in the US are sterilized with EtO ("Ethylene Oxide Sterilization for Medical Devices," 2019). In order to prevent shortages of critical medical equipment, USFDA has been

working with medical device manufacturers to find alternative locations and methods for sterilization.

Between October 1, 2018 and March 31, 2019, the USEPA conducted air monitoring for EtO in various locations in the United States and found that the levels of EtO concentrations that are considered to be "urban background" are in the range of 0.1-0.2 ppb (https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-data-summary-national-air-toxics-trends). In regard to longer-term levels around EtO-emitting facilities, as an example, the mean and 95th percentile modeled 5-year concentrations for one sterilizer facility were ≈0.17 and 0.50 ppb, respectively (https://www.atsdr.cdc.gov/HAC/pha/sterigenic/Sterigenics_International_Inc-508.pdf).

2.2.3 Problem Formulation

In early 2017, as part of a standard yearly review of newly-derived toxicity factors, the TCEQ Toxicology, Risk Assessment, and Research Division (TRARD) reviewed the USEPA's cancer-based toxicity factor derivation for EtO (finalized in 2016) to determine if the TCEQ would provisionally adopt the USEPA's number for use in deriving protective concentration levels (PCLs) for the Texas Risk Reduction Program (TRRP). In March 2017 the TRARD decided that, instead of adopting the USEPA's EtO toxicity factor, it would derive an interim EtO toxicity factor for the TCEQ's use in the remediation program with a plan to conduct a complete future evaluation of EtO inhalation carcinogenicity for use in both air permitting and remediation. The TCEQ decided to complete this thorough evaluation because EtO is emitted in Texas and has been determined to be a carcinogen by the International Agency for Research on Cancer (IARC 2012), by the World Health Organization (WHO 2003), and by the US Environmental Protection Agency (USEPA 2016).

The purpose of the following assessment is to derive a chronic inhalation ESL and URF for EtO following TCEQ guidelines and practices for use in TCEQ's air permitting and remediation programs, respectively.

2.2.4 Document and Review History

In August 2017, the TCEQ announced a 90-day public information request for scientific information about EtO that may be of use in the TCEQ's review. The TCEQ then completed a systematic review and dose-response assessment of EtO carcinogenicity and released the draft DSD on June 28, 2019 for public comment, which ended in late September. The TCEQ reviewed and responded to the public comments and revised the draft DSD in response to the scientifically justified public comments. The TCEQ then posted a revised draft DSD and responses to public comments (both dated January 31, 2020) and engaged the Risk Science Center at the University of Cincinnati for an expert peer review to determine if the TCEQ's proposed EtO URF is scientifically adequate and appropriate for estimating cancer risk at

ambient (low-level) concentrations. The peer review was completed, and a final report sent to TCEQ on April 30, 2020. Based on the peer review the TCEQ produced this final draft of the DSD that included scientifically justified revisions recommended by the peer reviewers.

Chapter 3 Hazard Assessment: Carcinogenic Potential

3.1 Relevant Data

Generally, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered by the TCEQ either to be "Carcinogenic to Humans" or "Likely to Be Carcinogenic to Humans" (TCEQ 2015). The TCEQ considers published toxicity values and their respective key studies as a starting place for gathering toxicity information to develop a DSD. However, because existing toxicity factors or guideline levels may be outdated, the TCEQ also evaluates peer-reviewed studies available after the date these toxicity factors or guideline levels were published to ensure that the latest data are considered prior to developing a toxicity factor. EtO has been evaluated for carcinogenic potential by IARC (2012), the USEPA (2016), and the WHO (2003). These agencies' carcinogenic classifications for EtO are provided in Table 3. The TCEQ used the IARC and the USEPA evaluations as the starting points for the carcinogenic weight of evidence hazard assessment and added relevant studies that were published after 2016, the date of the most recent agency's evaluation.

Table 3: Carcinogenic Weight of Evidence

Group	Classification
IARC (2012)	Group I: Carcinogenic to humans
USEPA (2016)	Carcinogenic to humans
WHO (2003)	Highly likely to be carcinogenic to humans

3.1.1 Summary of Human Studies

In their analysis, USEPA (2016) reviewed more than 25 epidemiology studies about EtO carcinogenicity published between 1982-2011 (Chapter 3 and Appendix A & J of USEPA 2016). These studies largely encompassed occupational cohorts of workers in sterilization facilities and EtO production or chemical workers in the United States or Europe. Many of the studies represented updates of earlier cohort analyses, such that there were ≈12 cohorts of workers studied in total. The USEPA's overall conclusion from these studies is that there is some evidence of increased cancer risk with increasing dose of EtO at particular tumor sites, principally for lymphohematopoietic cancers, with more recent studies suggesting an association with breast cancer (Section A.3, page A-36). However, they also concluded that there are inadequacies and limitations of the epidemiology database and so the epidemiology

evidence is not conclusive. The details of several of the key cohort studies are discussed elsewhere in this document (Section 4.1.2).

Two recent reviews of the EtO epidemiology data have been published: Marsh et al. (2019) and Vincent et al. (2019). The purpose of the Marsh et al. (2019) study was to "conduct a systematic literature review and meta-analysis of studies of lympho-hematopoietic cancers (LHC) and breast cancer risk among persons occupationally exposed to ethylene oxide." Of the studies included in the Marsh analysis, only one (Divine 1990) was not included in the USEPA (2016) review. The Divine (1990) study was unpublished data obtained by the Marsh et al. team and used in their meta-analysis. Marsh et al. conducted a study quality analysis, and in addition used the relative risk (RR) estimates from 11 studies to calculate a meta-RR estimate for all LHC (meta-RR of 1.48, 95% Confidence Interval (CI) 1.07-2.05) and 5 studies to calculate a meta-RR estimate for breast cancer (meta-RR of 0.97, 95% CI 0.80-1.18). The authors noted that the RRs for LHC studies published in the 2000s and 2010s were lower than those for studies published in the 1980s and 1990s. The authors concluded that those studies that are most informative (i.e., those published more recently and of higher study quality) do not support an association between increased exposure to EtO and increased risk of LHC or breast cancer. Marsh et al. (2019) noted that the risk estimates that they used were based on estimates compared to the general population, and not using internal controls. The choice of using internal or external referent groups can affect the conclusions reached by an epidemiology study, and the concept is discussed more in the following Section 3.1.1.2 in relation to the healthy worker effect.

Vincent et al. (2019) performed focused reviews of the epidemiological, toxicological, and MOA evidence of EtO carcinogenicity, focusing on studies identified in USEPA (2016). The authors conducted a study quality evaluation for the epidemiology information and divided the studies into overall low-, medium-, and high-quality categories. Vincent et al. found that for both breast cancer and LHC, the studies in the high and medium quality categories did not find statistically significant associations between EtO and cancer, whereas those in the low-quality categories did find positive, statistically significant associations. A meta-analysis of risk estimates from the three high-quality LHC studies generated a meta-RR of 0.98 (0.81, 1.18), from the two medium-quality studies a meta-RR of 1.31 (0.83, 2.07), and from the three low-quality studies a meta-RR of 3.55 (2.2, 5.75). A meta-analysis of risk estimates from the three high-quality breast cancer studies generated a meta-RR of 0.92 (0.84, 1.02). There were not enough breast cancer studies in the medium or low-quality groups (one each) to perform a meta-analysis. The authors concluded from these analyses that higher quality epidemiology studies provided no evidence of increased risk of LHC or breast cancers with EtO exposure.

In addition, a new study published in 2020 investigated the 2013-2016 data from the National Health and Nutrition Examination Survey (NHANES) on EtO blood levels in the general US population and self-reported cancer diagnoses (Jain 2020). Data from 3,955 adults were

evaluated for the cancer analyses, of whom 1,973 were female (see Table 1 of the study). The author found no association between measured blood EtO and breast cancer in women (see the text and Table 4 of Jain 2020; p-value=0.52). While this study had the benefit of considering the general population exposed to environmentally-relevant EtO concentrations as well as much higher EtO doses from smoking, it did not have the long-term exposure information or the follow-up of the occupational exposure cohorts discussed above.

3.1.1.2 Healthy Worker Effect

The healthy worker effect is a form of bias in epidemiology studies that relates to the reference population. In theory, a population of workers may be healthier and less likely to develop the disease of interest compared to the general population, and by comparing worker populations to the general population (the external reference group) in the calculation of standardized mortality rates (SMRs) or standardized incidence rates (SIRs), the effect of the exposure on the workers may be underestimated. Therefore, if there is evidence of a healthy worker effect, then use of an internal reference population (a similar group of workers who did not have the exposure of interest) is warranted.

The epidemiological analyses of the studies cited in this evaluation often used both external and internal referents and therefore this choice requires evaluation. Mikoczy et al. (2011) is a case in point. While study authors suggest that a healthy worker effect was indicated by significantly decreased overall mortality and cardiovascular disease mortality, this cannot be assumed to necessarily extend to the incidence of a specific cancer. For example, the suggestion of the authors of Mikoczy et al. (2011) that a finding of significantly decreased overall mortality and cardiovascular disease mortality is indicative of a healthy worker effect for breast cancer incidence is inconsistent with the results of a relatively recent and large study (366,114 workers) conducted specifically to examine the potential for the healthy worker effect in cancer incidence studies (Kirkeleit et al. 2013). In Kirkeleit et al. (2013), all-cause mortality and both ischemic heart disease and circulatory system disease mortality were statistically significantly decreased in male workers (n=283,002) and female workers (n=83,112) compared to the general population (Table 3 of the study), consistent with similar findings in Mikoczy et al. (2011). In contrast, the SIRs for lymphoid and hematopoietic cancers in male workers and female workers in Kirkeleit et al. were 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27), respectively, consistent with the lack of a statistical difference as in Mikoczy et al. (i.e., SIR of 1.35 (0.54, 2.78) for lymphohematopoietic cancer; Table 5 of the study). Similarly, the Kirkeleit et al. (2013) study found that breast cancer incidence in over 83,000 female workers was as expected based on the general population (i.e., SIR of 1.02 (0.95, 1.09)). This strongly supports that the breast cancer SIR of 0.52 for the lowest cumulative exposure group in Mikoczy et al. (2011) is an anomalous study artifact that should not be used for internal analyses. This SIR was not based on a reference population only, but rather on workers who were both unexposed and who were exposed to lower levels of EtO. Similarly, for other studies such as Steenland et al. (2003),

a presumption of the presence of a healthy worker effect for breast cancer incidence does not appear to be a robustly supported justification for internal analyses, which have the potential to use less reliable/stable referent rates based on much smaller worker populations than that used in Kirkeleit et al. (2013).

In conclusion, while the TCEQ will evaluate all applicable findings from relevant epidemiology studies, analyses that used external referent groups in drawing conclusions are of higher priority, unless there is evidence demonstrating the presence of biases such as the healthy worker effect for the endpoint of interest, which would necessitate the use of an internal referent group.

3.1.2 Summary of Animal Studies

USEPA (2016) and Vincent et al. (2019) reference three chronic inhalation rodent EtO exposure studies, and a fourth is described in IARC (2012). The National Toxicology Program (NTP 1987) exposed B6C3F1 mice (50/group) to 0, 50, or 100 ppm EtO for 6 hours/day, 5 days/week, for 2 years. They observed a dose-dependent increase in lung tumors in male and female mice (statistically significant at 100 ppm) and a dose-dependent increase in mammary tumors (statistically significant at 50 ppm only), uterine cancers, and malignant lymphomas (statistically significant at 100 ppm) in female mice (statistical analyses are as reported by USEPA 2016).

Adkins et al. (1986) exposed female A/J mice (30/group) to 0, 70, or 200 ppm EtO for 6 hours/day, 5 days/week for 6 months. The authors repeated the study and both times observed statistically significant increases in frequency and incidence of lung adenomas in EtO-treated mice (significant at both 70 and 200 ppm).

Lynch et al. (1984a, b), exposed male F344 rats (80/group) to 0, 50, or 100 ppm EtO for 7 hours/day, 5 days/week for 2 years. The authors observed dose-dependent increases in splenic mononuclear cell leukemia (statistically significant at 50 ppm and 100 ppm), testicular peritoneal mesothelioma, and brain mixed cell glioma (both significant at 100 ppm). The Snellings et al. research group exposed male and female F344 rats (120/group) to 0, 10, 33, or 100 ppm EtO for 6 hours/day, 5 days per week, for 2 years (Snellings et al. 1984, Garman et al. 1985). Male and female rats had a dose-dependent increase in splenic mononuclear cell leukemia (significant starting at 33 ppm in males and at 10 ppm in females), and in primary brain tumors (significant starting at 33 ppm in males and at 100 ppm in females). The male rats also showed a dose-dependent increase in testicular peritoneal mesothelioma (significant at 100 ppm).

Therefore, laboratory animal studies have shown that chronic inhalation of EtO causes tumors in multiple organ systems, including lymphohematopoietic tumors in rats and mice, and mammary tumors in mice, but not in rats.

3.2 Mode of Action (MOA)

For the purposes of toxicity factor development of putative carcinogens, the TCEQ uses MOA information for two primary purposes: (1) as part of the weight of evidence for the carcinogenic classification; and (2) to inform low-dose extrapolation for the dose-response assessment. As per TCEQ guidelines (2015) and shown in Figure 1, either a mutagenic or an unknown MOA dictate a non-threshold approach to dose-response modeling (i.e., deriving a URF through linear low-dose extrapolation).

For this assessment the TCEQ evaluated EtO MOA information presented in USEPA (2016), IARC (2012), and Vincent et al. (2019). These analyses provide information showing that EtO is mutagenic and likely clastogenic, with little evidence available to support other potential pathways of carcinogenesis (e.g., cytotoxicity with regenerative cell proliferation, immune suppression, or epigenetic mechanisms). Although the MOA analyses in the aforementioned assessments could certainly be further evaluated and refined, the TCEQ has determined that the weight of evidence supports a mutagenic and likely clastogenic MOA for EtO. This conclusion was applied to both the hazard and dose-response assessments in this document.

The following section summarizes MOA information that was evaluated in USEPA (2016), IARC (2012), and Vincent et al. (2019). Unless otherwise specified, exposure durations for animal experiments were 6 hours/day, 5 days/week for the noted number of weeks.

3.2.1 MOA Evidence Summary

When EtO is inhaled into the lungs, it rapidly partitions to the blood where it is distributed systemically. There are two pathways to directly de-toxify EtO in the blood stream: (1) hydrolysis to ethylene glycol then to oxalic acid, formic acid, and carbon dioxide; and (2) glutathione conjugation (pathways shown in Figure 3-1 of USEPA, 2016). If not detoxified through these pathways, EtO (an epoxide) can directly cause alkylation of proteins or DNA through a S_N2-type chemical reaction (i.e., a substitution-nucleophilic-bimolecular reaction). There is evidence that EtO can cause alkyl adducts on DNA (Wu et al. 1999, Walker et al. 1992a, van Sittert et al. 2000, Rusyn et al. 2005, Walker et al. 1990) and hemoglobin protein (Rusyn et al. 2005, Walker et al. 1992b) throughout the body in rodents in a dose- and duration-responsive manner at concentrations as low as 4-week exposures to 3 ppm EtO (Wu et al. 1999). There is also evidence of EtO-associated hemoglobin protein adducts in humans (van Sittert et al. 1993, Schulte et al. 1992, Yong et al. 2001). Several studies have investigated EtO-associated DNA adducts in people with occupational exposure to EtO, but statistically significant increases have not typically been observed (Yong et al. 2007, van Delft et al. 1994), possibly because of a high level of inter-individual variability in levels of the most common EtO-associated DNA adduct (Yong et al. 2007).

Once DNA adducts are formed, these can be repaired by DNA repair machinery, although mis-repair or replication through an EtO-induced DNA adduct or through a mis-repaired DNA strand can lead to DNA mutations or possibly to chromosomal breaks (pathways shown in Figure 10 of Vincent et al. 2019). Increases in DNA base mutations with EtO exposure have been observed in the *Hprt* gene in splenic lymphocytes in rats exposed by inhalation for 4 weeks to 50-200 ppm (van Sittert et al. 2000, Tates et al. 1999, Walker et al. 2000). There is also evidence for EtO-induced mutagenesis in bone marrow in transgenic mutation-reporter mice exposed for 48 weeks (but not in mice exposed for 12 or 24 weeks) to 100 or 200 ppm EtO (Recio et al. 2004), although some inconsistency in responses has been observed, with both negative and positive findings in Big Blue™ reporter mice with 4 weeks of EtO exposure to 50, 100, or 200 ppm EtO (Walker et al. 1997, Sisk et al. 1997, Walker et al. 2000). In addition, *Kras* gene mutations were more frequent in the lung tumors from mice treated with 50 or 100 ppm EtO for 2 years in the NTP study compared with lung tumors from control mice (Hong et al. 2007). A few studies have been conducted in humans with occupational exposures to EtO that have shown variable associations between EtO exposure and mutations in the *HPRT* gene of peripheral blood lymphocytes; however, low sample sizes in these studies make interpretation of the results difficult (Tates et al. 1995, Tates et al. 1991, Major et al. 2001).

Cytogenetic changes associated with EtO exposure in humans and rodents have been more extensively studied than point mutations, and Figure 10 of Vincent et al. (2019) outlines a pathway by which cytogenetic changes could occur following EtO exposure. In experimental exposures of rats to EtO via inhalation, shorter exposures (< 12 weeks) to EtO at concentrations > 50 ppm induced dose-dependent increases in sister chromatid exchanges (SCEs), but not typically chromosomal aberrations or micronuclei in peripheral or splenic lymphocytes (Kligerman et al. 1983, Preston and Abernethy 1983, van Sittert et al. 2000, Lorenti Garcia et al. 2001). Donner et al. (2010) exposed mice to 0, 25, 50, 100, or 200 ppm EtO for 6, 12, 24, or 48 weeks and observed increases in chromosomal aberrations in peripheral blood lymphocytes at 100 ppm and above with 12 weeks of exposure, at 50 ppm and above with 24 weeks of exposure, and at 25 ppm and above with 48 weeks of exposure. These findings demonstrate dose- and duration-responsive changes in SCEs in rats and chromosomal aberrations in mice with inhalation exposure to EtO.

In humans, various investigators have studied the association between EtO exposure (typically occupational) and cytogenetic changes. The following summary focuses on results from studies with more than 15 individuals in each exposure group. Karelova et al. (1987) found that EtO-exposed workers had significantly higher numbers of chromosomal aberrations in peripheral blood lymphocytes compared to control workers (exposure range of 0-4.8 ppm with duration range of 1-15 years). A study of US hospital sterilization workers exposed to >0-32 ppm-hours found higher SCEs in peripheral blood lymphocytes than unexposed controls, and those exposed to > 32 ppm-hours had a further significant increase in SCEs, but there was no increase

in micronuclei associated with EtO exposure (Schulte et al. 1992). Mayer et al. (1991) observed a higher level of SCEs in peripheral blood lymphocytes in hospital sterilization workers compared to controls (mean exposure duration was 8 years with a concentration range of < 0.1-2.4 ppm EtO), but no difference in micronuclei or chromosomal aberration frequency. van Sittert et al. (1985) also did not find an association between chromosomal aberrations in workers in an EtO-manufacturing plant (exposure duration 1-5 years or 6-14 years to <0.05-8 ppm EtO) compared to matched controls, although they did observe a positive correlation between years of employment and chromosome breaks. Sarto et al. (1984) found that workers in hospital sterilizing units exposed to EtO had dose-dependently higher SCEs in peripheral blood lymphocytes compared to controls (low exposure group mean time-weighted 8-hour average of 0.35 ppm, high exposure group 10.7 ppm). There was also an increase in chromosomal aberrations, particularly in the high exposure group. Tomkins et al. (1993) investigated EtO-exposed engineers (< 1 ppm EtO time-weighted 8-hour average) and matched controls and found no difference in chromosomal aberrations or SCEs. Hogstedt et al. (1983) reported increased chromosomal aberrations but not micronuclei or SCEs in peripheral blood lymphocytes, and increased micronuclei in bone marrow cells of occupationally-exposed workers (EtO time-weighted 8-hour average < 1 ppm with 1.7-3.2 years mean exposure duration) compared to matched controls. Richmond et al. (1985) investigated cytogenetic changes in the peripheral lymphocytes of workers exposed to EtO while sterilizing disposable medical devices (1-10 years of exposure to 1-40 ppm EtO). The study authors found increased SCEs and chromosomal aberrations in the high exposure group compared to controls, but not in the lower exposure group compared to controls. Ribeiro et al. (1994) found increased micronuclei and chromosomal aberrations in lymphocytes of sterilization workers exposed to EtO (3-14-year exposure duration, 2-5 ppm EtO) compared to controls. These studies provide evidence of cytogenetic changes in peripheral blood lymphocytes and bone marrow cells associated with occupational exposures to EtO.

3.2.2 WOE for a Mutagenic MOA

In this section, based on Section 3.4.3 of USEPA (2016) and the data discussed above, the evidence for a mutagenic MOA for EtO carcinogenicity is examined under the MOA framework in the USEPA's 2005 Guidelines for Carcinogen Risk Assessment (USEPA 2005a). This MOA framework is organized around the Hill considerations (Hill 1965). These considerations are denoted in *underlined italics* in the discussion below. Unless otherwise noted, specific references for the statements below can be found in Sections 3.3 and 3.4 of USEPA (2016) and in the MOA summary in Section 3.2.1 of this DSD.

The USEPA hypothesized that EtO carcinogenicity is based on a mutagenic MOA, which is presumed to apply to all the tumor types. The hypothesized key events are: (1) DNA adduct formation by EtO, which is a direct-acting alkylating agent; (2) active processes such as errors in DNA repair or replication resulting in DNA mutations in oncogenes and tumor suppressor

genes, as well as chromosomal alterations; (3) clonal expansion of mutated cells during later stages of cancer development; eventually causing (4) tumor formation. Mutagenicity is a well-established potential cause of carcinogenicity; many, but not all, mutagens are carcinogens (USEPA 2005a). More details about specific events in steps 1 and 2 of this process are described in Figure 10 of Vincent et al. (2019).

Is the hypothesized MOA sufficiently supported in the test animals?

Numerous studies have demonstrated that EtO forms protein and DNA adducts in mice and rats. In addition, increases in reporter gene mutations have been observed in the lung, T-lymphocytes, bone marrow, and testes of transgenic mice and in T-lymphocytes of rats exposed to EtO via inhalation at concentrations similar to those inducing tumors in the rodent carcinogenesis bioassays. While stronger proof would be provided by, for example, evidence of mutations and DNA damage in target tissue at *in vivo* exposure concentrations ≤ those that induced tumors (see Section 5.7.5.1.2 of TCEQ 2015), most of the studies did not conduct such assays. There is also some evidence from rodent inhalation studies that levels of EtO similar to those that cause cancer will induce SCEs and chromosomal aberrations in mice, although the results are not consistent. Donner et al. (2010) observed a clear duration effect in mice, with chromosomal aberrations being induced at the same EtO exposure levels as were used in the cancer bioassays only following longer exposure durations (≥12 weeks). In addition, in tumors from EtO-exposed mice in the cancer bioassays, shifts occurred in the mutational spectra of the proto-oncogenes *Hras* and *Kras*, as well as the tumor suppressor *Trp53*, that were consistent with EtO forming DNA adducts on purine bases. The evidence for a mutagenic MOA for EtO has *strength* (i.e., statistically significant increases in DNA damage or mutations with EtO exposure) and *consistency* (i.e., similar results across different experimental systems).

Specificity (i.e., the concept that a single cause is associated with a single disease) is not expected for a multisite mutagen and carcinogen such as EtO (USEPA 2005a). Laboratory animal studies have shown that EtO causes tumors in both sexes of more than one species, in multiple organ systems, and can induced tumors by more than one route of exposure (see Section 3.2 of USEPA 2016). In addition to direct DNA reactivity, tumors observed at multiple sites, in multiple species, and from multiple routes of exposure is a property for mutagenicity as the key event for a mutagenic MOA (USEPA 2007). A *temporal relationship* (that is, early events occurring before late events) is evident, with DNA adducts, point mutations, and chromosomal effects observed in acute and subchronic assays.

Dose-response relationships (i.e., increasing response with increasing dose or concentration exposure) have been observed between EtO exposure *in vivo* and DNA adducts, SCEs, and *Hprt* and *Trp53* mutations.

Biological plausibility and *coherence* (i.e., that the MOA is consistent with current biological understanding and with other known carcinogenic agents) is clearly appropriate because EtO is a direct-acting alkylating agent that can form DNA adducts. Such adducts can lead to mutation formation which, if it occurs in cancer-relevant genes such as proto-oncogenes or tumor suppressor genes, can contribute to cancer formation.

From the perspective of alternative hypotheses to a mutagenic MOA, there is no compelling evidence of other potential MOAs such as cytotoxicity and regenerative proliferation.

Is the hypothesized MOA relevant to humans?

In general, in the absence of disputing evidence, chemicals that are systemic mutagens in test animals (such as is demonstrated for EtO above) are presumed to be human mutagens as well. In addition, there is some human evidence supporting a mutagenic MOA for EtO carcinogenicity. Several human studies found exposure-response relationships between EtO exposure and hemoglobin adducts (e.g., van Sittert et al. 1993, Schulte et al. 1992), similar to findings in rodent cells. There has been limited investigation of DNA adducts in EtO-exposed humans, but EtO has yielded positive results in *in vitro* mutagenicity studies of human cells. There is further evidence as well for EtO-induced chromosomal aberrations, SCEs, and micronucleus formation in peripheral blood lymphocytes in humans, with some evidence of positive relationships with increasing exposure concentration. While this data informs the EtO MOA, hemoglobin adducts and genotoxic effects such as chromosomal aberrations in humans should not be characterized as directly supporting a mutagenic MOA.

USEPA (2016) and IARC (2012) conclude that the WOE supports a mutagenic MOA for EtO carcinogenicity. Although other processes might contribute to the development of EtO-induced cancers and some of the genotoxic endpoints investigated in humans are not mutations (e.g., cytogenetic changes), the TCEQ agrees that the available evidence best supports direct genotoxicity/mutagenicity as the putative MOA mediating EtO-induced carcinogenicity (USEPA 2016). However, uncertainties remain. These include, for example, a lack of data for clear demonstration that early events (i.e., mutations) occur at earlier time points and at lower doses than later events (i.e., tumor formation), and the quality of many of the studies is uncertain, particularly because most were conducted before contemporary guidelines for genotoxicity assays and (in the case of the human studies) with low samples sizes and potentially poor exposure assessments. In addition, there is little available data to test alternative MOA hypotheses, such as cytotoxicity and regenerative hyperplasia. However, despite these shortcomings, the TCEQ still considers that the weight of evidence best supports a putative MOA of direct genotoxicity/mutagenicity for EtO carcinogenicity. As per TCEQ guidelines (2015) and shown in Figure 1, either a mutagenic or an unknown MOA dictate a non-threshold

approach to dose-response modeling (i.e., derivation of a URF through linear low-dose extrapolation).

3.3 Overall Carcinogenic Hazard Determination for EtO

In making the carcinogenic hazard determination for EtO, the TCEQ considered the human, animal, and MOA information together, as well as the evaluations by other groups including USEPA (2016) and IARC (2012).

USEPA (2016) considered the human study evidence of EtO carcinogenicity to be substantial but inconclusive, and IARC (2012) determined that the human evidence was limited. These determinations are consistent with the recent reviews by Marsh et al. (2019) and Vincent et al. (2019), particularly when considering the findings using the external referent population (see Section 3.1.1.2 on the healthy worker effect). The TCEQ concurs with USEPA and IARC's determinations that the human epidemiological evidence showing that EtO is carcinogenic is limited and inconclusive at best. EtO shows little human carcinogenic potential given the equivocal results from the epidemiology studies despite occupational exposure to EtO concentrations that were thousands to millions of times higher than environmentally-relevant levels.

The TCEQ agrees that since the epidemiological evidence is less than convincing, additional lines of evidence are required for the EtO carcinogenic classification. Both IARC (2012) and USEPA (2016) considered the animal evidence of EtO carcinogenicity to be sufficient. Four chronic inhalation exposure studies of EtO have shown dose-dependent increases in:

- lung tumors in male and female mice,
- mammary tumors, uterine tumors, and malignant lymphomas in female mice,
- leukemia and brain tumors in male and female rats, and
- testicular tumors in male rats.

Given this information the TCEQ concurs that there is sufficient evidence of EtO carcinogenicity in animals.

As discussed extensively in Section 3.2, the TCEQ determined that direct genotoxicity/mutagenicity is the likely MOA for EtO carcinogenesis, which can in theory apply to any tumor site. USEPA (2016) and IARC (2012) came to the same conclusion.

Based on this information the TCEQ determines that EtO is *likely to be carcinogenic to humans*, and so in the following chapter the agency conducted a carcinogenic dose-response assessment for EtO. Considering the admittedly inconclusive human evidence for EtO-induced cancer in

workers exposed long-term to extremely high EtO concentrations[a], both the classification of EtO as *carcinogenic* or *likely carcinogenic to humans* and the derivation of carcinogenicity-based toxicity factors by the TCEQ and other regulatory agencies may be viewed as conservative. In the following section the TCEQ makes a hazard determination for tumor sites that are likely to be associated with EtO exposure in humans.

3.3.1 Hazard Assessment for Specific Tumor Sites Associated with EtO Exposure

While animal and human studies have shown associations between EtO exposure and cancer at multiple tumor sites, most of the evidence as well as the evaluations by USEPA (2016), IARC (2012), Marsh et al. (2019), and Vincent et al. (2019) have focused on two cancers: lymphohematopoietic cancers and breast cancers. Given that there is little evidence for other EtO-associated tumor types in humans, the TCEQ in this review also focuses on the evidence for these two cancers.

Regarding carcinogenic classification under USEPA (2005a), USEPA (2016) states that there is substantial evidence that EtO exposure is causally associated with lymphohematopoietic cancers, although altogether the human evidence is inconclusive. The TCEQ concurs with USEPA that the epidemiological evidence for EtO-induced lymphohematopoietic cancer is less than conclusive.

3.3.1.1 Site-Specific Carcinogenic Hazard Determinations for EtO

There is epidemiological evidence, albeit inconsistent, for associations between EtO exposure and lymphohematopoietic cancer and female breast cancer in highly exposed workers. USEPA (2016) uses both lymphohematopoietic cancer and female breast cancer to derive URFs. The TCEQ concurs with USEPA that while the epidemiological evidence for EtO-induced lymphohematopoietic cancer is less than conclusive, it may be used to derive a URF. Thus, like USEPA (2016), the TCEQ has adopted lymphohematopoietic cancer as a key cancer endpoint.

[a]Epidemiological evidence would be expected to be conclusive for cancer if EtO were a particularly potent carcinogen considering the large number of workers (both male and female) that were exposed long-term to extremely high EtO concentrations; such as the 17,500+ male and female workers in the NIOSH cohort exposed to long-term means (3.5-4.6 ppm EtO) up to 2,000,000 times higher than central tendency environmental levels (using background and environmental exposure means ≈0.0024-0.0034 ppb per USEPA 2016).

However, while the TCEQ and USEPA (2016) also acknowledge that the epidemiological evidence for EtO-induced breast cancer is less than conclusive, the TCEQ assesses the strength of evidence for EtO-induced breast cancer as particularly weak. In the following section the TCEQ details a more in-depth WOE evaluation for the potential causal relationship between EtO exposure and breast cancer.

3.3.1.1.1 Breast Cancer WOE

3.3.1.1.1.1 Epidemiological Evidence

The WOE based on Table 4 below shows that the SIRs/SMRs across individual EtO studies of breast cancer are consistently not statistically significantly elevated, most being less than 1.[b] Considering these results, it is not surprising that two recent meta-analyses of EtO studies that have examined breast cancer reported meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded, "Evaluations of workers exposed during sterilization processes do not support the conclusion that EO exposure is associated with an increased risk of breast cancer." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." These meta-analysis studies are highlighted in the table below. Across studies, the weight of epidemiological evidence that EtO is associated with increased breast cancer risk is exceptionally weak.

Table 4: Human Studies Relevant to the Breast Cancer Weight of Evidence

Study Type	Workers (n)	EtO Exposure Level (ppm)	Observed (O)	Expected (E) [a]	O/E (95% CI)
Individual Studies					
Steenland et al. (2003)	7,576 female workers	Median ≈14 ppm-years; Mean >1 ppm [b]	230 [c]	258.4	**0.89** [d] (0.78, 1.01)
Steenland et al. (2004)	18,235 workers (≈55% female)	Mean of 26.9 ppm-years	103	104 [e]	**0.99** (0.84, 1.17) **0.99** [f] (0.81, 1.20)

[b] Table 4 uses external referents for individual studies, as internal analyses appear not to be scientifically justified for breast cancer (Section 3.1.1.2).

Study Type	Workers (n)	EtO Exposure Level (ppm)	Observed (O)	Expected (E) [a]	O/E (95% CI)
	only female workers				
Mikoczy et al. (2011)	2,046 workers (≈60% female) 615 female 287 female 295 female	Means ≤1.11 ppm; Peaks up to 40-75 ppm Mean of 0.02 ppm in lowest cumulative exposure group Mean of 0.021 ppm in middle cumulative exposure group Mean of 1.11 ppm in highest cumulative exposure group	33	38.54	**0.86** [g] (0.59, 1.20) **0.52** [h] (0.25-0.96) 1.06 (**0.58**, 1.78) 1.12 (**0.65**, 1.79)
Norman et al. (1995)	928 female	TWA 50-200 ppm; 5-20 ppm post-corrective action 1980	12	7.64	1.57 [I,j] (**0.90**, 2.75)
Coggon et al. (2004)	1,012 female	TWA generally < 5 ppm; Peaks up to > 700 ppm	11	13.1	**0.84** [k] (0.42, 1.50)
Hogstedt et al. (1986)	153 female	TWA 20±10 ppm	0	---	**No breast cancer reported**
Meta-Analysis Studies					
Marsh et al. (2019) [l]					**0.97** (0.80, 1.18)
Vincent et al. (2019) [l]					**0.92** (0.84, 1.02)

TWA - time-weighted average

[a] Based on external referent US population; see the text for information regarding why a healthy worker effect should not be expected for breast cancer incidence, an endpoint relied upon by USEPA (2016).

[b] Using the 233 cases with interviews as a surrogate, mean exposure level would be expected to be > 1 ppm since the mean is higher than the median in a lognormal distribution, median cumulative exposure for the 233 cases was 14.0 ppm-years, and mean years exposed was 13.0 (Table 2 of the study), so mean cumulative exposure >14 ppm-years/mean duration of 13 years = >1 ppm mean exposure.

[c] From Table 3 of the study based on workers whose exposure did not lag out to zero using a 15-year lag period, consistent with USEPA (2016) and TCEQ; expected (E) value of 258.4 was calculated (i.e., E=O/0.89).

[d] For a 15-year lag, consistent with that used by USEPA (2016) and TCEQ.
[e] Inferred from Steenland et al. (2004) Table 1.
[f] Breast cancer did not show any overall excess, although there was an excess in the highest cumulative exposure quartile (>12,322 ppm-days) using a 20-year lag and internal exposure-response analyses found a positive trend for breast cancer using the log of cumulative exposure with a 20-year lag but not with cumulative exposure (Tables 1, 5, and 8 of study).
[g] From Table 3 of Mikoczy et al. (2011) and includes induction latency period of ≥15 years, consistent with that used by USEPA (2016) and TCEQ.
[h] This statistically significantly decreased breast cancer risk occurred in female workers exposed to a mean of ≈20 ppb EtO; this inordinately decreased SIR for the lowest cumulative exposure group produced statistically increased SIRs for higher cumulative exposure groups which did not experience increased breast cancer risk compared to the general population despite EtO mean exposures up to ≈1,110 ppb and more robust female worker data suggest that it represents an anomalous study artifact.
[i] For the most appropriate method identified by the study authors (Method 2) for the longest follow-up period (through 1987) with the most appropriate/matching U.S. Surveillance, Epidemiology, and End Results (SEER) Program rates (through 1987) used to calculate the expected number (E).
[j] Includes two breast cancers diagnosed within 1 month of employment; reasonably excluding these two breast cancers diagnosed within 1 month of beginning work would not be expected to significantly reduce person-years but would result in a lower and still statistically insignificant estimated O/E (e.g., 10/7.64 = 1.31).
[k] For female workers with known continuous workplace exposure, the breast cancer mortality SMR was 0.70 (5 observed vs. 7.2 expected).
[l] This meta-analysis included all the individual studies above except for Hogstedt et al. (1986), which found no breast cancers and therefore did not report any effect estimate for breast cancer.

As a note, the SIRs/SMRs cited in Table 4 are those associated with comparisons to external reference populations. As is discussed in Section 3.1.1.2 above, there is no evidence of a healthy worker effect for breast cancer, and therefore the TCEQ did not use the epidemiological results generated using an internal referent population in these studies. Steenland et al. (2003) stated that they used internal referents because of the potential for under-ascertainment; however, since that study found that there was complete breast cancer ascertainment in the sub-cohort with interviews, the TCEQ still considers the external referent comparisons to be the most appropriate.

Steenland et al. (2003) found no excess of breast cancer incidence among the cohort as a whole compared to the US population; only finding an increase in the highest exposure quintile in certain internal analyses; that is, categorical with exposure lagged 15 years for cumulative exposure and duration of exposure (see Tables 4 and 5 of Steenland et al. 2003). However, without scientific justification for internal analyses in this case (as discussed above), it is noted that when using the external referent: (1) the RR for even the highest exposed group (>14,620 ppm-days) was not statistically increased (i.e., 1.27 (0.94, 1.69)) and the RRs for all lower exposure groups were < 1, consistent with no excess risk (see Table 3 of Steenland et al. 2003); and (2) the overall RR for breast cancer incidence was 0.89 (0.78, 1.01) (see Table 4 above), indicative of no excess risk overall among 7,476 female workers with relatively high exposure to

EtO. Thus, no association of EtO with increased risk is demonstrated for the cohort overall or for any exposure category.

Furthermore, an external expert peer reviewer indicated that without careful control in the analysis, the role of parity would result in a spurious positive association between EtO exposure and breast cancer risk (TCEQ 2020). Parity is "strongly related to risk of breast cancer (higher parity predicts lower risk) and strongly related to remaining in the work force to accrue greater exposure (more live births predict cessation of employment)." That is, "women with no or few children have elevated risk of breast cancer and work for longer periods of time, thus accruing greater cumulative exposure." The reviewer further commented that it is not clear that parity was effectively handled in the analysis for the NIOSH cohort, and that the finding that duration of exposure was more strongly associated with breast cancer incidence than cumulative exposure is consistent with parity bias. The reviewer concluded that "an informed, unbiased evaluator could well come to the judgment that TCEQ did, i.e., not considering breast cancer in the overall EtO assessment."

In summary, the weight of the epidemiological evidence does not support the conclusion that EtO causes breast cancer in humans.

3.3.1.1.1.2 Laboratory Animal Data

The TCEQ and the USEPA acknowledge that human data are insufficient to establish that EtO is a human breast cancer carcinogen. As a result, USEPA (2016) relies on support from laboratory animal studies in classifying EtO as *carcinogenic to humans* and for the human breast cancer endpoint. However, upon closer scientific scrutiny, the sites of EtO-induced cancers in animal models are of questionable human relevance for being predictive of, and therefore being used as confirming evidence for, the site(s) of human cancers.

While laboratory animal data are often used to support various aspects of regulatory assessments, interspecies differences in carcinogenic responses are common (e.g., tumor types, sensitivity), even between rodents (e.g., EtO-induced mammary tumors in mice but not rats). Specifically to address this issue, IARC (2019) analyzed tumor site concordance using a dataset of the 111 distinct Group 1 (*carcinogenic to humans*) agents identified up to and including Volume 109. Sixty agents had both a human tumor site and an animal tumor site identified and were used to evaluate concordance across 39 tumor sites in animals and humans (see Figures 21.1 and 21.2 of IARC 2019). Reported results show that breast cancer is more frequently/commonly induced in laboratory animal species than in humans. More telling is that while there is 47% overlap between agents that cause lymphoid and hematopoietic cancers in humans and animals, there is only a 20% overlap between agents that have been shown to cause breast cancer in humans and animals (Table 21.7 of IARC 2019). The IARC (2019)

consensus statement is that "At present, the state of the science does not support tumour site concordance as a general principle."

Accordingly, current best available science indicates that animal data should not generally be used to support specific sites of chemically-attributable carcinogenesis in humans; even more so when laboratory animal results are inconsistent and the human database is relatively robust. For example, EtO-induced murine mammary tumors are not even predictive for rats.[c] Additionally, while lung cancer was statistically increased in both male and female mice at incidences of 53% and 45%, respectively (Table 3-3 in USEPA 2016), lung cancer is not a candidate endpoint in humans because the human data shows no increased lung cancer mortality with EtO exposure (i.e., no interspecies site concordance; SMR of 1.05 (0.95, 1.17) in Table 1 of Steenland et al. 2004). Similarly, EtO induced statistically significant increases in brain tumors in rats of both sexes (Table 3-5 in USEPA 2016), but again these results are not predictive for humans. In fact, brain cancer for the NIOSH cohort is statistically significantly decreased (i.e., SMR of 0.59 (0.36, 0.91) in Table 1 of Steenland et al. 2004), the opposite of what the rat data would suggest.

Therefore, laboratory animal data for EtO-induced cancers cannot be relied upon to identify cancer sites or otherwise predict EtO carcinogenic response in humans. This applies to cancer sites generally and EtO-induced breast cancer specifically since: (1) the state of the science does not support tumor site concordance as a general principle (IARC 2019); (2) specific to breast cancer, there is little overlap between agents that have been shown to cause breast cancer in humans and animals (i.e., there are substantial interspecies differences), with discordance generally being the case (IARC 2019); and (3) specific to EtO, animal data are not reliable predictors of the purported sites of EtO-induced carcinogenesis in humans (e.g., lung and brain cancer in laboratory animals). Thus, the laboratory animal data are of dubious relevance for confirmation of, or adequately supporting, the insufficient epidemiological evidence for breast cancer as a known site of EtO-induced carcinogenesis in humans.

3.3.1.1.1.3 Summary of Breast Cancer WOE

In summary, the epidemiological evidence for EtO causing human breast cancer is very weak, with most of the available studies showing no association when the external reference population is used as a comparison group. This is the same conclusion reached by Marsh et al. (2019) in their recent meta-analysis, which found that there was no evidence from the

[c] Vincent et al. (2019) evaluated animal study results, concluding that they provide no strong indication that EtO causes mammary tumors.

epidemiology studies of a relationship between EtO exposure and breast cancer. The meta-analysis conducted by Vincent et al. (2019) reached a similar conclusion, stating that "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition, more recently Jain (2020) found that "For the general US population, levels of ETO were not found to be associated with cancers including breast cancer." When considering the evidence from animal studies, the TCEQ found that while there was an increase in mammary tumors in mice chronically exposed to EtO (NTP 1987), there was no increase in mammary tumors in rats chronically exposed to EtO (Snellings et al. 1984). In addition, IARC in 2019 released an assessment of tumor site concordance, which found that only 20% of the evaluated Group 1 chemicals showed site-concordance of mammary/breast tumors between animals and humans. While the MOA determination that EtO is carcinogenic through a mutagenic MOA generically supports tumor sites at any location, there is no specific MOA or metabolic information that identifies breast tissues as a susceptible site for EtO-induced carcinogenesis in humans to lend support to the weak, inconclusive epidemiological data. Therefore, the TCEQ determines that there is insufficient evidence for identifying breast cancer as a hazard of EtO exposure in humans.

Chapter 4 Carcinogenic Dose-Response Assessment

Per TCEQ guidelines (TCEQ 2015), when a toxicity factor or guideline air level is identified in the scientific literature or databases, it is reviewed to determine whether the approaches used to develop the toxicity factor or guideline level are similar to the procedures that would be used by the TCEQ for the given chemical dose-response assessment. The TCEQ's scientific literature search identified USEPA (2016) as a recent carcinogenic dose-response assessment for EtO for consideration under TCEQ guidelines (TCEQ 2015). However, the TCEQ identified several substantial scientific issues with USEPA's assessment (see Appendix 6), and the procedures that USEPA used to derive their URF are different than the standard procedures that the TCEQ would utilize for the EtO carcinogenic dose-response assessment (e.g., standard model fit criteria calculations, use of a standard dose-response model). Consequently, the TCEQ did not adopt USEPA's URF, consistent with relevant guidelines (TCEQ 2015). In the sections that follow, the TCEQ reviews information relevant to the carcinogenic dose-response assessment for EtO and then conducts an original assessment to derive an EtO inhalation URF based on TCEQ guidelines and best principles.

4.1 Relevant Data

4.1.1 Systematic Review

The following is a summary of the systematic review of EtO literature that was conducted by TCEQ based on our published systematic review guidelines (TCEQ 2017), with full details discussed in Appendix 1. The TCEQ conducted literature searches with a cut-off date of

December 2018, as well as evaluations of the literature cited in other EtO evaluations. The collected studies were divided into groups by evidence stream (i.e. human, animal) and effect group (i.e., acute, chronic non-carcinogenic, carcinogenic). For the purposes of this DSD, only the human carcinogenic/epidemiologic data were considered for several reasons:

1. In order to expedite the process, it was decided that only a health-based chronic carcinogenic toxicity factor would be derived for EtO in this DSD. Other toxicity factors (i.e. health- and welfare-based acute and chronic non-carcinogenic) may be evaluated at a later date with an additional systematic review continuing where this systematic review ended.
2. Sufficient human data exist for EtO such that animal data, although used to inform the carcinogenicity classification, would not be used to derive a chronic carcinogenic toxicity factor. TCEQ (2015) states that in general, human data are preferred over animal data when developing toxicity factors.
3. Similarly, mechanistic data provide crucial information for the MOA analysis but do not provide the necessary dose-response information required for derivation of a chronic carcinogenic toxicity factor (e.g., they do not provide information on the critical adverse health effect).
4. And finally, human data looking solely at cytogenetic changes, sister chromatid exchanges, or chromosomal abnormalities were considered useful in developing the MOA of EtO, but not useful as a basis for derivation of a health-based toxicity factor.

After full text review and screening with the inclusion/exclusion criteria listed in Table 18, eight human carcinogenic studies were identified for further consideration in this systematic review. Several human studies (directly or indirectly related to carcinogenicity) were reviewed and later excluded for various reasons (Table 19). Each of the identified studies was reviewed in detail and the primary data were extracted for potential use in the development of the chronic carcinogenic toxicity factor in this DSD (Table 20). Each of the selected studies was also evaluated for study quality and risk of bias (ROB) based on a number of attributes determined prior to this review, with scoring for each of the included studies shown in Table 24. After addressing the study quality and (ROB) for each of the selected studies, the primary information from each of the studies was compiled together and each study was assessed for use as a key, supporting, or informative study (Table 25).

4.1.2 Epidemiological Studies

After final review of the included studies, the Valdez-Flores et al. (2010) study had the most thorough and complete analysis (e.g., data from both the NIOSH and UCC cohorts, multiple cancer endpoints examined) and was therefore selected as the key study. While the Valdez-Flores et al. (2010) study also utilized a default lifetime duration (70 years) consistent with TCEQ guidance (TCEQ 2015), there were aspects that were not ideal, such as the lack of

exposure-lagged results. So rather than select a POD from the key study, the TCEQ selected data from both cohorts (i.e., the NIOSH and UCC cohorts) to initially evaluate and conduct an independent assessment using the same modeling approach but with supplemental analyses (e.g., the evaluation of various exposure lags). Selection of data from the NIOSH and UCC cohorts as the epidemiological data to initially evaluate and use of specific, TCEQ-directed dose-response assessment analyses (rather than selection of a study POD) provide the best basis for a carcinogenic assessment of EtO for several reasons:

1. Both the NIOSH and UCC cohorts have adequate size, exposure information, and follow-up, making consideration of these data ideal for toxicity factor development (e.g., weight of evidence, more analyses to consider).
2. The Valdez-Flores et al. (2010) study makes use of the Cox Proportional Hazard model, a standard model preferred under TCEQ guidelines (TCEQ 2015) and one that the TCEQ has used previously in dose-response assessments (also considered by USEPA 2016).
3. Although Valdez-Flores et al. (2010) did not include exposure lag results in their publication, supplemental analyses involving a reassessment of the data using various exposure lags allow for the consideration of even more assessment results in the DSD.
4. Additionally, since published in 2010, an update to the UCC data through 2013 has become available to the first author of the Valdez-Flores et al. (2010) study (submitted for publication), with whom the TCEQ contracted to perform supplemental analyses; consequently, results from the new study update with a longer follow-up period can also be included in the DSD (although the unpublished update was not used as the basis for the TCEQ's URF; see Appendix 2).
5. Finally, conducting these new analyses will allow for the appropriate consideration of model fit to the individual data (rather than the categorical data) for the model assessment ultimately selected by the TCEQ.

Based on the systematic review conducted by the TCEQ (Appendix 1) as well as review of USEPA (2016) and other dose-response assessments (e.g., Valdez-Flores et al. 2010, Kirman et al. 2004), the assessment of excess cancer risk in the NIOSH and/or UCC cohorts provides the best basis for a carcinogenic assessment of EtO. These studies are summarized below.

4.1.2.1 NIOSH Cohort

The NIOSH retrospective cohort study is an analysis of close to 20,000 workers who were occupationally exposed to EtO at sterilization facilities in the US from 1938 through 1985. There have been multiple analyses of the NIOSH cohort (Steenland et al. 1991, Stayner et al. 1993, Steenland et al. 2003, Steenland et al. 2004), with Steenland et al. (2003, 2004) providing the most recent analysis and worker follow-up through 1998. The most recent update included 17,530 workers (55% female) in 13 US sterilizing facilities that used exposure estimates and measurements of EtO from 1938-1985. This cohort is by far the largest EtO occupational cohort

and has the added benefits of an extensive exposure assessment (discussed in the next section), both male and female workers, and little reported exposure to chemicals other than EtO.

The following sections summarize the exposure assessment conducted by Steenland et al. and the study results.

4.1.2.1.1 NIOSH Cohort Exposure Assessment

For the NIOSH cohort, the EtO exposure regression model was based on exposure estimates from the years 1938-1978 (no exposure measurements were available for this time period) and based on extensive personal monitoring data from 18 sterilization facilities from 1976 to 1985 as well as information on factors influencing exposure, such as engineering controls (Hornung et al. 1994). This exposure model was used to estimate exposures for each individual in the cohort as a function of facility, exposure category, and time period. The investigators estimated the cumulative exposure (ppm-days) for each individual worker by multiplying the estimated exposure (ppm) for each job (exposure category) held by the worker by the number of days spent in that job and summing over all the jobs held by the worker.

Uncertainties are inevitably associated with historical exposure reconstruction. The earlier time period before EtO exposure data was collected was likely a time period with relatively high exposures that would substantially contribute to cumulative exposure estimates (ppm-days, both unlagged and lagged). Because the study authors assumed that exposures were constant during the 1938-1978 period (they were fixed at the 1978 exposure level), the exposure estimates are likely to be biased low. A full review of the exposure estimates is beyond the scope of this DSD, but have been reviewed elsewhere (Bogen et al. 2019, Li et al. 2019). The USEPA Science Advisory Board (SAB) agreed that earlier exposure estimates are likely of lower reliability (because there were no exposure measurement data that could be included in the exposure model prior to 1979) and actual EtO exposures were likely to have been higher than is reflected in the estimates (p. I-41 of USEPA 2016). However, for the later monitoring data the regression model was able to account for 85% of the variation in average EtO exposure levels when evaluated against independent test data from the same set of data.

The TCEQ notes that this worker population was exposed to extremely high concentrations of EtO compared to ambient exposures experienced by the general population. For example, Tables IV and V of Hornung et al. (1994) provide measured and estimated worker exposure means of 3.5-4.6 ppm, which are up to 2,000,000 times higher than central tendency environmental levels (using background and environmental exposure means of ≈0.0024-0.0034 ppb per USEPA 2016). Animal carcinogenicity studies were conducted at even higher EtO exposure concentrations (10-100 ppm; see Section 3.1.2). On any given day, estimated

exposure for a job could have ranged from 50-77,000 ppb (pp. D-4 and D-37 of USEPA 2016), which is ≈15,000-32,000,000 times higher than central tendency environmental levels of EtO.

4.1.2.1.2 NIOSH Cohort Study Findings

Steenland et al. (2004) present follow-up results for the cohort mortality study previously discussed by Steenland et al. (1991) and Stayner et al. (1993). Findings in the most current follow-up include statistically increased lymphohematopoietic cancer mortality (i.e., non-Hodgkin's lymphoma with a 10-year exposure lag, hematopoietic cancer and lymphoid cell line tumors with a 15-year lag) in males but not females of the highest EtO exposure group (see Tables 4, 6, and 7 of the study), and statistically increased breast cancer mortality in females of the highest EtO exposure group with a 20-year lag but not without (see Tables 5 and 8 of the study).

Steenland et al. (2003) present results of a breast cancer incidence study of a subcohort of 7,576 women from the NIOSH cohort that showed statistically increased odds ratios for the highest exposure group with a 15-year lag but not without (see Tables 4 and 5 of the study). No statistically significant increases in breast cancer were found for any exposure group using external referents and either 0- or 15-year exposure lags (see Table 3 of the study). These Steenland et al. studies were included in recent scientific literature reviews and meta-analyses of EtO studies for these cancer endpoints that are summarized in Section 3.1.1 (Vincent et al. 2019, Marsh et al. 2019).

4.1.2.2 UCC Cohort

Swaen et al. (2009) redefined and updated the UCC cohort of male workers employed in US industrial facilities where EtO was produced or used. Previous studies of the UCC cohort were published by Greenberg et al. (1990) and Teta et al. (1993). All 2,063 men in the cohort were employed between 1940 and the end of 1988 and were observed for mortality through 2003. Workers from EtO departments at the Kanawha Valley, West Virginia sites hired after 1988 were determined to have no appreciable EtO exposure and were, therefore, not added to the cohort. Cause-specific standardized mortality ratios (SMRs) were calculated. Internal referent comparison analyses were made by applying Cox proportional hazards models to the data.

4.1.2.2.1 UCC Cohort Exposure Assessment

The exposure assessment for the Swaen et al. (2009) update relied on the qualitative categorization of departments that produced and used EtO developed by Greenberg et al. (1990), and on quantitative estimates of average EtO exposure intensity by these department categories and by time period (1925-1988) developed by Teta et al. (1993). Time period cut points were chosen as follows: 1925, the start-up of EtO production in the Kanawha Valley; 1940, start of cohort observation and first period with published estimates of exposure; 1957, chlorohydrin process for EtO production completely shut-down; and 1974, the period when

airborne exposures declined substantially due to process and exposure controls. The combination of the average exposure for the four different time periods and the three classifications of departments into low, medium, and high exposure levels created the exposure matrix. Cumulative EtO exposure (ppm-years) for each study subject was then estimated by multiplying the estimated time-period and department-specific exposure concentrations by duration in months for each individual's assignments to EtO departments and summing the products over all assignments up through December 1988 (Swaen et al. 2009). The average cumulative EtO exposure was 67.16 ppm-years (≈16,118 ppm-days, as 67.16 ppm-years × 240 days/year), about twice that of the NIOSH cohort. As of Swaen et al. (2009), the average follow-up period for the UCC cohort was 10 years longer than the NIOSH cohort (36.5 versus 25.8 years) and the percent deceased was 3-fold greater than the NIOSH cohort (51% versus 16%). However, the number of expected cancer deaths for the UCC cohort (a measure of study power) was between 2-3 times lower because of the much smaller cohort size in both number and person-years (e.g., 75,306 versus 450,906 person-years for the UCC cohort compared to the NIOSH cohort, respectively). Nevertheless, this is an important cohort that contributes to the human EtO carcinogenicity database.

As mentioned above, uncertainties are inevitably associated with historical exposure reconstruction. For example, USEPA (2016) characterizes the EtO exposure assessment for the UCC cohort as more uncertain than that for the NIOSH cohort (e.g., greater likelihood for exposure misclassification, use of surrogate exposure data; see Section 4.1 of USEPA 2016). USEPA further indicates that there are substantial uncertainties in the exposure estimates for the early years when the highest exposures occurred (Section A.2.20 of USEPA 2016), something both cohorts have in common.

4.1.2.2.2 UCC Cohort Study Findings

Swaen et al. (2009) report that no indications were found for excess cancer risks from EtO exposures, including the lymphohematopoietic malignancies (e.g., 11 leukemia deaths occurred and 11.8 were expected, 12 non-Hodgkin's lymphoma deaths occurred and 11.5 were expected). Cox proportional hazards modeling for all cause, leukemia, and lymphoid malignancies mortality revealed no trends or associations with cumulative EtO exposure. In recognition of exposure estimate uncertainty, it is also important to note that no statistically significantly elevated SMRs were found in the analysis by hire date, and there were no statistically significant increases in the longest duration category and no suggested trends by duration (all surrogates of exposure). Study authors concluded that the cohort showed no long-term carcinogenic effects associated with EtO exposure.

Similarly, an as of yet unpublished update of the UCC cohort through 2013 (submitted as Bender et al., unpublished as of the date of this DSD) concludes that examination of mortality from all causes of death, all cancers, leukemia, non-Hodgkin's lymphoma, and lymphoid

malignancies revealed no evidence for an exposure-related response; EtO exposure in this cohort was not associated with an observable increase in lymphohematopoietic cancer mortality (personal communication with Ciriaco Valdez-Flores, an author of a risk assessment paper based in part on the Bender et al. update). The average cumulative dose of EtO (67 ppm-years) is reported to be around two times that for the NIOSH cohort, with a ≈63% longer follow-up period (≈41 years) and a similar number of lymphoid cancer deaths in males (27 in NIOSH versus 25 in UCC) despite the number of person-years for males in the NIOSH cohort (189,868 person-years) being considerably greater than that in the UCC cohort (83,524 person-years). For completeness, modeling results based on these updated data will be evaluated for comparison to NIOSH results. However, the TCEQ URF was based on unpublished follow-up data for the UCC cohort (see Appendix 2).

4.1.3 Animal Studies

Human (i.e., epidemiological) data are available for a carcinogenic assessment of EtO and are preferred over animal data for toxicity factor (i.e., URF) development (TCEQ 2015). Therefore, animal carcinogenicity data used for the EtO dose-response assessment (see Section 4.2 of USEPA 2016 for relevant information). However, laboratory animal carcinogenicity data for EtO are summarized in Sections 3.1.2 and 3.2.1 and are considered for both the MOA evaluation and the carcinogenic potential hazard assessment detailed in Chapter 3.

4.1.4 Key Study

USEPA (2016) utilized the NIOSH cohort for their URF. The NIOSH cohort has several positive study attributes:

- Adequate human data for deriving quantitative cancer risk estimates (i.e., URFs);
- Large number of workers (17,530) from 13 sterilizing facilities;
- Gender diverse (e.g., 55% female);
- Individual worker exposure estimates; and
- Little reported exposure to chemicals other than EtO.

The TCEQ will also use the NIOSH cohort as the key study. However, the UCC cohort will also be evaluated as a supporting study for comparison and a more complete carcinogenic evaluation based on human data. Although the exposure assessment for the UCC cohort appears more uncertain than that for the NIOSH cohort (e.g., see Section 4.1 of USEPA 2016), it is nevertheless an important contribution to the human EtO carcinogenicity database. The weighting of potential URFs based on the NIOSH and UCC cohorts based on relevant metrics supports use of the NIOSH cohort as the key cohort (Appendix 2). Lastly, an analysis using UCC data (i.e., exposure estimates, number of lymphoid cancer mortalities) to validate the predictiveness of TCEQ's dose-response model for the NIOSH cohort also supports TCEQ's assessment using the NIOSH cohort as the key cohort (Section A3.3.3 of Appendix 3).

4.1.5 Key Cancer Endpoint(s)

There is epidemiological evidence, albeit inconsistent, for associations between EtO exposure and lymphohematopoietic cancer and female breast cancer in highly exposed workers. However, in Section 3.3.1.1 the TCEQ conducted a weight of evidence evaluation and concluded that there is insufficient evidence that EtO causes human breast cancer.

The TCEQ concurs with USEPA that while the epidemiological evidence for EtO-induced lymphohematopoietic cancer is also less than conclusive, it may be used to derive a URF and thus the TCEQ has adopted lymphohematopoietic cancer as a key cancer endpoint. Lymphohematopoietic cancer (also referred to as lymphoid cancer herein) includes non-Hodgkin's lymphoma, multiple myeloma, and lymphocytic leukemia (as developed in Steenland et al. 2004).

4.2 Considerations for Choice of Dose-Response Models

The TCEQ considers multiple factors when deciding on the dose-response model and low-dose extrapolation method for a toxicity factor derivation (e.g., MOA, type of endpoint). First and foremost is the consideration of the chemical's MOA. For example, MOA information can help inform expectations about the shape of the curve at low doses and the decision between a threshold or non-threshold dose-response model (Figure 1). For model(s) that are consistent with the chemical's MOA (if known) and TCEQ guidelines (TCEQ 2015), model-fit criteria such as p-values and Akaike Information Criteria (AIC) values may then be evaluated to aid in model selection (e.g., the evaluation of model fit for dose-response data modeled using benchmark dose software). Another important consideration when evaluating model fit/accuracy among multiple dose-response models under consideration is how well each model predicts the actual data, in this case the cancer mortality numbers in the NIOSH and UCC cohort studies.

The sections below outline the MOA considerations that led to the TCEQ's choice of the Cox proportional hazards model as the first choice for modeling lymphoid cancers associated with EtO exposure from the NIOSH cohort data (Section 4.2.1). Then we describe the model fit considerations for the Cox model compared to the USEPA's choice of a linear two-piece spline model (Section 4.2.2). Finally, the TCEQ evaluates the model predictiveness of these two models using the NIOSH and UCC cohort data (Section 4.2.3).

4.2.1 MOA-Informed Dose-Response Modeling

Use of MOA information to inform the dose-response assessment is a main focus of the TCEQ (2015) guidelines as shown in Figure 1, and for USEPA (2005a, b) guidelines. Generally, the MOA and other information may support one of the following low-dose extrapolation approaches: (1) Nonthreshold (typically a linear extrapolation to zero); (2) Threshold (typically identifying a point of departure (POD) and applying uncertainty factors); or (3) Both 1 and 2 (TCEQ 2015).

Thus, to the extent that the MOA for a chemical is understood, it informs the low-dose extrapolation procedure for that chemical. Examples of different shapes of dose-response curves are shown in Figure 2.

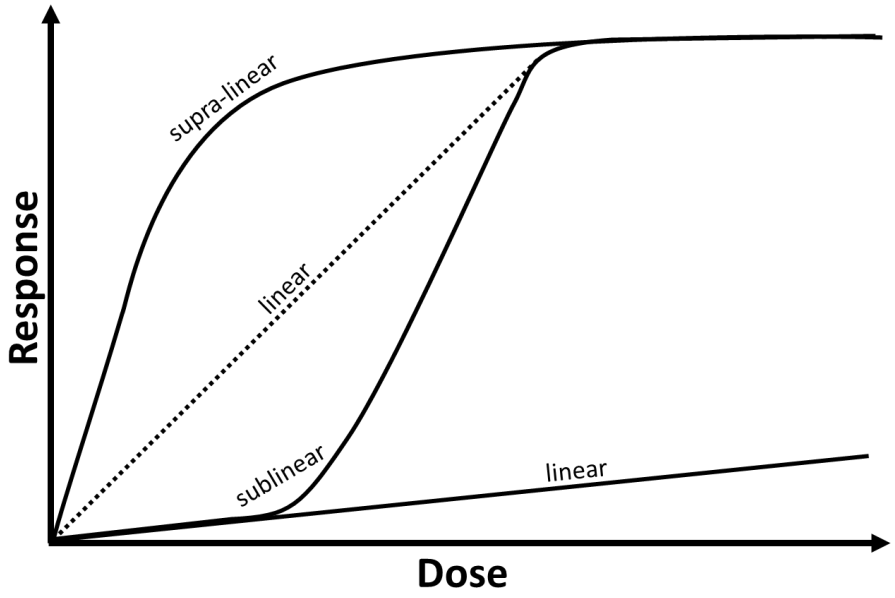


Figure 2: Dose-response curve examples

MOA information can suggest the likely shape of the dose-response curve at lower doses (TCEQ 2015, USEPA 2005a). That is, toxicological principles can inform expectations about low-dose risk when truly low-dose data are unavailable. In this case, in the key epidemiological cohort (NIOSH) used by the TCEQ and USEPA (2016), estimated mean worker exposures to EtO were up to 2,000,000 times higher than central tendency ambient environmental EtO levels (see Section 4.1.2.1.1). EtO MOA information is discussed in Section 3.2, which supports a putative mutagenic MOA for EtO carcinogenicity. EtO is a direct acting DNA-reactive chemical that is also produced endogenously, and as such there are expected to be normal detoxification processes and baseline levels of DNA repair enzymes that have evolved to efficiently detoxify and/or repair substantial levels of endogenous EtO and associated adducts in the endogenous concentration range. This information suggests a no more than linear low-dose response component near the endogenous range with a transition to a steeper dose-response slope at some point above the endogenous range where the body can no longer effectively detoxify EtO and/or repair the EtO-induced DNA damage. Thus, across a complete range of doses from truly low (e.g., endogenous) to high (e.g., occupational exposures), the expected dose-response could be characterized as sublinear overall across doses (see Figure 2). However, if the low dose range in/near the endogenous range (that is expected to be responsible for overall sublinearity)

is relatively narrow, and sufficient data are not available to reveal the full shape of the dose-response from truly low doses to high doses (e.g., endogenous to occupational), then the higher dose data that are available could simply appear as linear. Regulatory inhalation dose-response assessments that utilize human data are frequently based on occupational studies, which generally exclusively involve relatively high doses, as is the case here.

In contrast to direct acting mutagenic chemicals such as EtO, supra-linear responses are generally associated with an MOA that involves the saturation of metabolic activation where fewer electrophiles are formed per unit dose at higher exposures, which is not the case for EtO (Swenberg et al. 2008).[d]

Kirman and Hays (2017) expressed this conclusion similarly. That is, based on relevant considerations, an overall sublinear dose-response would be expected over the range of possible exposures to EtO, from those that result in total body burdens (endogenous + exogenous) within the normal endogenous level range to those that result in a total body burden significantly greater than the normal range where the normally effective detoxification/repair processes are overwhelmed. This conclusion is reasonably consistent with that of the USEPA, "EPA considers it highly plausible that the dose-response relationship over the endogenous range is sublinear (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases."

For exogenous EtO exposures, USEPA cites direct mutagenic activity as mechanistic justification for default linear low-dose extrapolation (pp. 4-22 and 4-37 of USEPA 2016). In regard to the shape of the EtO dose-response overall, Vincent et al. (2019) consider the MOA and dose-response analysis of the early effect data in humans/animals (as well as modeling results of relevant cancer endpoints in rodents; most notably, leukemia incidence in female F344 rats) to

[d] The TCEQ (2015) guidelines require sufficient mechanistic or biological data to support the application of a supra-linear model, with a supra-linear model here defined as a model with a dose-response curve that is steeper than linear as illustrated in Figure 2 where the low-dose slope is steep beginning at zero dose and then transitions at higher doses to a shallower slope. By TCEQ's definition this can include curvilinear models or multi-part linear spline models with this same shape. Mechanistic and/or biological data for EtO adequate to justify use of an overall supra-linear model do not exist. USEPA (2016) acknowledged to the SAB that the MOA information for EtO does not support a supra-linear dose-response (e.g., the linear two-piece spline model), stating "the EPA is not aware of a mechanistic explanation" (p. I-29 of USEPA 2016; also see pp. I-34 and 4-71). Similarly, the TCEQ is not aware of any MOA or mechanistic data for EtO that would suggest that a supra-linear dose response should be expected. Rather, MOA-relevant information for EtO suggests a no more than linear dose-response.

conclude that there is no evidence that a dose-response other than linear is justified. Since lymphoid cancer was the primary driver of the USEPA carcinogenic assessment (i.e. was associated with the greatest risk), perhaps the most relevant mutagenicity data discussed by USEPA (2016) was that in the bone marrow of mice exposed to 25-200 ppm EtO by inhalation *in vivo* (Recio et al. 2004, Figure 3).

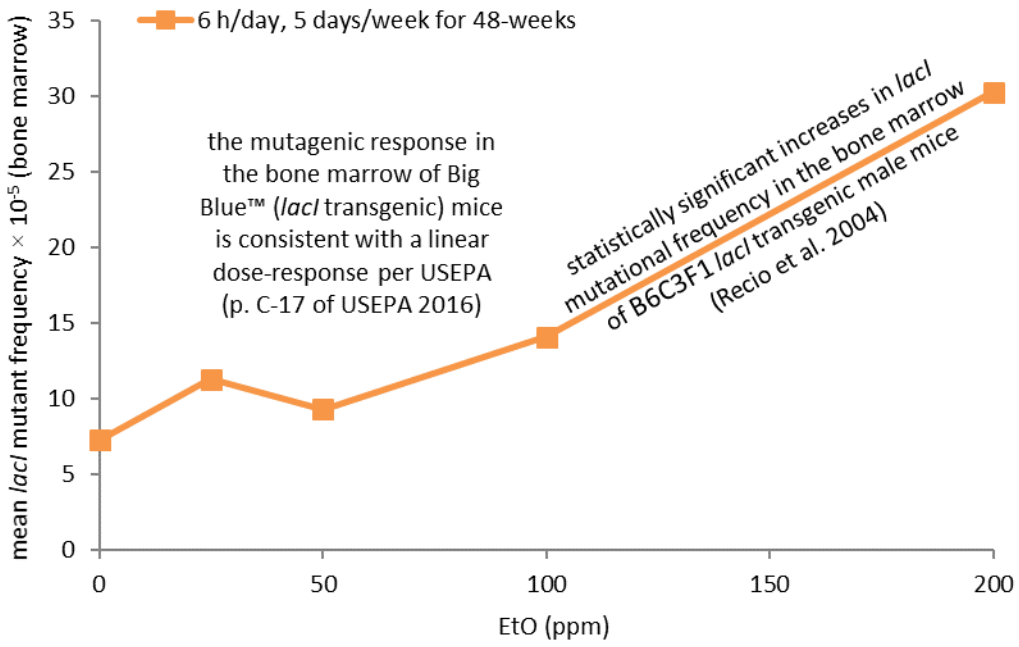


Figure 3: Overall linear dose-response for EtO-induced mutations in the bone marrow of Big Blue™ mice (Recio et al. 2004)

The TCEQ notes that the overall linear dose-response for mutagenicity in bone marrow is consistent with a linear dose-response (see C-17 of USEPA 2016) and did not plateau even at exposure concentrations as high as 200 ppm. Similarly, the relationship between EtO exposure and EtO blood levels in B6C3F1 mice exposed to ≤200 ppm is linear (Brown 1998). Furthermore, because exposure, absorption, and distribution are obligatory steps in the series of events leading to EtO-induced carcinogenesis (e.g., lymphoid cancer) and the linearity/nonlinearity of toxicokinetics is relevant to expectations about the shape of the dose-response for carcinogenic risk, it is noted:

- Fennell and Brown (2001) reported that simulated EtO blood levels (area under the curve) after exposure to EtO concentrations between 1 ppm and 100 ppm were similar for mice, rats, and humans and were linearly related to the exposure concentration (see Figure 3-2 of USEPA 2016);

- Similarly, Kirman and Hays (2017) reported that in humans, the relationship between blood EtO levels and EtO exposure ≈1.4 ppm and below is linear (R^2=0.998, see Figure 3 of the study); and
- Following the efficient absorption of EtO into the blood, which follows a linear relationship, EtO is rapidly distributed to all organs and tissues (USEPA 2016).

In summary, studies show that EtO absorption and tissue concentrations are *linearly related* to inhalation EtO concentration, at least in the range of exposures used in the relevant studies (≤100 ppm; USEPA 2016). As mentioned above, there is also a linear relationship between inhalation EtO concentration and the mutagenicity in bone marrow observed in Recio et al. (2004). Thus, there is a linear relationship from EtO in air to absorption, distribution, and tissue concentration, as well as between EtO in air and mutagenicity in the bone marrow of EtO-exposed mice. Tissue concentrations of EtO are expected to be approximately equal in mice, rats, and humans exposed to a particular air concentration of EtO (≤100 ppm; USEPA 2016).[e] Following distribution to target tissue, EtO can cause genotoxic effects as a direct acting mutagen and mutagenicity is a well-established potential cause of carcinogenicity (e.g., many mutagens are carcinogens per USEPA 2005a).

The consideration of MOA-relevant information for EtO suggests that an overall dose-response that is no more than linear is expected for EtO-induced carcinogenicity, and that linear low-dose extrapolation is appropriate and health-protective. These MOA-based considerations are consistent with use of a POD from Cox proportional hazards modeling as the preferred methodology for low-dose extrapolation from epidemiology study data under TCEQ guidelines (TCEQ 2015). Cox proportional hazards modeling is indistinguishable from linear over the EtO dose range in the key epidemiological study, which is consistent with the expected dose-response for EtO-induced carcinogenicity based on the MOA.

4.2.2 Model Fit Criteria

Although some models have a biological or mechanistic basis (e.g., Chemical Industry Institute of Toxicology biologically-based model for formaldehyde), many models used for dose-response assessment do not (e.g., often only to the extent that low-dose linearity is viewed as consistent with a mutagenic MOA). Thus, in this respect model fit alone is a lesser consideration compared to data (e.g., MOA data) that may (or may not) support use of a particular model.

[e] Interspecies differences in carcinogenic potency are likely the result of toxicodynamic differences (USEPA 2016).

Model fit is a topic of interest for EtO although not a deterministic consideration on its own when:

- MOA/mechanistic data for EtO must also be considered (TCEQ 2015); and
- The accuracy of models for predicting the underlying modeled cancer data differs significantly.

This section uses standard model fit criteria (i.e., p-values and AIC values) to evaluate dose-response model fit to the NIOSH lymphoid cancer data (TCEQ's key cohort and cancer endpoint, as well as the primary driver of USEPA's URF) for two dose-response models that have been considered for EtO:

1) The standard Cox proportional hazards model preferred under TCEQ guidance (TCEQ 2015) and supported by MOA considerations (Section 4.3); and
2) The linear two-piece spline model used by USEPA (2016) (linear two-piece spline model with knot at 1,600 ppm-days).

The TCEQ standard Cox proportional hazards model derivation is further described in Section 4.3 of this DSD, and the derivation of the linear two-piece spline model is described in Section 4.1.1 of USEPA (2016).

Standard p-values and AIC values for these models are presented in Table 5 below.

Table 5: p-Values and AIC Values for the Cox and Linear Two-Piece Spline Dose-Response Models for Lymphoid Cancer Mortality in the NIOSH Cohort

Model [a]	p-value [b]	AIC [c]
Cox proportional hazards model (log-linear model)	0.22	464.4
Linear two-piece spline model with knot at 1,600 ppm-days [d]	0.14	464.5

AIC - Akaike information criteria, NIOSH - National Institute for Occupational Safety and Health
[a] Cumulative exposure (15-yr lag) is the exposure variable.
[b] p-values from likelihood ratio test; $p < 0.05$ considered good statistical fit.
[c] For the lymphoid cancer data, Statistical Analysis System (SAS) proc NLP (where NLP = nonlinear programming) consistently yielded −2LLs and AICs about 0.4 units lower than SAS proc PHREG for the same models, including the null model, presumably for computational processing reasons, and proc NLP was used for the linear RR models. Thus, AICs for linear models are equivalent to AICs ≈0.4 units higher for log-linear models. In order to make the AICs comparable for different models, the AICs for the linear models have been increased by 0.4 to reflect the discrepancy in the -2LogL values reported by the SAS proc NLP and by SAS PHREG.
[d] Degrees of freedom k=3 for the linear two-piece spline model, the number of parameters that were estimated in excess of the parameters estimated for the null model (i.e., estimation of the "knot" value through statistical optimization outside of SAS, the slope below the knot, and the slope above the knot).

Table 5 shows that the linear two-piece spline model with a "knot" at 1,600 ppm-days used by USEPA (2016) does not fit the data statistically significantly better than the null model (zero slope) at the 5% significance level (i.e., the linear two-piece spline model does not explain the variability in the data statistically significantly better than the null model). Likewise, the standard Cox regression model preferred under TCEQ (2015) does not fit the data statistically significantly better than the null model. Additionally, the AIC values for the Cox and the linear spline models are similar. Thus, based on standard statistical model fit criteria (i.e., p-values and AIC values), neither model provides a statistically superior fit to the modeled individual lymphoid cancer mortality data.[f]

Since standard statistical model fit criteria (i.e., p-values and AIC values) do not demonstrate a statistically superior fit with either model, other relevant scientific considerations increase in importance. For example, in addition to being consistent with implications of the MOA for dose-response model selection, use of the standard Cox proportional hazards model would be consistent with the USEPA SAB recommendation that "the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered.", because the Cox model has fewer parameters than the linear spline model. Another consideration, which is particularly important, is the ability of a dose-response model to accurately predict the underlying data modeled, which is evaluated in the next section.

4.2.3 Model Accuracy Evaluation - Model Predictions Versus Observed

To evaluate the two primary EtO dose-response models (i.e., the standard Cox proportional hazards model and the linear two-piece spline model), the models were used to estimate the number of lymphoid cancer deaths predicted to occur at the EtO exposure levels estimated for the NIOSH cohort compared to the number of cancer deaths that were actually observed in the cohort (details in Appendix 3). As discussed in Section A3.3.1 of Appendix 3, U.S. background hazard rates are appropriate for calculating the model-predicted number of lymphoid cancer deaths due to the absence of a healthy worker effect for lymphoid cancer mortality both in the NIOSH cohort specifically (Steenland et al. 2004) and in general (Kirkleit et al. 2013; the healthy worker effect concept is discussed in Section 3.1.1.2). Despite study- and cancer endpoint-specific results that do not demonstrate a healthy worker effect for lymphoid cancer, results from a TCEQ sensitivity analysis that nevertheless assumes a healthy worker effect for lymphoid

[f] Statistical model fit criteria have been developed such that visual fit, a less object and less scientifically sophisticated method, need not be relied upon. However, consistent with the model fit criteria, it is noted that objective examination of accurate depictions of model fit to the individual data modeled reveals no readily apparent superior visual model fit (see section A6.3.1.2 in Appendix 6).

cancer mortality in NIOSH workers support findings reported in this section (see Section A3.3.2 of Appendix 3).

This model evaluation exercise (also called a ground-truthing exercise) demonstrated that the linear two-piece spline model (maximum likelihood estimate (MLE) with the "knot" at 1,600 ppm-days; 15-year exposure lag) predicted a total of 92 lymphoid cancer deaths (95% CI of 70 to 122) with the EtO exposure levels estimated for the NIOSH cohort (Table 6 and Figure 4). However, only 53 total deaths from lymphoid cancers were actually observed, demonstrating that the MLE for linear two-piece spline model statistically significantly over-estimates the observed risk. Similarly, use of the upper bound for the linear two-piece spline model was also statistically significantly over-predictive for the NIOSH cohort, predicting 141 lymphoid cancer mortalities (95% CI of 108 to 188) compared to the 53 actually observed.

By contrast, the MLE for the Cox proportional hazards model is reasonably accurate, predicting 52 lymphoid cancer mortalities (95% CI of 40 to 70) compared to the 53 actually observed (Table 6 and Figure 4). The upper bound for the standard Cox proportional hazards model is also reasonably accurate, predicting 59 lymphoid cancer deaths (95% CI of 45 to 78) from EtO exposure compared to the 53 actually observed.

Table 6: Total NIOSH Cohort Lymphoid Cancer Mortalities Predicted by Cox and Linear Two-Piece Spline Models

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% CI [a] on Predicted if the Model were True
Standard Cox model – 15-yr lag (MLE)	2.81E-06	52.42	98.9%	(40.1, 70.0)
Standard Cox model – 15-yr lag (95% UCL)	7.17E-06	58.75	110.8%	(44.9, 78.4)
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (MLE)	**7.58E-04** [b]	**91.69**	**173.0%**	**(70.1, 122.4)**
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (95% UCL)	**1.80E-03** [c]	**141.09**	**266.2%**	**(107.9, 188.4)**

MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, UCL - upper confidence limit

[**Boldface** values indicate that the model over-prediction of lymphoid cancer deaths is statistically significant.]

[a] Confidence intervals are the result of the variability associated with the ratio of the observed and expected number of lymphoid deaths in the reference population (see Appendix 3).

[b] The best estimate and standard error of the slope below the knot are 7.58E-04 and 6.32E-04, respectively. The slope and corresponding standard error after the knot are -7.48E-04 and 6.31E-04, respectively, from footnote d to USEPA Table D-36.

[c] The slope after the knot for the 95% upper confidence limit for the model is -1.79E-03 (-7.48E-04 to 1.645×6.32E-04, which is the 95% LCL on the slope above the knot). This conservatively assumes perfect negative correlation of the slope before and after the knot. **Thus, the over-prediction may be larger than what is shown in the table.** The assumption of perfect negative correlation is consistent with the covariance values obtained by USEPA (see footnote to Table D-36 in the appendices of USEPA's 2016 report where the covariance is approximately equal to the negative of the variances for the slopes above and below the knot (i.e., covariance=-3.99E-07, Var1=3.99E-07, and Var2=3.98E-07).

Similarly, for quintile-specific results, this model accuracy analysis demonstrated that use of the MLE for the linear two-piece spline model is statistically significantly over-predictive for all but one of the exposure quintiles (Table 7 and Figures 5-8). Moreover, for every cumulative EtO exposure group, the upper bound for the linear two-piece spline model statistically significantly over-predicts the observed 11 lymphoid cancer mortalities that occurred in each exposure quintile. The model used by USEPA (2016) predicts statistically significant increases in lymphoid cancer mortality even in the lowest EtO exposure group (i.e., the lower ends of the 95% CIs for the MLE and upper bound of the linear two-piece spline model are 11.7 and 16.7 for lymphoid cancer mortalities, respectively, compared to the 9 lymphoid cancer mortalities in the controls), which was not observed in the data.

On the other hand, the MLE for the standard Cox proportional hazards model is reasonably accurate at predicting the observed risk, and neither significantly over- nor under-predicts the number of lymphoid cancer mortalities (11) that occurred in each exposure quintile group (Table 7 and Figures 5-8). Likewise, the Cox model assessment does not significantly over- or under-predict the lymphoid cancer deaths observed in any NIOSH cumulative EtO exposure, but rather remains reasonably accurate at predicting the observed risk.

Table 7: Quintile-Specific NIOSH Cohort Lymphoid Cancer Mortalities Predicted by Cox and Linear Two-Piece Spline Models

Model [a]	Quintile 2 [b]	Quintile 3	Quintile 4	Quintile 5
Lymphoid Cancer Deaths Observed in NIOSH Cohort	*11*	*11*	*11*	*11*
Standard Cox model – 15-yr lag (MLE)	14.4 (8.1, 28.9)	8.0 (4.5, 16.1)	9.4 (5.2, 18.8)	9.1 (5.1, 18.3)
Standard Cox model – 15-yr lag (95% UCL)	14.5 (8.1, 29.0)	8.1 (4.5, 16.2)	9.8 (5.5, 19.6)	15.0 (8.4, 30.0)
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (MLE)	**20.9 (11.7, 42.0)**	17.6 (9.8, 35.2)	**20.8 (11.6, 41.7)**	**20.9 (11.7, 41.9)**
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (95% UCL)	**29.9 (16.7, 60.0)**	**30.5 (17.1, 61.2)**	**35.8 (20.0, 71.7)**	**33.4 (18.7, 67.1)**

MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, UCL - upper confidence limit

[**Boldface** values indicate that the model over-prediction of lymphoid cancer deaths for the quintile is statistically significant.]

[a] The footnotes to Table 6 apply here also, except that the assumption of perfect negative correlation of the slopes before and after the knot in USEPA's 95% UCL for the linear two-piece spline model does not affect the predictions in quintile 2.

[b] Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted by all models with a 95% confidence interval of (6.0, 25.2).

In summary, as shown here and in more detail in Appendix 3, the linear two-piece spline model statistically significantly over-predicts the number of lymphoid cancer mortalities in the key NIOSH cohort whether based on the MLE or the associated 95% UCL. This over-prediction applies to the cohort as a whole and to the cumulative exposure groups. By contrast, the standard Cox proportional hazards model (TCEQ's preferred model under TCEQ 2015) reasonably accurately predicts the number of lymphoid cancer mortalities observed in the key cohort and its various exposure quintiles, including the lowest exposure quintile.

In a similar manner as with the NIOSH cohort data, the TCEQ also evaluated the predictiveness of the Cox proportional hazards and linear two-piece spline models, fit to the NIOSH dose-response data, for the lymphoid cancer mortalities observed in the UCC cohort. Despite substantial differences in the exposure assessments for the NIOSH and UCC cohorts (see Section 4.1.2 of this DSD and Section 4.1 of USEPA 2016), using UCC cohort data to evaluate the validity of the models derived based on the NIOSH dose-response assessment results in the same conclusion; namely that the Cox proportional hazards model is reasonably accurate at predicting the number of lymphoid cancer mortalities observed in the UCC cohort while the linear two-piece spline model is statistically significantly over-predictive whether using the MLE or upper bound (see Section A3.3.3 of Appendix 3). Thus, the Cox model is demonstrated to be reasonably predictive and realistic, lending strong support to its scientific credibility for regulatory agency use (e.g., EtO URF derivation).

This evaluation of the accuracy of dose-response model predictions, especially in conjunction with the consideration of relevant guidance (TCEQ 2015), the MOA (Section 4.2.1), and model fit criteria (Section 4.2.2), strongly supports use of the standard Cox proportional hazards model for derivation of an inhalation URF for EtO.

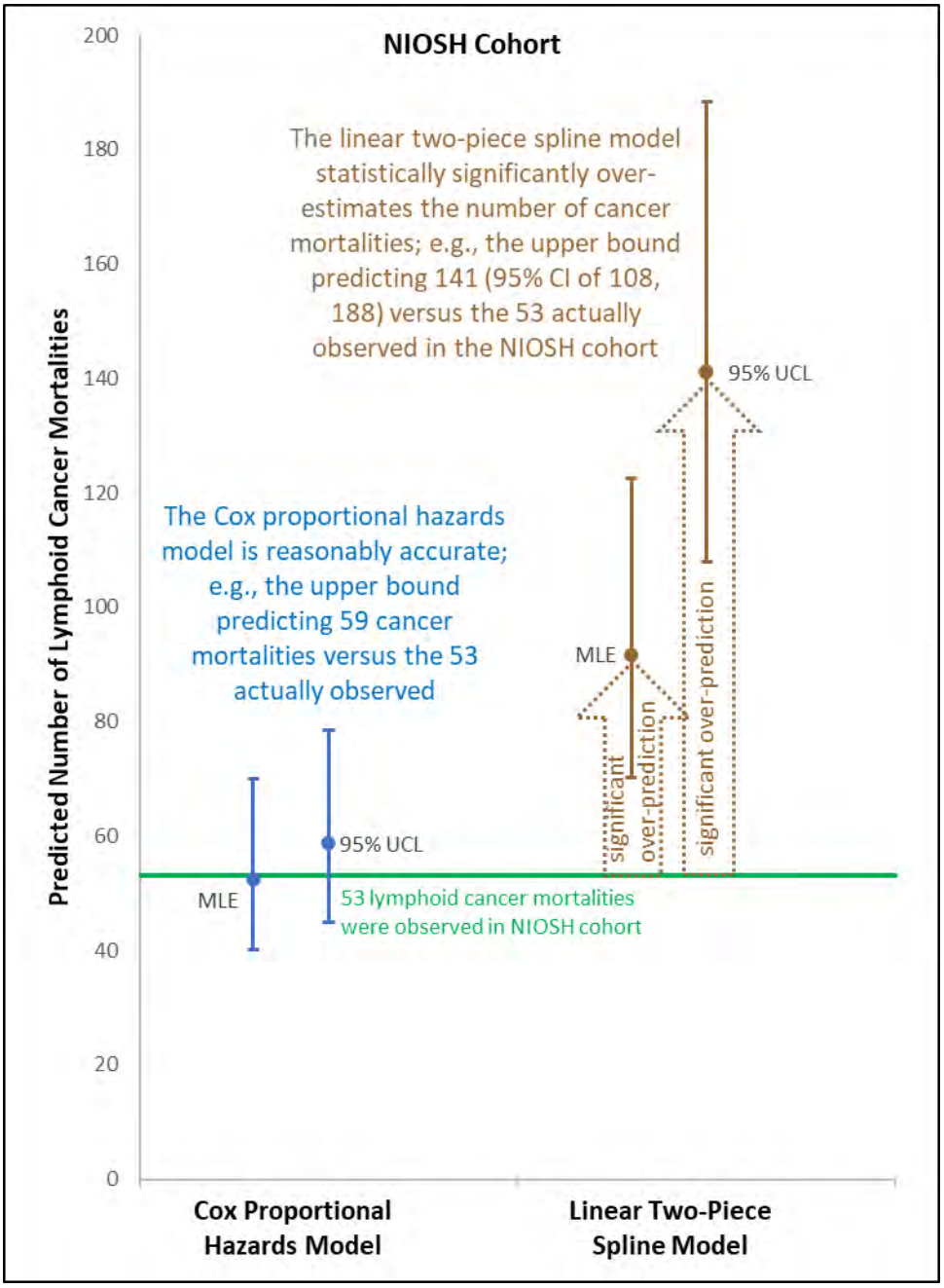


Figure 4: Total NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models

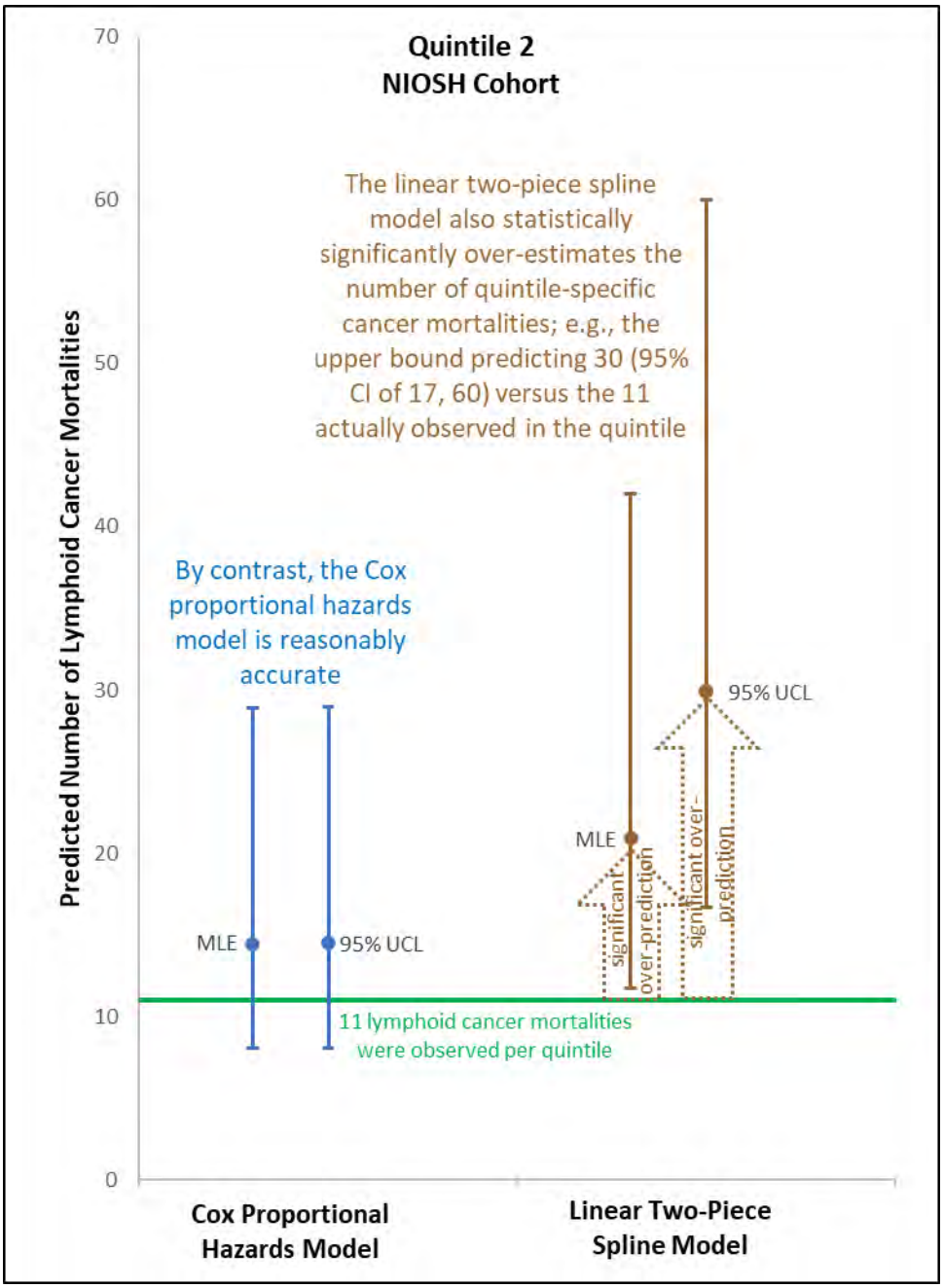


Figure 5: Quintile 2 - NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models

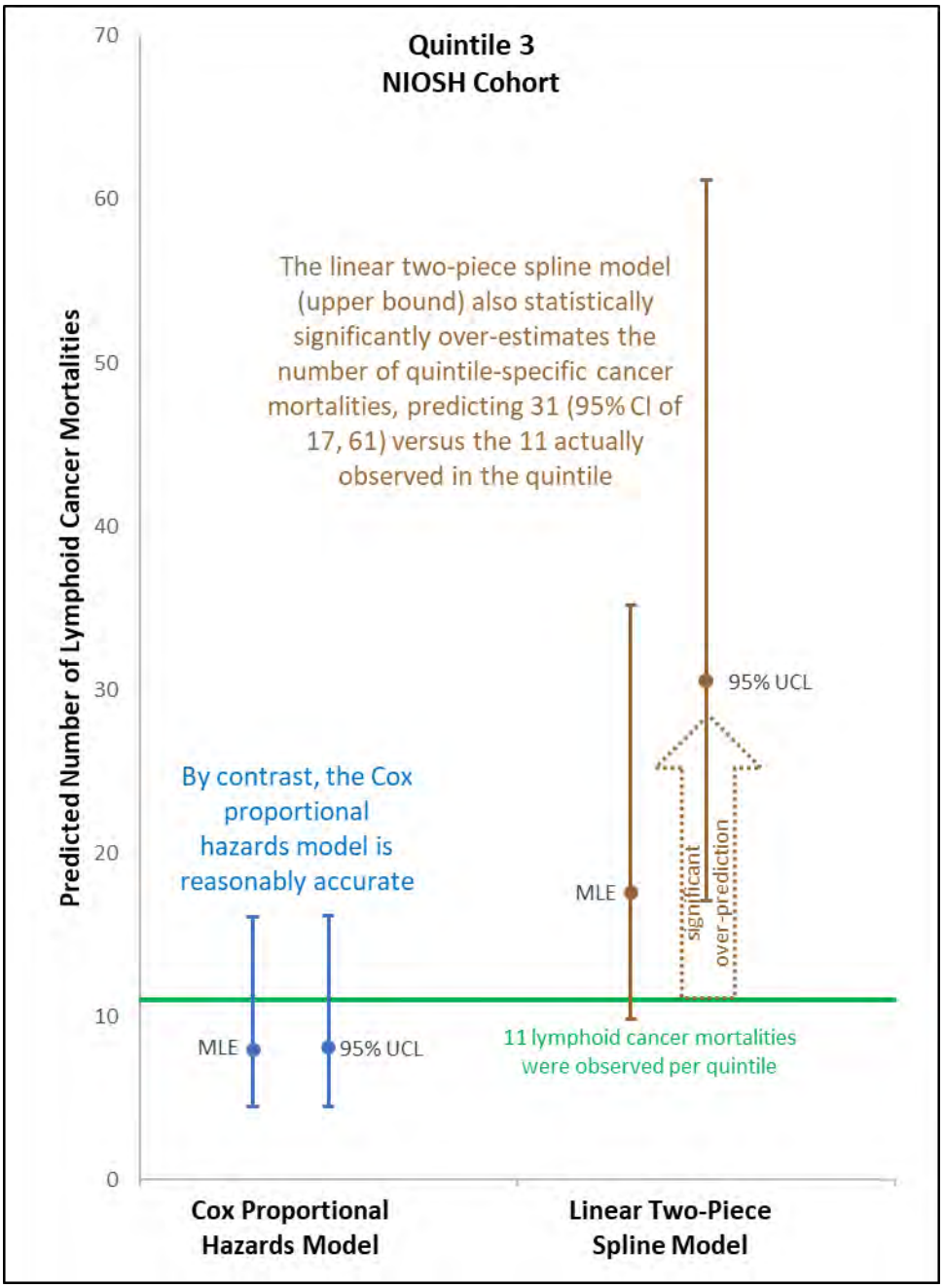


Figure 6: Quintile 3 - NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models

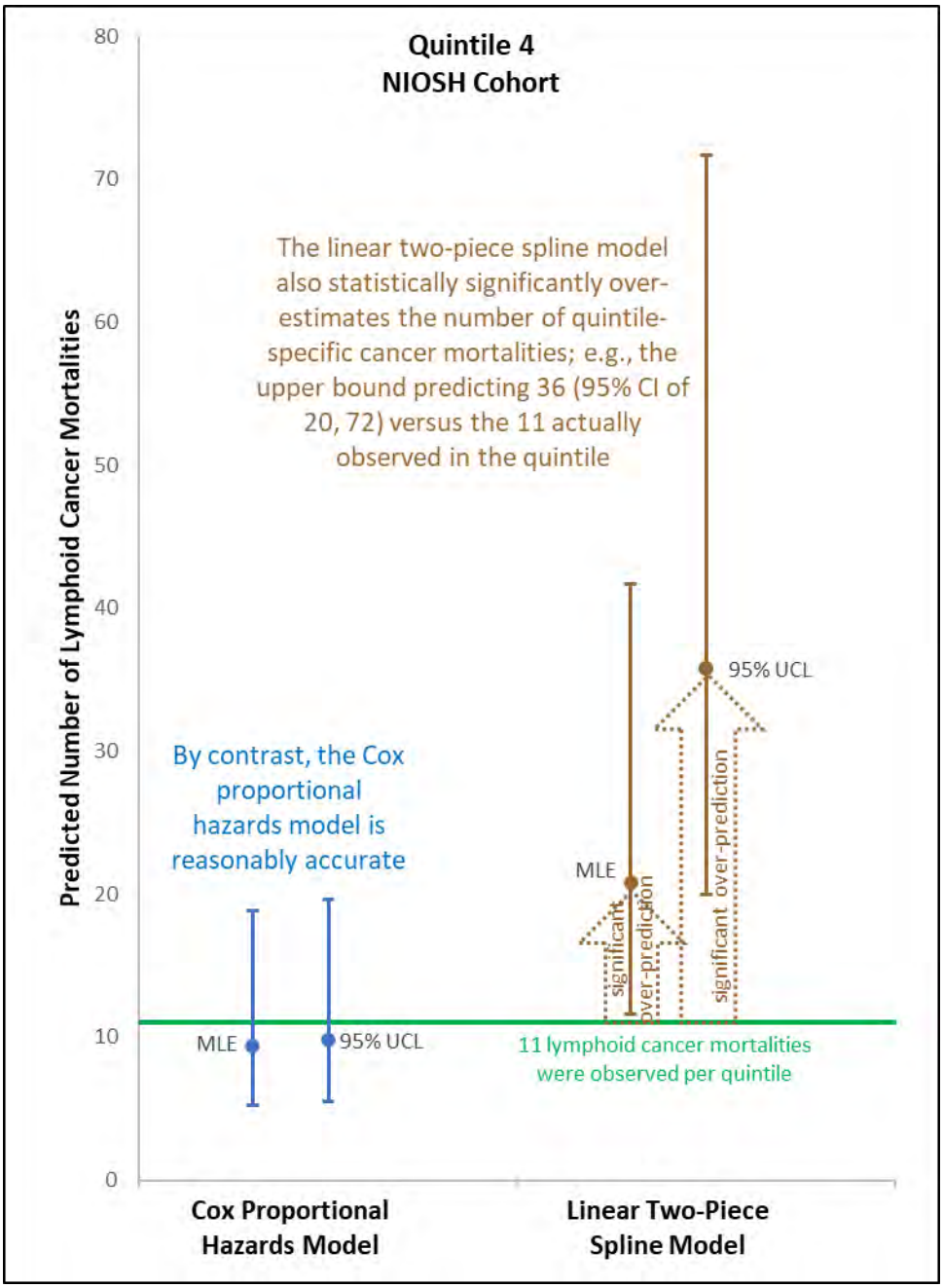


Figure 7: Quintile 4 - NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models

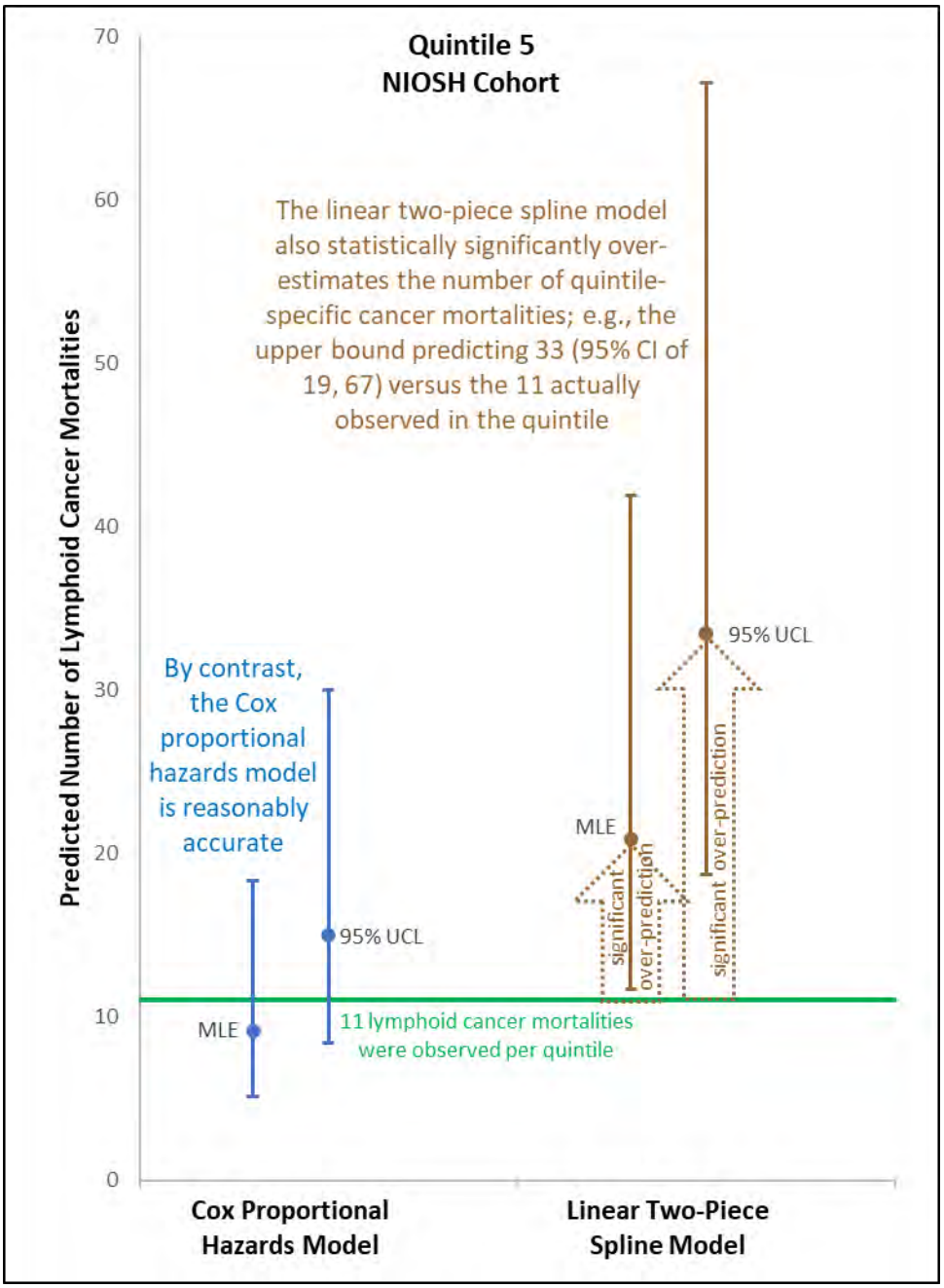


Figure 8**: Quintile 5 - NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models**

4.2.4 Selection of the Dose-Response Model

In selecting the dose-response model for the EtO carcinogenic assessment, the TCEQ has considered the following:

- Relevant guidance (TCEQ 2015);
- EtO's carcinogenic MOA;
- Standard statistical model fit criteria (p-values and AIC values); and
- Evaluation of the accuracy of dose-response model predictions for key underlying epidemiological cancer data.

Taken together and as discussed in the previous sections, these considerations strongly support use of the standard Cox proportional hazards model for derivation of the URF for EtO. The European Commission's Scientific Committee on Occupational Exposure Limits adopted the same modeling approach for their EtO cancer assessment (SCOEL 2012). Additionally, use of the standard Cox proportional hazards model abides by the USEPA SAB recommendation that "the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered." Thus, based on the bulleted considerations above, the TCEQ selects the standard Cox model for the carcinogenicity assessment of EtO.

In summary, use of the standard Cox proportional hazards model is justified based on:

1. TCEQ guidance - as the preferred epidemiology modeling methodology under TCEQ guidelines (see Section 7.7.5 of TCEQ 2015), Cox regression has been used previously by the TCEQ such as for the 1,3-butadiene carcinogenic assessment (TCEQ 2008);
2. Carcinogenic MOA - the Cox proportional hazards model is indistinguishable from linear across doses of interest and appropriate for dose-response assessment of a direct-acting mutagenic carcinogen, particularly in the absence of mechanistic data supporting the competing model (Section 4.2.1);
3. Standard model fit criteria - the more parsimonious Cox proportional hazards model fits the data just as well as the linear two-piece spline model used by USEPA (2016) (Section 4.2.2); and
4. Statistically accurate model predictions of the observed NIOSH and UCC lymphoid cancer data - the Cox proportional hazards model is shown to neither statistically over- nor under-predict the observed data, unlike the linear two-piece spline that is statistically significantly over-predictive (Section 4.2.3).

Cox proportional hazards modeling results are provided and discussed in the following section.

4.3 Cox Proportional Hazards Model Results

In accordance with sections above, Cox proportional hazards modeling results are used to derive the URF for EtO based on lymphoid cancer as the key cancer endpoint in the NIOSH cohort (UCC cohort results are used as supporting information). Briefly, the Cox proportional hazards model defines a risk set for every case (e.g., every cancer mortality from the specific cause), rather than needing a control (i.e., unexposed) group to derive the slope of the relative risk model. The Cox modeling risk sets include all the individuals that are at risk at the time the case occurred (e.g., the time of the cancer mortality from the specific cause), both exposed and unexposed workers. Thus, the TCEQ uses the full risk set, including unexposed and exposed individuals, for every case in the NIOSH study, each possibly having more than 17,000 individuals in the risk set.[g]

Valdez-Flores et al. (2010) is a published study that provides Cox proportional hazards modeling results for EtO and lymphoid cancer in the NIOSH and UCC cohorts. However, the results do not incorporate any exposure lag, and exposure lags are often appropriate for modeling carcinogenic risk from long-term exposure to a chemical (e.g., USEPA 2016 utilizes an exposure lag of 15 years for the NIOSH cohort). Therefore, in preparing this DSD, the TCEQ contracted with the first author on the Valdez-Flores et al. (2010) study to provide Cox model exposure-lagged results that had been previously developed for lymphoid cancer in the course of his research.

4.3.1 Parameter Estimates

The lymphoid cancer parameter estimates provided in the sections below are based on all individual worker data in the full NIOSH and UCC datasets.

4.3.1.1 Key NIOSH Study

Tables 8 and 9 contain log-linear (Cox regression) model results for lymphoid cancer mortality in the NIOSH (male + female) and NIOSH (male only) workers, respectively, at various EtO

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[g] By contrast, for example, using 100 randomly selected controls for each case (from the pool of all those who survived without the cancer of interest to at least the age of the index case) leads to potentially less precise RRs that are not easily reproducible (e.g., Steenland et al. 2004). This is because of the randomness in the selection of the 100 individuals used compared to using the full risk set for every case.

exposure lags. None of the exposure lags results in a model that fits the NIOSH study lymphoid cancer data statistically significantly better than the log-linear (Cox regression) model with no lag (at the 5% significance level). Results for the supporting UCC cohort are provided in the next section.

Table 8: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male + female) - MLE and Standard Error (SE) of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln(Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	3.48×10^{-6}	(1.83×10^{-6})	726.188 (0.1088)	2.571 (n/a)
5	3.45×10^{-6}	(1.95×10^{-6})	726.495 (0.3224)	2.264 (1.0000)
10	3.11×10^{-6}	(2.23×10^{-6})	727.308 (0.4841)	1.451 (1.0000)
15 [d]	2.81×10^{-6}	(2.65×10^{-6})	727.899 (0.6505)	0.860 (1.0000)
20	1.67×10^{-6}	(3.87×10^{-6})	728.598 (0.9227)	0.161 (1.0000)
25	1.48×10^{-6}	(5.19×10^{-6})	728.687 (0.9646)	0.072 (1.0000)
30	2.03×10^{-6}	(6.74×10^{-6})	728.680 (0.9613)	0.079 (1.0000)

MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, SE - standard error

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 728.759 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag. None of the exposure lags results in a model that fits the cancer data statistically significantly better than the model with no lag at the 5% significance level.

[d] Exposure lag used by USEPA (2016).

Table 9: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male only) - MLE and SE of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln(Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	3.89×10^{-6}	(1.77×10^{-6})	354.312 (0.0696)	3.293 (n/a)
5	3.85×10^{-6}	(1.89×10^{-6})	354.761 (0.2412)	2.844 (1.0000)
10	3.47×10^{-6}	(2.17×10^{-6})	355.795 (0.4045)	1.810 (1.0000)
15 [d]	3.12×10^{-6}	(2.61×10^{-6})	356.553 (0.5910)	1.052 (1.0000)
20	1.63×10^{-6}	(4.08×10^{-6})	357.467 (0.9333)	0.138 (1.0000)
25	6.50×10^{-7}	(6.06×10^{-6})	357.594 (0.9945)	0.011 (1.0000)
30	1.70×10^{-6}	(8.66×10^{-6})	357.604 (0.9995)	0.001 (1.0000)

MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, SE - standard error

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 357.605 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag. None of the exposure lags results in a model that fits the cancer data statistically significantly better than the model with no lag at the 5% significance level.

[d] Exposure lag used by USEPA (2016).

4.3.1.2 Supporting UCC Study

For the supporting UCC (male only) cohort, Table 10contains log-linear (Cox regression) model results at the same EtO exposure lags used for the key NIOSH study (Tables 8 and 9). These results are based on an update of the UCC cohort through 2013 that is not yet published. None of the EtO exposure lags results in a model that fits the UCC cohort lymphoid cancer data statistically significantly better than the log-linear (Cox regression) model with no lag (at the 5% significance level).

Table 10: Lymphoid Cell Lineage Tumor Mortality - UCC/Dow 2013 update (males) - MLE and SE of the Estimate for Different EtO Exposure Lags

Lag (years)	MLE	(SE)	Deviance [a]: -2 × Ln (Likelihood) (p-value vs null) [b]	Likelihood Ratio Test Statistic: Deviance (null model) – Deviance (model) (p-value vs zero lag) [c]
0	-1.42×10^{-5}	(9.17×10^{-6})	299.443 (0.0592)	3.559 (n/a)
5	-1.50×10^{-5}	(9.44×10^{-6})	299.216 (0.1506)	3.786 (0.6338)
10	-1.58×10^{-5}	(9.74×10^{-6})	299.021 (0.1366)	3.981 (0.5159)
15 [d]	-1.60×10^{-5}	(9.94×10^{-6})	299.059 (0.1392)	3.943 (0.5355)
20	-1.52×10^{-5}	(9.91×10^{-6})	299.497 (0.1733)	3.505 (1.0000)
25	-1.53×10^{-5}	(1.03×10^{-5})	299.744 (0.1961)	3.258 (1.0000)
30	-1.51×10^{-5}	(1.07×10^{-5})	300.156 (0.2410)	2.846 (1.0000)

MLE - maximum likelihood estimate, SE - standard error, UCC – Union Carbide Corporation

[a] Deviance is -2 × Logarithm of the Likelihood. -2 × Ln (Likelihood) = 303.002 when beta = 0 (null model). The decrease in the deviance at a specific exposure lag (compared with the deviance at 0-years lag) has to be at least 3.84 for the improvement in the deviance to be statistically significant at the 5% significance level. The decrease in the deviance at a non-zero exposure lag (compared with the deviance for the null model) has to be at least 5.99 for the improvement in the deviance to be statistically significant at the 5% significance level.

[b] p-value vs null compares the maximum likelihood of the model fit to the maximum likelihood of the null model. A small p-value indicates that the model with the specified lag fits the data better than the null model.

[c] p-value vs zero lag compares the maximum likelihood of the model fit with the specified lag to the maximum likelihood of the model with zero lag. A small p-value indicates that the model with the specified lag fits the data better than the model with zero lag. None of the exposure lags results in a model that fits the cancer data statistically significantly better than the model with no lag at the 5% significance level.

[d] Exposure lag used by USEPA (2016).

In summary, none of the EtO exposure lags results in a model that fits the key NIOSH cohort or supporting UCC cohort lymphoid cancer data statistically significantly better than the log-linear (Cox regression) model with no lag (Tables 8 to 10). This statistical consideration does not give rise to a preference for any particular exposure lag duration; however, from a biological perspective it is reasonable to include an exposure lag of some duration to account for a latency period between exposure and cancer. For this reason, as well as consistency with USEPA (2016), the TCEQ utilized an exposure lag of 15 years for derivation of risk-based air concentrations and URFs.

4.3.2 Risk-Based Air Concentrations and URFs

Consistent with the discussion above, results with a 15-year lag duration were utilized for URF derivation and are highlighted and bolded in the tables below. The calculations include adjustments for ADAFs using the approach described in Sielken and Valdez-Flores (2009a). However, as this approach has little effect on 15-year lagged results compared to more standard calculations used by USEPA and TCEQ (2015) for application of ADAFs, the TCEQ will conservatively consider the results with the 15-year lag duration to be ADAF-unadjusted.

Risk-based air concentrations and URFs are based on lymphoid cancer mortality. As discussed in TCEQ guidelines (TCEQ 2015), uncertainty is increased if the endpoint used in calculating excess risks (e.g., cancer incidence) is different than the endpoint used in the dose-response modeling (e.g., cancer mortality). It is most appropriate, when excess risks for the inference population are being calculated, for the health endpoint to be the same health endpoint as was used in the dose-response modeling. The computational details of the BEIR IV methodology are different for incidence and mortality (e.g., see Sielken and Valdez-Flores 2009b). Accordingly, the TCEQ does not generally use a mortality-based exposure-response model as the basis for the calculation of excess risks for an incidence response (or vice versa). This DSD adheres to the general principle in TCEQ guidance (TCEQ 2015) that the health endpoint used for dose-response modeling and the excess risk calculation should match. Thus, since the available data are for mortality, lymphoid cancer mortality (not incidence) serves as the basis for the TCEQ's risk-based air concentrations and URFs.

4.3.2.1 Key NIOSH Study

Tables 11 and 12 contain environmental EtO air concentrations corresponding to the 1/100,000 excess risk level (policy-based target risk per TCEQ 2015) and associated URFs for lymphoid cancer mortality in the NIOSH (male + female) and NIOSH (male only) workers, respectively. The Cox proportional hazard model was used to directly estimate the 1/100,000 extra risk level, which is at the low end of the observable range, based on the full NIOSH data set (Appendix 4).

Table 11: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male + female) - MLE and 95% Lower Confidence Limit (95% LCL) of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	8.02×10^{-3}	4.30×10^{-3}	1.25×10^{-3}	2.32×10^{-3}
5	8.82×10^{-3}	4.57×10^{-3}	1.13×10^{-3}	2.19×10^{-3}
10	1.08×10^{-2}	4.93×10^{-3}	9.30×10^{-4}	2.03×10^{-3}

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
15 [b]	**1.32×10^{-2}**	**5.18×10^{-3}**	**7.57×10^{-4}**	**1.93×10^{-3}**
20	2.49×10^{-2}	5.18×10^{-3}	4.01×10^{-4}	1.93×10^{-3}
25	3.20×10^{-2}	4.73×10^{-3}	3.12×10^{-4}	2.11×10^{-3}
30	2.71×10^{-2}	4.19×10^{-3}	3.69×10^{-4}	2.38×10^{-3}

LCL – lower confidence limit, MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, SE - standard error, UCL – upper confidence limit, URF – unit risk factor
[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration; 1/100,000 excess risk levels were estimated directly from the Cox proportional hazard model, consistent with USEPA (2005a) on selection of a POD at the lower end of the observable range of responses.
[b] Exposure lag used by TCEQ.

Table 12: Lymphoid Cell Lineage Tumor Mortality - NIOSH (male only) - MLE and 95% LCL of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	5.83×10^{-3}	3.34×10^{-3}	1.71×10^{-3}	3.00×10^{-3}
5	6.43×10^{-3}	3.56×10^{-3}	1.56×10^{-3}	2.81×10^{-3}
10	7.84×10^{-3}	3.86×10^{-3}	1.28×10^{-3}	2.59×10^{-3}
15 [b]	**9.67×10^{-3}**	**4.07×10^{-3}**	**1.03×10^{-3}**	**2.46×10^{-3}**
20	2.08×10^{-2}	4.06×10^{-3}	4.81×10^{-4}	2.46×10^{-3}
25	5.94×10^{-2}	3.64×10^{-3}	1.68×10^{-4}	2.75×10^{-3}
30	2.64×10^{-2}	2.81×10^{-3}	3.79×10^{-4}	3.56×10^{-3}

LCL – lower confidence limit, MLE - maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, SE - standard error, UCL – upper confidence limit, URF – unit risk factor
[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration; 1/100,000 excess risk levels were estimated directly from the Cox proportional hazard model, consistent with USEPA (2005a) on selection of a POD at the lower end of the observable range of responses.
[b] Exposure lag used by TCEQ.

For lymphoid cancer in the NIOSH cohort (male + female), Table 11 provides an EtO air concentration of 13 ppb (1.32E-02 ppm) as corresponding to a no significant excess risk level of 1 in 100,000 based on the MLE for the cohort (15-year exposure lag). Based on the 95% LCL (i.e., lower limit on the effect concentration LEC_{01}), 5.2 ppb (5.18E-03 ppm) is the EtO air concentration corresponding to a 1 in 100,000 excess risk. Results for NIOSH (male only) are

similar with somewhat lower risk-based air concentrations. That is, **Error! Reference source not found.** provides MLE and 95% LCL 1 in 100,000 excess risk EtO air concentrations of 9.7 ppb (9.67E-03 ppm) and 4.1 ppb (4.07E-03 ppm), respectively.

4.3.2.2 Supporting UCC Study

Table 13 contains environmental EtO air concentrations corresponding to the 1/100,000 excess risk level (policy-based target risk per TCEQ 2015) and associated URFs for lymphoid cancer mortality in the UCC (male only) cohort.

Table 13: Lymphoid Cell Lineage Tumor Mortality - UCC/Dow 2013 Update (males) - MLE and 95% LCL of the Environmental EtO Concentration at 1 in 100,000 Excess Risk

Lag (years)	MLE Environmental Concentration (1/100,000 excess risk) ppm [a]	95% LCL Environmental Concentration (1/100,000 excess risk) ppm [a]	MLE URF per ppm	95% UCL URF per ppm
0	n/a [c]	2.59×10^{-2}	0	3.86×10^{-4}
5	n/a	4.76×10^{-2}	0	2.10×10^{-4}
10	n/a	1.24×10^{-1}	0	8.06×10^{-5}
15 [b]	**n/a**	**8.70×10^{-2}**	**0**	**1.15×10^{-4}**
20	n/a	3.08×10^{-2}	0	3.25×10^{-4}
25	n/a	2.35×10^{-2}	0	4.25×10^{-4}
30	n/a	1.79×10^{-2}	0	5.58×10^{-4}

LCL – lower confidence limit, MLE - maximum likelihood estimate, UCC – Union Carbide Corporation, UCL – upper confidence limit, URF – unit risk factor

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration; 1/100,000 excess risk levels were estimated directly from the Cox proportional hazard model, consistent with USEPA (2005a) on selection of a POD at the lower end of the observable range of responses.

[b] Exposure lag used by TCEQ.

[c] n/a implies that the estimated dose-response relationship was non-increasing.

For lymphoid cancer in the UCC cohort (males), an EtO air concentration of 87 ppb (8.70E-02 ppm) corresponds to a no significant excess risk level of 1 in 100,000 based on the 95% LCL for the cohort (15-year exposure lag). This air concentration is approximately 17-21 times higher than the corresponding risk-based values based on the 95% LCL for NIOSH (male + female) workers (5.2 ppb; Table 11) and NIOSH (male only) workers (4.1 ppb; Table 12). No risk-based air concentration based on the MLE is provided in Table 13 because of the negative slope of the dose-response model (as shown in Table 10), consistent with no increased risk with cumulative EtO exposure for the cohort as modeled and reported.

The fact that the associated MLE, which represents the best fit to the data (i.e., by definition, the MLE maximizes the likelihood of the observed data), is consistent with no excess lymphoid cancer mortality risk for the UCC cohort suggests that the use of statistical bound results (i.e., LEC_{01}) for estimating excess risk for both the UCC cohort and other populations (e.g., the general population) may be conservative. Furthermore, as part of the WOE, it suggests that use of lymphoid cancer excess risk results based on the NIOSH cohort, particularly the 95% upper statistical bound on excess risk, may be conservative. This is further supported by the fact that none of the slopes for lymphoid mortality in the key NIOSH cohort (male + female, male only) or supporting UCC cohort (males) is statistically significantly greater than zero at the 5% significance level. Thus, any excess risk estimates based on these lymphoid cancer analyses may be conservative, erring on the side of health protection against the potential carcinogenic effects of EtO, particularly if the 95% UCL URF is utilized for calculation of the EtO air concentration corresponding to 1 in 100,000 excess risk.

4.3.3 Selected URF and Air Concentration at 1 in 100,000 Excess Risk

Tables 11 and 12 contain URFs and 1 in 100,000 excess risk EtO air concentrations based on lymphoid cancer in the key NIOSH (male + female) and NIOSH (male only) workers, respectively. For protection against lymphoid tumors, a value based on males is more conservative. For example, the URF (MLE) for NIOSH (male + female) is 7.57E-07 per ppb (15-year lag; Table 11) whereas the URF (MLE) for NIOSH (male only) is 1.03E-06 per ppb (15-year lag; Table 12), which is 36% higher. Thus, 9.7 ppb is the EtO air concentration corresponding to 1 in 100,000 excess risk based on the MLE for the NIOSH (male only) data, while 13 ppb is the corresponding air concentration based on the MLE for the NIOSH (male + female) data.

Accordingly, and erring on the side of health protection for both males and females, the final EtO URF will be based on the NIOSH (male only) data with a 15-year lag duration. Again, modeling results indicate that a lymphoid cancer URF value based on males is conservative for application to females; that is, results in higher excess risk estimates for females compared to a URF based on males and females combined. Furthermore, as both a scientifically reasonable and health-protective selection (e.g., in consideration of the available lymphoid cancer data being based on cancer mortality), the URF (95% UCL) of 2.5E-06 per ppb will serve as the final URF (ADAF-unadjusted) for lymphoid tumors (Table 13).

EtO URF = 2.5E-06 per ppb or 1.4E-06 per µg/m^3 (ADAF-unadjusted)

The corresponding 1 in 100,000 excess risk EtO air concentration for lymphoid tumors based on this ADAF-unadjusted URF is 4.0 ppb or 7.1 µg/m^3 (i.e., 1E-05/2.5E-06 per ppb = 4.0 ppb; 1E-05/1.4E-06 per µg/m^3 = 7.1 µg/m^3). See the next section for a discussion of the application of ADAFs. A lymphoid cancer 1 in 100,000 excess risk EtO air concentration value based on the full NIOSH (male + female) cohort would be somewhat higher at 5.2 ppb. Similarly, as

mentioned above, based on the URF (MLE) values, EtO air concentrations corresponding to 1 in 100,000 excess risk for both the NIOSH (male + female) full cohort and NIOSH (male only) cohort would be somewhat higher at 13 ppb and 9.7 ppb, respectively (Tables 11 and 12).

4.3.3.1 Evaluating Susceptibility from Early-Life Exposures

Per Section 3.2, the WOE supports mutagenicity as the putative carcinogenic MOA for EtO. A mutagenic MOA is considered relevant to all populations and life stages. See Section 3.5.2 of USEPA (2016) for available information on potentially susceptible life stages and populations (e.g., those with higher hemoglobin N-(2-hydroxyethyl)-valine (HEV) adduct levels due to a null GSTT1 genotype or with DNA repair deficiencies). USEPA (2016) indicates that there are no data on the relative susceptibility of children (or young animals of other species) to EtO (e.g., the potential for decreased detoxification/clearance by hydrolysis as a primary metabolic pathway and/or glutathione conjugation). In the absence of chemical-specific data to evaluate potential child/adult differences in susceptibility, USEPA (2005b) provides default ADAFs to account for potentially increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA. An adjustment using these ADAFs is performed because this URF will be applied to the general population. Therefore, because of the WOE supporting a mutagenic MOA and the lack of chemical-specific data on potential differences in susceptibility, increased early-life susceptibility should be assumed and ADAFs applied (TCEQ 2015). As previously mentioned, the results utilized by the TCEQ (e.g., Tables 11 and 12) incorporate USEPA (2005b) ADAFs through the approach described in Sielken and Valdez-Flores (2009a). However, as mentioned in Section 4.3.2, this approach has little effect on the results with a 15-year lag duration utilized to derive the URF compared to more standard ADAF calculations used by USEPA and TCEQ (2015), so the TCEQ conservatively considered the results to be ADAF-unadjusted. Accordingly, the TCEQ calculated an ADAF-adjusted $^{chronic}ESL_{nonthreshold(c)}$ for EtO consistent with equation 5-17 of the TCEQ guidelines (TCEQ 2015):

$$^{Chronic}ESL_{nonthreshold(c)} = \frac{6.0 \times 10^{-6}}{URF} = \frac{6.0 \times 10^{-6}}{2.5 \times 10^{-6}\ per\ ppb \quad or\ 1.4 \times 10^{-6}\ per\ \mu g/m^3}$$

$^{chronic}ESL_{nonthreshold(c)}$ = 2.4 ppb or 4.3 µg/m^3 (ADAF-adjusted, two significant figures)

This equation takes into account the ADAF-adjustment for a carcinogen with a mutagenic MOA. Refer to Section 5.7.5.3 of TCEQ (2015) for a complete derivation of the equation. Briefly, it assumes a 10-times greater risk from exposure occurring between the ages of 0 and 2, and a 3-times greater risk from exposure occurring between the ages of 2 and 16, within a lifetime exposure of 70 years. This is the same set of equations and risks as is used by USEPA (2005b).

Rounded to two significant figures, the ADAF-adjusted EtO $^{chronic}ESL_{nonthreshold(c)}$ is 2.4 ppb or 4.3 µg/m^3. Appendix 5 puts these risk-based results into biological context utilizing information on normal endogenous EtO levels.

To calculate the ADAF-adjusted URF with the ADAF-unadjusted URF (URF_{unadj}):

$$URF_{ADAF-adjusted} = \left(URF_{unadj} \times 10 \times \frac{2yrs}{70yrs}\right) + \left(URF_{unadj} \times 3 \times \frac{14yrs}{70yrs}\right) + \left(URF_{unadj} \times \frac{54yrs}{70yrs}\right)$$

$$= \left(2.5 \times 10^{-6} \times 10 \times \frac{2yrs}{70yrs}\right) + \left(2.5 \times 10^{-6} \times 3 \times \frac{14yrs}{70yrs}\right) + \left(2.5 \times 10^{-6} \times \frac{54yrs}{70yrs}\right)$$

$URF_{ADAF\text{-}adjusted}$ = 4.1E-06 per ppb or 2.3E-06 per µg/m^3 (two significant figures)

4.4 Final EtO URF and $^{chronic}ESL_{nonthreshold(c)}$

The ADAF-unadjusted URF is 1.4E-06 per µg/m^3 (2.5E-06 per ppb) based on lymphoid cancer. **The corresponding $URF_{ADAF\text{-}adjusted}$ is 2.3E-06 per µg/m^3 (4.1E-06 per ppb)**. **The ADAF-adjusted EtO $^{chronic}ESL_{nonthreshold(c)}$ is 4.3 µg/m^3 or 2.4 ppb,** rounded to two significant figures.

4.5 Long-Term ESL and Value for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values for EtO:

- $URF_{unadjusted}$ = 1.4E-06 per µg/m^3 (2.5E-06 per ppb) for lymphoid cancer
- $URF_{ADAF\text{-}adjusted}$ = 2.3E-06 per µg/m^3 (4.1E-06 per ppb) for lymphoid cancer
- $^{chronic}ESL_{nonthreshold(c)}$ = 4.3 µg/m^3 (2.4 ppb) (ADAF-adjusted; rounded to two significant figures)

The long-term ESL for air permit reviews and the evaluation of long-term ambient air monitoring data, set at an excess risk of 1 in 100,000 (policy-based target risk per TCEQ 2015), is the ADAF-adjusted $^{chronic}ESL_{nonthreshold(c)}$ of 4.3 µg/m^3 (2.4 ppb). The $URF_{ADAF\text{-}adjusted}$ is 2.3E-06 per µg/m^3 or 4.1E-06 per ppb.

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Appendix 1 Systematic Review and Evidence Integration

A1.1 Problem Formulation and Protocol

Problem formulation identifies and defines the causal questions and describes the extent of the evaluation. These questions structured the systematic review for EtO:

- What are the physical and chemical properties of EtO?
- What is the critical effect following exposure to EtO?
- Are there sensitive subpopulations?
- What is the mode of action (MOA)?
- Does route of exposure play a role?
- Is EtO carcinogenic, and if so, is it carcinogenic by a specific route of exposure?

Protocol development is another important aspect in the initial process. A protocol is typically developed around a PECO statement: Populations, Exposure, Comparator/Control, and Outcomes. These identifiers are used to lay out the framework for the literature search and inclusion/exclusion criteria. The PECO statement for EtO followed these criteria:

Table 14: PECO Statement Used by the TCEQ to Develop Toxicity Factors for EtO

Population	General human population and any relevant sensitive subpopulations, animals, and vegetation
Exposure	Exposure to EtO, surrogates with demonstrated similar MOAs, and any identified metabolites
Comparator/ Control	Populations exposed to concentrations below the concentration that causes the most sensitive critical effect
Outcome(s)	The most sensitive critical effect directly related to EtO exposure

The protocol used for the systematic review and the development of toxicity factors for EtO is as follows:

1. Identify the chemical of interest and define the causal questions
2. Conduct a systematic review for the dose-response assessment
    a. Conduct a systematic literature search
    b. Identify the inclusion/exclusion criteria
    c. Extract the relevant data from each data stream (human, animal, mechanistic)
    d. Assess the study quality and conduct a risk of bias analysis
    e. Weigh the evidence in each data stream and then integrate the evidence across the data streams
    f. Rate the confidence in the evidence

3. Derive toxicity factors (TCEQ 2015)
    a. Review the essential data, including chemical/physical properties and selected key studies from the systematic review
    b. Conduct MOA analysis
    c. Choose the appropriate dose metric considering toxicokinetics and MOA
    d. Select critical effect, based on human equivalent exposure considering each key study
    e. Extrapolate from the adjusted POD to lower exposures based on MOA analysis

A1.2 Systematic Literature Review and Study Selection

As a first step, publically available databases were searched using explicitly stated search criteria. Please see TCEQ (2015) for a list of available databases that were searched. The search terms used in literature review for EtO, along with the number of results from PubMed, are found in Table 15. Additional references were also identified using the reference sections from some of the selected studies. This literature review was conducted in December 2018, and therefore studies published after this date were not available at the time of the review.

Table 15: Search Strings Used in the Literature Review of EtO

Search Term/String	PubMed Results
ethylene oxide	9,626
“ethylene oxide”	7,478
“ethylene oxide” OR oxirane	10,374
“ethylene oxide” OR oxirane OR 75-21-8	10,374

These 10,374 studies were imported into the desktop application SWIFT-Review by Sciome and briefly searched to ensure that the key studies used in several other reviews were present in the data set. The data set was further narrowed down using the tag levels created by the SWIFT-Review software. The tags used and the number of studies with certain tagged studies removed are found in Table 16.

Table 16: SWIFT-Review Tags and Results

Data Set/Tag	Number of Studies
Initial PubMed Search	10,374
Tag – Health Outcomes, any (excluded studies with no tag)	7,468
Tag – Evidence Stream, any (excluded studies with no tag)	4,914
Tag – MeSH Chemicals, only Ethylene Oxide (excluded everything else)	1,520

Additionally, several governmental and private sector organizations were searched for published literature and toxicity values for EtO (Table 17), and the available documents along with their relevant references were added to the pool of selected material as needed.

Table 17: Available Reviews and Inhalation Toxicity Values for EtO

Organization	Year	Toxicity Value
Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles	1990	Intermediate MRL
Integrated Risk Information System (IRIS) USEPA	2016	Inhalation Unit Risk
Office of Environmental Health Hazard Assessment (OEHHA) CalEPA	2000	Chronic REL Inhalation Slope Factor

MRL – minimal risk level, REL – reference exposure level

Following this initial review, specific inclusion and exclusion criteria were used to narrow down the pool of available data. The criteria along with examples of the kinds of studies that were excluded can be found in Table 18.

Table 18: Inclusion/Exclusion Criteria used in the Review of EtO

Study Type	Inclusion Criteria	Exclusion Criteria
General	Complete study available for review	- Only abstract is available - Study in a language other than English - Unpublished report/unable to retrieve
	Study contains original data or utilizes existing data in a novel way	- Study is a review article or meta-analysis - Study comments on a previous method without providing a sufficient alternative
	Exposure concentration is known or can be reasonably estimated	- Exposure concentration unknown - Exposure environment/conditions unsuitable to concentration estimation
	Study examines effects related to chemical exposure	- Study measures concentration in air, factories, etc. - Study does not examine health effects
	Study focused on the chemical of concern	- Study examined mixture effects - Study on treatment following EtO exposure
	Route of exposure is relevant to exposure and toxicity factor development	- Exposure through intravenous, intraperitoneal, or subcutaneous injection - Study examining oral or dermal exposure
Animal	Relevant animal model and endpoints examined	- Study used non-mammalian animal models - Endpoint studied not relevant to human health - Endpoint not applicable to toxicity factor development
	Appropriate study populations and methods were used	- Study lacked appropriate numbers or doses - Exposure method unsuitable for dose-response
Human/Epi	Relevant endpoints examined	- Study focused solely on cytogenetic changes - Study only measured sister chromatid exchanges (SCEs), protein adducts, or chromosomal changes
	Study populations allowed for significant findings and follow ups	- Case studies examining single high-dose exposures - Studies without appropriate follow-up studies - Historical studies that have been updated

epi - epidemiological

Studies were then divided into groups by evidence stream (i.e. human, animal) and effect group (i.e., acute, chronic non-carcinogenic, carcinogenic). For the purposes of this DSD, only the human carcinogenic/epidemiologic data were considered for several reasons:

1. In order to expedite the process, it was decided that only a health-based chronic carcinogenic toxicity factor would be derived for EtO in this DSD. Other toxicity factors (i.e. health- and welfare-based acute and chronic non-carcinogenic) may be evaluated at a later date with an additional systematic review continuing where this systematic review ended.
2. Sufficient human data exist for EtO such that animal data, although used to strengthen the carcinogenicity classification, would not be used to derive a chronic carcinogenic toxicity factor. TCEQ (2015) states that in general, human data are preferred over animal data when developing toxicity factors.
3. Similarly, mechanistic data provide crucial information for the MOA analysis but do not provide the necessary dose-response information required for derivation of a chronic carcinogenic toxicity factor.
4. And finally, human data looking solely at cytogenetic changes, sister chromatid exchanges, or chromosomal abnormalities were considered useful in developing the MOA of EtO, but not useful as a basis for derivation of a health-based toxicity factor.

After full text review and screening with the inclusion/exclusion criteria listed above, eight human carcinogenic studies were identified for further use in this systematic review. Several human studies (directly or indirectly related to carcinogenicity) were reviewed and later excluded for various reasons (Table 19).

Table 19: Excluded Human Studies Related to Carcinogenicity

Reason for Exclusion	Study	
No exposure or dose-response information available to directly derive a toxicity factor (Not useful in the development of a carcinogenic-based toxicity factor)	Ambroise et al. 2005 Austin and Sielken 1988 Bisanti et al. 1993 Coggon et al. 2004 Fondelli et al. 2007 Gardner et al. 1989 Greenburg et al. 1990 Greife et al. 1988 Hagmar et al. 1991 Kardos et al. 2003	Kiesselbach et al. 1990 Kiran et al. 2010 Kirman and Hays 2017 Morgan et al. 1981 Mosavi-Jarrahi et al. 2009 Norman et al. 1995 Olsen et al. 1997 Swaen et al. 1996 Wong and Trent 1993
Follow-up study available	Greenberg et al. 1990 Hagmar et al. 1995 Hogstedt et al. 1979a Hogstedt et al. 1986	Stayner et al. 1993 Steenland et al. 1991 Teta et al. 1993
Review, methods, or case study	Hogstedt et al. 1979b Hornung et al. 1994 Kita 1991 Shore et al. 1993 Sielken and Valdez-Flores 2009a	Sielken and Valdez-Flores 2009b Steenland et al. 2011 Valdez-Flores et al. 2011 Valdez-Flores and Sielken 2013

A1.3 Data Extraction

Each of the identified studies was reviewed in detail and the primary data were extracted for potential use in the development of the chronic carcinogenic toxicity factor in this DSD (Table 20).

Table 20: Data Extraction from Epidemiological Studies

Study (cohort)	Size	Exposure Measurement	Tumor Type(s)	Notable Results [a]	Notes
Hogstedt 1988 (Swedish, chemical)	539 m 170 f	Years of employment, 1-9 years, ≥ 10 years	Stomach	SMRs – 597, 608	Exposure estimates conducted in original study but not presented here.
			Blood/Lymphatic	SMRs – 380, 330	
			Leukemia	SMRs – 322, 880	
Kirman 2004 (NIOSH + UCC)	18,254 (NIOSH) (55% m, 45% f) 1,896 m (UCC)	ppm-years, 7.4, 64.8, 187.4, 477.7	Leukemia	POD-ED_{001} estimated at 265 ppm-years, URFs: linear 4.5×10^{-7} /µg/m^3 Quadratic 4.5×10^{-8} /µg/m^3 (no lag or latency periods)	Concentration at 1×10^{-5} cancer risk: Linear – 22 µg/m^3 (12 ppb) Quadratic – 222 µg/m^3 (120 ppb) Nonlinear – 37 µg/m^3 (21 ppb)
Mikoczy 2011 (Swedish, sterilant)	862 m 1,309 f	ppm-years, 0-0.13, 0.14-0.21, ≥ 0.22	Breast	SIRs – 0.52, 1.06, 1.12	Compared with/out 15-year latency and between follow-ups
			LHN	SIRs – 1.35, 1.32, 1.08	
Steenland 2003 (NIOSH)	7,576 f (5,139 f interviewed)	ppm-days, 0, >0-647, 647-2026, 2026-4919, 4919-14620, 14620+	Breast (Compared to US population)	SIRs – 0.88, 0.77, 0.77, 0.94, 0.83, 1.27 (15-year lag, cumulative)	Subset of the NIOSH cohort, multiple other comparisons presented, including cumulative, categorical, and log cumulative exposure, positive trends for continuous exposure, duration of exposure, and log of cumulative exposure. Overall SMR for NIOSH cohort for breast cancer is 0.99. Exposure-response analysis showed highest group SMR of 1.27, with 20-year lag increased to 2.07 (95% CI: 1.0-3.54)
			Breast (Compared to study population, whole cohort)	Odds Ratios – 1.00, 1.07, 1.00, 1.24, 1.17, 1.74* (15-year lag, categorical, cumulative)	
			Breast (Compared to study population, only interviewed cohort)	Odds Ratios – 1.00, 1.06, 0.99, 1.24, 1.42, 1.87* (15-year lag, categorical, cumulative)	

Study (cohort)	Size	Exposure Measurement	Tumor Type(s)	Notable Results [a]	Notes
Steenland 2004 (NIOSH)	7,645 m 9,885 f	ppm-days, 0, >0-1199, 1200-3679, 3680-13499, 13500+	NHL	SMRs – 2.09, 0.61, 0.88, 0.79, 2.37* m, 10-year lag, cumulative	Multiple other comparisons presented, including cumulative, categorical, and log cumulative exposure, 10, 15, and 20-year lag, positive trend for lymphoid tumors
		ppm-days, 0, >0-646, 647-2779, 2780-12321, 12322+	Breast	SMRs –0.80, 1.05, 1.01, 1.15, 2.07* f, 20-year lag, cumulative	
Swaen 2009 (UCC)	2,063 m	ppm-years, 0-15, 15-65, 65+	None	Authors state no long-term carcinogenic effects associated with EtO exposure	Cohort experienced more than twice the average estimated cumulative exposure compared to NIOSH cohort
Teta 1999 (multiple reviewed, dose-response done for NIOSH and UCC)	Multiple, meta-analysis 8,214 m & 10,040 f (NIOSH) 1,896 m (UCC)	ppm-years, 0, 0-33, 33-125, 125-285, >285	Lymphoid (lymphocytic leukemia and NHL)	Added Risk (environmental) UCC – none NIOSH – 10^{-8} – 10^{-5} /ppb	Compared 0 and 10-year latency, and 0 and 5y lag periods, POD-ED_{001} values ranged from 0.81-1.58 ppm assuming a 10-year latency and a 5-year lag period. POD-ED_{001} of 0.81 ppm gives a URF of 0.12/ppm, and a concentration at 1×10^{-5} cancer risk of 0.083 ppb (0.15 μg/m^3)
			Leukemia	Added Risk (environmental) UCC – 10^{-12} – 10^{-6} /ppb NIOSH – 10^{-15} – 10^{-6} /ppb	
Valdez-Flores 2010 (NIOSH + UCC)	7,634 m & 9,859 f (NIOSH) 2,063 m (UCC)	ppm-days, dose ranges varied by endpoint	Examined 12 cancer endpoints in 6 subcohorts	No statistically significant increases in SMRs, trends, cumulative continuous, or categorical exposure.	No heterogeneity between dose-response models of the two major cohorts and the pooled study, combining increases the power.

NIOSH - National Institute of Occupational Safety and Health, SMR – Standardized Mortality Ratio, SIR – Standardized Incidence Ratio, NHL – Non-Hodgkin's Lymphoma, LHN – Lymphohematopoietic neoplasms, m – males, f – females, UCC – Union Carbide Corporation, ED_{001} – effective dose at 1E-03 excess risk

[a] Due to space constraints, only notable results are presented here. See individual studies for a more in-depth review.

* Denotes statistical significance at α=0.05 level, 95% confidence interval does not include 1

A1.4 Study Quality and Risk of Bias (ROB)

Each of the selected studies was evaluated for study quality and ROB based on a number of attributes determined prior to this review. For this review, study quality methods were adapted from the USEPA version of the Health Assessment Workspace Collaboration (HAWC) online software. For epidemiology studies, seven evaluation domains are used to critically assess different aspects of study design and conduct relating to reporting, risk of bias, and study sensitivity. Each domain receives a score of Good, Adequate, Deficient, Critically Deficient, or Not Reported, and once all domains are evaluated, a confidence rating of High, Medium, or Low confidence or Uninformative is assigned to each study. The evaluated domains and explanations are found in Table 21, while the general guidance for scoring each of the studies are found in Tables 22 and 23.

Table 21: Study Quality Domains for Epidemiology Studies (taken from HAWC)

Domain	Study Design Questions and Aspects
Selection and Performance/ Participant Selection	**Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?** Study design, where and when was the study conducted, and who was included? Recruitment process, exclusion and inclusion criteria, type of controls, total eligible, comparison between participants and nonparticipants (or followed and not followed), final analysis group. Does the study include potential vulnerable/susceptible groups or life stages?
Exposure Methods/ Measures	**Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?** Source(s) of exposure (consumer products, occupational, an industrial accident) and source(s) of exposure data, blinding to outcome, level of detail for job history data, when measurements were taken, type of biomarker(s), assay information, reliability data from repeat measures studies, validation studies.
Outcome Methods/Results Presentation	**Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?** Source of outcome (effect) measure, blinding to exposure status or level, how measured/classified, incident versus prevalent disease, evidence from validation studies, prevalence (or distribution summary statistics for continuous measures).
Confounding	**Is confounding of the effect of the exposure unlikely?** Background research on key confounders for specific populations or settings; participant characteristic data, by group; strategy/approach for consideration of potential confounding; strength of associations between exposure and potential confounders and between potential confounders and outcome; degree of exposure to the confounder in the population.
Analysis	**Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?** Extent (and if applicable, treatment) of missing data for exposure, outcome, and confounders, approach to modeling, classification of exposure and outcome

Domain	Study Design Questions and Aspects
	variables (continuous versus categorical), testing of assumptions, sample size for specific analyses, relevant sensitivity analyses.
Selective Reporting	**Is there concern for selective reporting?** Are results presented with adequate detail for all the endpoints of interest? Are results presented for the full sample as well as for specified subgroups? Were stratified analyses (effect modification) motivated by a specific hypothesis?
Sensitivity	**Are there concerns for study sensitivity?** What exposure range is spanned in this study? What are the ages of participants (e.g., not too young in studies of pubertal development)? What is the length of follow-up (for outcomes with long latency periods)? Choice of referent group and the level of exposure contrast between groups (i.e., the extent to which the 'unexposed group' is truly unexposed, and the prevalence of exposure in the group designated as 'exposed'). Is the study relevant to the exposure and outcome of interest?
Overall Study Confidence	**Once the evaluation domains have been classified, these ratings will be combined to reach an overall study confidence classification of High, Medium, Low, or Uninformative.** This classification will be based on the classifications in the evaluation domains and will include consideration of the likely impact of the noted deficiencies in bias and sensitivity on the results.

Table 22: Study Quality Domain Scoring

Score	Reasoning
+ +	**Good** – Study meets or exceeds domain properties, may have minor deficiencies but none that would affect the outcome of the study or the development of toxicity factors.
+	**Adequate** – Study meets most of the domain properties, may have some deficiencies but none are severe or are expected to have a serious effect on the development of toxicity factors.
-	**Deficient** – Study has one or more deficiencies that are likely to affect the outcome of the study or the development of toxicity factors, but development may still occur with some added uncertainty.
- -	**Critically Deficient** – Study has serious deficiencies that would severely inhibit the development of toxicity factors. These studies are typically classified as "uninformative" unless a detailed explanation otherwise is provided.
NR	**Not Reported** – Domain properties are not provided in the study or referred to in previous author's studies. Depending on the domain and type of study, these studies should be carefully considered prior to use.

Table 23: Study Quality Confidence Rating Scoring

Score	Reasoning
+ +	**High** – Overall a well conducted study, no serious deficiencies identified, no concern for issues with sensitivity or risk of bias (ROB), most domains should be scored good or adequate.
+	**Medium** – Some deficiencies may be noted, but nothing that would cause significant concern for issues with sensitivity or ROB, most domains should be scored adequate.
-	**Low** – Deficiencies noted, some severe, and some concern over bias or sensitivity that may impact the assessment, study has domains that scored deficient.
- -	**Uninformative** – Severe deficiencies that would seriously impact the assessment, study is typically unusable for toxicity factor development without a detailed explanation. Any study with a domain listed as "Critically Deficient" should be considered for this category.

Scoring for each of the included studies is shown in Table 24. Each reviewer (composed of two members of the TCEQ Toxicology, Risk Assessment, and Research Division and authors on this DSD) scored the included studies independently, then came together as a group to agree on a single score for each domain/study (individual scoring not shown).

Table 24: Study Quality and Risk of Bias Scoring Visual

Domain/Study	Hogstedt 1988	Kirman 2004	Mikoczy 2011	Steenland 2003	Steenland 2004	Swaen 2009	Teta 1999	Valdez-Flores 2010
Selection and Performance/Participant Selection	+	+ +	+	+	+ +	+	+ +	+ +
Exposure Methods/Measures	-	+	-	+	+	-	+	+
Outcome Methods/Results Presentation	+	+	+ +	+	+	+	+	+ +
Confounding	-	+	-	+ +	+	+	+	+
Analysis	+	+	+	+	+ +	+	+	+ +
Selective Reporting	+	+	+	+	+	+	+	+
Sensitivity	-	+	-	+	+	+	+	+
Overall Study Confidence	-	+	+	+	+	+	+	+

A1.5 Evidence Integration

After addressing the study quality and ROB for each of the selected studies, the primary information from each of the studies was compiled and each study was assessed for use as a key, supporting, or informative study for the EtO carcinogenic dose-response assessment detailed in Chapter 4 (Table 25).

Table 25: Evidence Integration Table for Human Studies

Study	Cohort	Type	Reasoning
Hogstedt 1988	Swedish chemical workers	Informative	- Relatively small cohort with little information on co-exposures - Exposure concentrations or estimations not provided - Primary cohort to show increased leukemia mortality rates - Also presented increased stomach and blood/lymphatic cancer
Kirman 2004	NIOSH + UCC	Supporting	- Combined data from two largest cohorts and examined leukemia and lymphoid tumor mortality data - Provided results for several different extrapolation methods - Selected a single outcome and POD to carry through
Mikoczy 2011	Swedish sterilant workers	Informative	- Relatively small cohort with little exposure information presented - Healthy worker effect likely influenced the results - Non-significant increases in leukemia, NHL, and lymphohematopoietic cancer mortality - Significant increases in the rate ratios of breast cancer in the two highest exposure groups
Steenland 2003	NIOSH (females only)	Informative	- Subset of the largest cohort study available, additional nested case-control using subjects who answered personal interviews - Examined breast cancer mortality and incidence data - Positive trend for increased incidence, but not significantly increased
Steenland 2004	NIOSH	Supporting	- Update to the largest EtO-exposed cohort data available - Focused mainly on hematopoietic and breast cancers, and examined various exposure variables and lag periods - No significantly increased cancer incidences, but a positive trend observed for lymphoid tumors (males, 15-year lag)
Swaen 2009	UCC	Supporting	- Although a relatively smaller cohort, the strength of the update was made up for in the length of follow-up and number of deaths - Little to no exposure monitoring data available, estimates made from work history

Study	Cohort	Type	Reasoning
			- Examined a wide array of cancer types but no lag/latency periods included in the analysis - No cancer associations observed
Teta 1999	Meta-analysis, NIOSH, UCC	Supporting	- Very basic meta-analysis of 10 EtO cohorts but lacked dose-response data, detailed analysis on individual NIOSH and UCC cohorts only - Examined lymphoid and leukemia rates with various lags and latency periods and control groups using Poisson regression - UCC cohort showed no added risk, while NIOSH cohort predictions were in the range of 10^{-7} to 10^{-5} at 1 ppb environmental exposures
Valdez-Flores 2010	NIOSH + UCC	Key	- Combined most recent data from the UCC and NIOSH cohorts - Examined 12 cancer endpoints (breast, leukemia, lymphoid, etc.) and 6 sub-cohorts (NIOSH males, females, UCC males, etc.) using Cox proportional analyses without latency/lag periods - No statistically significantly increasing SMRs or trends in any of the cancer endpoints examined

EtO – ethylene oxide, NIOSH - National Institute for Occupational Safety and Health, SMRs – standardized mortality ratios, UCC – Union Carbide Corporation

After final review of the included studies, the Valdez-Flores et al. (2010) study had the most thorough and complete analysis (e.g., included data from both the NIOSH and UCC cohorts, examined multiple cancer endpoints) and was therefore selected as the key study. While the Valdez-Flores et al. (2010) study also utilized a default lifetime duration (70 years) consistent with TCEQ guidance (TCEQ 2015), there were aspects that were not ideal for the evaluation described in this DSD, such as the lack of results with lags in exposure. So rather than select a POD from the key study, the TRARD selected data from both cohorts (i.e., the NIOSH and UCC cohorts) to initially evaluate and conduct an independent assessment using the same modeling approach but with supplemental analyses (e.g., the evaluation of various exposure lags). Selection of data from the NIOSH and UCC cohorts as the epidemiological data to evaluate and use of specific, TCEQ-directed dose-response assessment analyses (rather than selection of a study POD) provide the best basis for a carcinogenic assessment of EtO for several reasons:

1. Both the NIOSH and UCC cohorts have adequate size, exposure information, and follow-up, making consideration of all the data ideal for toxicity factor development (e.g., weight of evidence, more analyses to consider).
2. The Valdez-Flores et al. (2010) study makes use of the Cox proportional hazards model, a standard model preferred under TCEQ guidelines (TCEQ 2015) and one that the TRARD has used previously in dose-response assessments (also considered by USEPA 2016).

3. Although Valdez-Flores et al. (2010) did not include results with exposure lags in their publication, supplemental analyses involving a reassessment of the data using various exposure lags allow for the consideration of even more assessment results in this DSD.
4. Additionally, since 2010, an update to the UCC data through 2013 has become available to the first author of the Valdez-Flores et al. (2010) study (submitted for publication, personal communication), with whom the TCEQ contracted to perform supplemental analyses; consequently, results from the new study update with a longer follow-up period can also be included in the DSD.
5. Unlike USEPA (2016) that uses a lifetime exposure duration value of 85 years, the TCEQ-directed dose-response analyses use a standard default of 70 years consistent with TCEQ guidance (TCEQ 2015).
6. Finally, conducting these new analyses will allow for the appropriate consideration of model fit to the individual data (rather than the categorical data) for the model assessment selected by the TCEQ.

A1.6 Confidence Rating

Table 26provides scoring criteria to rate the confidence and uncertainty for each aspect or element of the toxicity assessment. The table provides the name of the element and the magnitude of the confidence in each element using a qualitative ranking system of low, medium, or high confidence. Table 27 displays the overall confidence in the EtO carcinogenic assessment. Once the noncarcinogenic assessments are completed for EtO, the confidence rating will be updated to cover the entire assessment.

Table 26: Confidence Scoring Criteria for EtO Carcinogenic Assessment

Element	Low	Medium	High
Database Completeness	Only a single study or a few low-quality studies were available.	Several studies were available, but some important studies were missing.	Several high-quality studies were available for selection.
Systematic Review	A systematic approach was not used.	A systematic approach was considered and some methods were applied, but a full review was not conducted.	A systematic approach was used in study evaluation and clear criteria were established for judgment.
Key Study Quality	Selected study has deficiencies, but was still considered useful.	Selected study was reasonably well done but some restrictions must be considered.	Selected study was well done and can be used without restriction.
Critical effect	Critical effect or dose-response curve was moderate to severe. MOA information was not available.	Critical effect was moderate; other studies were deemed necessary to determine the critical effect.	Critical effect was minimal, or the confidence in the critical effect was high. MOA information was available.
Relevance of Critical Effect	Critical effect was only presumed to be relevant for the general population; MOA was not known for the critical effect.	Critical effect appeared to be relevant for the general population. MOA was known for the critical effect and possibly relevant to humans.	Critical effect based on a human study or matches observed human experience; MOA was well understood so critical effect was assumed relevant.
Point of Departure (POD)	Many uncertainties exist in POD; only a few dose groups; no dose-response modeling was used.	Some uncertainty exists in POD; few dose groups; difference between confidence limits was large.	Basis for POD well understood; multiple dose groups, dose-response modeling was conducted.
Sensitive Populations	Many uncertainties on sensitive population(s) existed and were not addressed.	Information on sensitive population(s) was not known but default procedures are presumed to be conservative.	Human data on sensitive populations were available and uncertainties were addressed.
Peer Review	Limited or no peer review; disregarded comments would significantly change risk value; no independent check.	Adequate peer review. Most substantive comments addressed; disregarded comments would not significantly change value.	High quality panel peer review with appropriate experts; all substantive comments addressed as per independent check.
Toxicity Value Comparison	Relevant risk values show a greater than 10-fold difference without justification.	Some relevant risk values agreed within 3-fold of each other, others disagreed within 10-fold without justification.	All relevant risk values agreed within 3-fold of each other or there was sufficient justification for differences.

Table 27: Confidence in the Toxicity Assessment

Element	Score	Basis
Database Completeness	Medium	- Several occupational cohorts (i.e., preferred human data) and animal studies available - Evidence of carcinogenic effects found in both human epidemiological and animal studies - However, estimated exposures are based on incomplete information, are remarkably high, and are not in/near lower range of interest (i.e., not environmentally relevant)
Systematic Review	High	- Systematic review conducted
Key Study Quality	High	- Valdez-Flores et al. (2010) was a well-conducted study of two cohorts and multiple cancer endpoints with standard Cox proportional hazards modeling but lacked the use of a lag period - Reassessment in this DSD of these key epidemiological data utilizing multiple exposure lags and new UCC cohort data allowed for informative supplemental and updated analyses
Critical effect	Low	- Human data not conclusive despite very high exposure (e.g., results vary between studies) - Model (slope > 0) not statistically significantly different than the null model (slope = 0) at the 5% significance level
Relevance of Critical Effect	Medium	- Assumed relevant although general population exposed to EtO concentrations that are orders of magnitude lower than the occupational study wherein lymphoid cancer was statistically increased only in the highest cumulative exposure group
Point of Departure (POD)	High	- Cox Proportional Hazard model used - Modeling results demonstrated to be predictive of cohort study findings
Sensitive Populations	Medium	- No specific data on sensitive subpopulations - Default ADAFs were applied to account for potentially increased susceptibility in children due to early-life exposure
Peer Review	High	- DSD proposed for public comment and reviewed by a consulting academic statistician and subject matter expert regarding potential statistical issues at TCEQ's direction - DSD reviewed by an external panel of 6 experts in the fields of occupational epidemiology, dose-response modeling, and risk assessment
Toxicity Value Comparison	High	- TCEQ Chronic ESL based on lymphoid cancer mortality is ≈2,000 times higher than the USEPA value based on lymphoid/breast cancer incidence at the same excess risk level (1E-05) - TCEQ's approach is supported by multiple lines of evidence as discussed in the DSD

Element	Score	Basis
		- Extensive comparisons, calculations, and explanations as to the differences with USEPA's methods are included in the DSD (e.g., USEPA's model assessment is demonstrated to be statistically significantly over-predictive; Appendix 6)

Confidence Scoring Summary			
Not Evaluated	**Low Confidence**	**Medium Confidence**	**High Confidence**
	Critical Effect	Database Completeness	Systematic Review
		Relevance of Critical Effect	Key Study Quality
		Sensitive Populations	Point of Departure
			Toxicity Value Comparison
			Peer Review

ADAF – age-dependent adjustment factor, DSD – development support document, ESL – effects screening level, UCC – Union Carbide Corporation

Appendix 2 Weighting of the NIOSH and UCC Cohorts

The weighting of data from the NIOSH and UCC cohorts was a consideration in determining the key cohort. In the TCEQ (2011) assessment of the carcinogenicity of nickel, a weighting factor of person-years × $1/SE^2$ for the β (MLE) was used to weight URFs from different studies. As stated in TCEQ (2011), generally there is more confidence in cohort studies with large worker populations and/or long follow-up periods, which increase person-years at risk. Similarly, variance in the β values used to derive URFs reflects uncertainty in the β estimates and can also be used as a weighting factor. Generally, there is more confidence in β values with smaller variance. In the carcinogenic assessment of inorganic arsenic (TCEQ 2012), the inverse of the variance ($1/SE^2$) for the β (MLE) was used to weight URFs. Inverse-variance weighting (without a person-years weighting factor) is a more standard statistical procedure used in meta-analyses (TCEQ 2015).

Standard error (SE) values for the slopes were obtained from Tables 9 and 10 (15-year lag) for the Cox proportional hazards model evaluation of lymphoid tumors in NIOSH cohort males (SE=2.61E-06) and UCC cohort males (SE=9.94E-06), respectively. For comparison, it is noted that the SE (2.65E-06; Table 8) for the full NIOSH cohort (male + female) provides similar weighting results. Both types of weighting factors previously used by the TCEQ were calculated (i.e., $1/SE^2$ and person-years × $1/SE^2$) and are provided in Table 28.

Table 28: Weighting Factors for the Lymphoid Tumor Analyses for the NIOSH and UCC Cohorts

Cohort	Gender	Slope SE	Weight $1/SE^2$	Weight Ratio NIOSH/ UCC	Person-Years	Total Weight Person-Years × $1/SE^2$	Relative Total Weight NIOSH/ UCC
NIOSH	M	2.61E-06	1.47E+11	14.5	189,868	2.79E+16	33.0
NIOSH	M/F	2.65E-06	1.42E+11	14.1	450,906	6.42E+16	76.0
UCC	M	9.94E-06	1.01E+10	---	83,524	8.45E+14	---

F – female, M – male, NIOSH - National Institute for Occupational Safety and Health (NIOSH), SE – standard error, UCC – Union Carbide Corporation

As shown in Table 28, using person-years × $1/SE^2$ as a weighting factor results in the NIOSH (male only) cohort receiving ≥33-fold greater weight than the UCC (males) cohort. Using $1/SE^2$ as a weighting factor produces >14-times greater weight for the NIOSH (male only) cohort than the UCC (males) cohort. Thus, based on the considerations inherent to the weighting factors applied, results suggest that for all practical purposes the URF (and corresponding 1 in 100,000 excess risk air concentration) can be based on the NIOSH cohort alone, because a weighted URF and ESL that consider both the NIOSH and UCC cohorts would be almost the same as one derived from the NIOSH cohort alone (i.e. within the rounding error of the calculated value). Accordingly, the TCEQ utilized the NIOSH cohort as the sole key cohort for derivation of the URF.

Appendix 3 Reality Check of Epidemiological Exposure-Response Model Results for EtO and Lymphoid Cancer Mortality

A robust method of dose-response model comparison is to see how well the parametric models predict the number of lymphoid cancer deaths (the key cancer endpoint) versus the actual number of deaths observed in the key NIOSH cohort. A good (i.e., reasonably accurate) parametric model should predict the observed number of lymphoid cancer deaths with some confidence (e.g., the observed number of lymphoid cancer deaths in the NIOSH cohort should be inside a 95% confidence interval of the predicted number of lymphoid cancer deaths).

Here, the standard Cox proportional hazards model of Sielken & Associates (S&A), which uses the full risk set as opposed to 100 randomly selected controls for each case, and some of the models from USEPA (2016), were used to check whether the models were reasonably accurate; that is, whether the models predicted within a margin of error, the number of lymphoid cancer deaths in the NIOSH cohort**.** Cox proportional hazards modeling is preferred under TCEQ guidelines (TCEQ 2015) and the linear two-piece spline model is used by USEPA (2016), so these are the two major models considered in this model evaluation. The estimated number of lymphoid cancer deaths for a specific model for the rate ratios were calculated using age-, sex-, race-, and calendar-year specific background hazard rates. Sections A3.3 and A3.4 of this appendix illustrate how the calculations to predict the number of expected deaths for each model were performed with methodology used in the calculation of standard mortality ratios (SMRs). The SMR is a measure that shows the ratio of observed to expected number of deaths in the cohort. Similarly, the 100(1-α)% confidence interval on the SMR is a confidence interval on the ratio of observed to expected number of deaths in the cohort (method for this calculation described in Section A3.3).

Herein, the inverse of the SMR (SMR^{-1}, the ratio of expected to observed number of deaths) is used as a measure of over-prediction or under-prediction of the actual number of observed deaths. Similarly, the inverse of the confidence limits of the 95% confidence interval on the SMR result in a 95% confidence interval on the inverse of the SMR. In turn, using the SMR^{-1} and its 95% confidence interval, a 95% confidence interval on the expected or predicted number of deaths can be easily calculated. Using this confidence interval on the predicted number of deaths can then be compared with the observed number of deaths. If the observed number of deaths is inside the 95% confidence interval, then the expected number and observed number of deaths are not statistically significantly different at the 5% significance level. If the observed number of deaths is below the lower end or above the upper end of the 95% confidence interval, then the expected number is statistically significantly different than the observed number of deaths at the 5% significance level.

At issue is the predictiveness (or lack thereof) of the Cox proportional hazards and linear two-piece spline models used by the TCEQ and USEPA (2016), respectively. The predictiveness of these models can be readily and objectively evaluated by direct numerical comparisons of the models' predictions to the number of cancer deaths in the EtO-exposed cohort. Upon performing this evaluation, the sections below show that only the log-linear model (standard

Cox proportional hazards model; TCEQ's preferred model) and the best estimates of the linear model predict the number of observed lymphoid deaths in the NIOSH cohort with 95% confidence. By contrast, the linear two-piece spline model with the "knot" at 1,600 ppm-days (used by USEPA) statistically significantly over-estimates (at the 5% significance level) the number of observed lymphoid cancer deaths. This remains the case even after restricting the model to assume zero increase in the rate ratio for cumulative exposures above the knot.

A3.1 Predicted Versus Observed Number of Lymphoid Cancer Deaths in the NIOSH Cohort

Table 29 and Figure 9 show the predicted number of lymphoid cancer deaths in the NIOSH cohort for male and female workers using several different EtO exposure-response models. There are 53 lymphoid cancer deaths in the NIOSH cohort (brown horizontal line in Figure 9). Exposure-response models fit to the NIOSH data were used to estimate the number of lymphoid cancer deaths that each model would predict in the NIOSH cohort, if the fitted model were true. The MLE of each model as well as the upper 95% confidence limit on the model parameters were used to obtain the predicted number of deaths. In addition to calculating the expected number of deaths predicted by each model and its upper bound on the slope, a 95% confidence interval in the predicted number of deaths was derived using a confidence interval for the ratio of the predicted to the observed number of lymphoid cancer deaths in the NIOSH cohort (method for this calculation described in Section A3.3).

The 95% confidence intervals for the number of lymphoid cancer deaths predicted by the log-linear models (Cox proportional hazards model) and its upper bounds (models 1, 2, 3, and 4) include the number of lymphoid cancer deaths actually observed (53) in the NIOSH cohort. The 95% confidence interval for the number of lymphoid cancer deaths predicted by the best estimate of the linear model (model 5) also includes the number of lymphoid cancer deaths actually observed in the NIOSH cohort, but the upper bound of the linear model (model 6) statistically significantly over-predicts the observed number of lymphoid cancer deaths.

Models 7, 8, 9, and 10 are two-piece spline models (USEPA 2016). Every two-piece spline model estimate of the lymphoid cancer deaths in the NIOSH cohort statistically significantly over-predicts the actual number of lymphoid cancer deaths in the NIOSH cohort. For comparison purposes, Models 11, 12, 13, and 14 are the two-piece spline models restrained by setting the slope after the knot equal to zero (i.e., the rate ratio increases with cumulative exposure up to the knot and stays flat after the knot). In every instance, even restrained two-piece spline models (with the slope after the knot set equal to zero) statistically significantly over-predict the actual number of lymphoid deaths in the NIOSH cohort, for both the MLE and 95% UCL.

In short, the standard Cox proportional hazards model is reasonably accurate at predicting the number of lymphoid cancer mortalities observed in the NIOSH cohort (53), neither statistically significantly over- nor under-estimating, while the two-piece spline models (including the linear

two-piece spline model) all statistically significantly over-estimate the number of lymphoid cancer mortalities observed.

Table 29: Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities using Cox, Linear, and Two-Piece Spline Models

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
Background (No Model)	n/a	50.39	95.1%	(38.5, 67.3)
1. S&A – Loglinear – 15-yr lag (MLE) [a] **– Model Preferred by TCEQ**	2.81E-06	52.42	98.9%	(40.1, 70.0)
2. S&A – Loglinear – 15-yr lag (95% UCL) [a]	7.17E-06	58.75	110.8%	(44.9, 78.4)
3. USEPA - Loglinear - 15-yr Lag (MLE) [a] USEPA Table 4-2	4.74E-06 [b]	54.52	102.9%	(41.7, 72.8)
4. USEPA - Loglinear - 15-yr Lag (95% UCL) [a] USEPA Table 4-2	1.03E-05 [c]	66.41	125.3%	(50.8, 88.7)
5. USEPA - Linear - 15-yr Lag (MLE) USEPA Table D-36	1.23E-05 [d]	57.58	108.6%	(44.0, 76.9)
6. USEPA - Linear - 15-yr Lag (95% UCL) USEPA Table D-36	**4.71E-05** [e]	**77.3**	**145.8%**	**(59.1, 103.2)**
USEPA (2016) Spline Models with Knot at 1,600 ppm-days				
7. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**4.89E-04** [f]	**88.24**	**166.5%**	**(67.5, 117.8)**
8. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**9.08E-04** [g]	**144.15**	**272.0%**	**(110.2, 192.5)**
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model used by USEPA	**7.58E-04** [h]	**91.69**	**173.0%**	**(70.1, 122.4)**
10. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**1.80E-03** [i]	**141.09**	**266.2%**	**(107.9, 188.4)**
Results using above USEPA models but assuming that slope for RR is zero after the "knot"				
11. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**4.89E-04**	**84.59**	**159.6%**	**(64.7, 112.9)**

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
12. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**9.08E-04**	**141.97**	**267.9%**	**(108.5, 189.5)**
13. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**7.58E-04**	**86.39**	**163.0%**	**(66.0, 115.3)**
14. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**1.80E-03**	**135.19**	**255.1%**	**(103.4, 180.5)**

MLE – maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, RR – rate ratio, S&A – Sielken & Associates, UCL – upper confidence limit

[**Boldface** values indicate that the model over-prediction of lymphoid cancer deaths is statistically significant.]

[a] The models used by S&A and USEPA [appearing as an appendix in USEPA (2016)] are the same models; however, USEPA did not use all of the individual data – Steenland et al. (2004) and USEPA (2016) only used a subsample of the individual data as discussed in Section 4.3.

[b] The best estimate and standard error of the slope are 4.74E-06 and 3.35E-06, respectively.

[c] The 95% upper confidence limit on the slope is 1.03E-05 (4.74E-06 + 1.645×3.35E-06).

[d] The best estimate and standard error of the slope are 1.23E-05 and 2.12E-05, respectively. The standard error (2.12E-05) of the slopes was inferred from the upper bound on the slope (4.75E-05) given in Table D-36; that is 1.23E-0-5 = (4.71E-05 – 1.23E-05)/1.645.

[e] The 95% upper confidence limit on the slope is 4.71E-05 from Table D-36.

[f] The best estimate and standard error of the slope below the knot are 4.89E-04 and 2.55E-04, respectively. The slope and corresponding standard error after the knot are -4.86E-04 and 2.56E-04, respectively, from Tables 4-4 and D-33 log-linear with knot @ 1600 ppm-days.

[g] The slope after the knot for the 95% upper confidence limit for the model is -9.07E-04 (-4.86E-04 - 1.645×2.56E-04, which a 95% LCL on the slope above the knot). This conservatively assumes perfect negative correlation of the slope below and after the knot. **Thus, the over-prediction may be larger than what is shown in the table.** The assumption of perfect negative correlation is consistent with the covariance values obtained by USEPA for linear two-piece spline model; e.g., see footnote to Table D-36 in the appendices of USEPA's report.

[h] The best estimate and standard error of the slope below the knot are 7.58E-04 and 6.32E-04, respectively. The slope and corresponding standard error after the knot are -7.48E-04 and 6.31E-04, respectively, from footnote to Table D-36.

[i] The slope after the knot for the 95% upper confidence limit for the model is -1.79E-03 (-7.48E-04 - 1.645×6.32E-04, which a 95% LCL on the slope above the knot). This conservatively assumes perfect negative correlation of the slope below and after the knot. **Thus, the over-prediction may be larger than what is shown in the table.** The assumption of perfect negative correlation is consistent with the covariance values obtained by USEPA (see footnote to Table D-36 in the appendices of USEPA's report where the covariance is approximately equal to the negative of the variances for the slopes above and below the knot; i.e., covariance=-3.99E-07, Var1=3.99E-07, and Var2=3.98E-07).

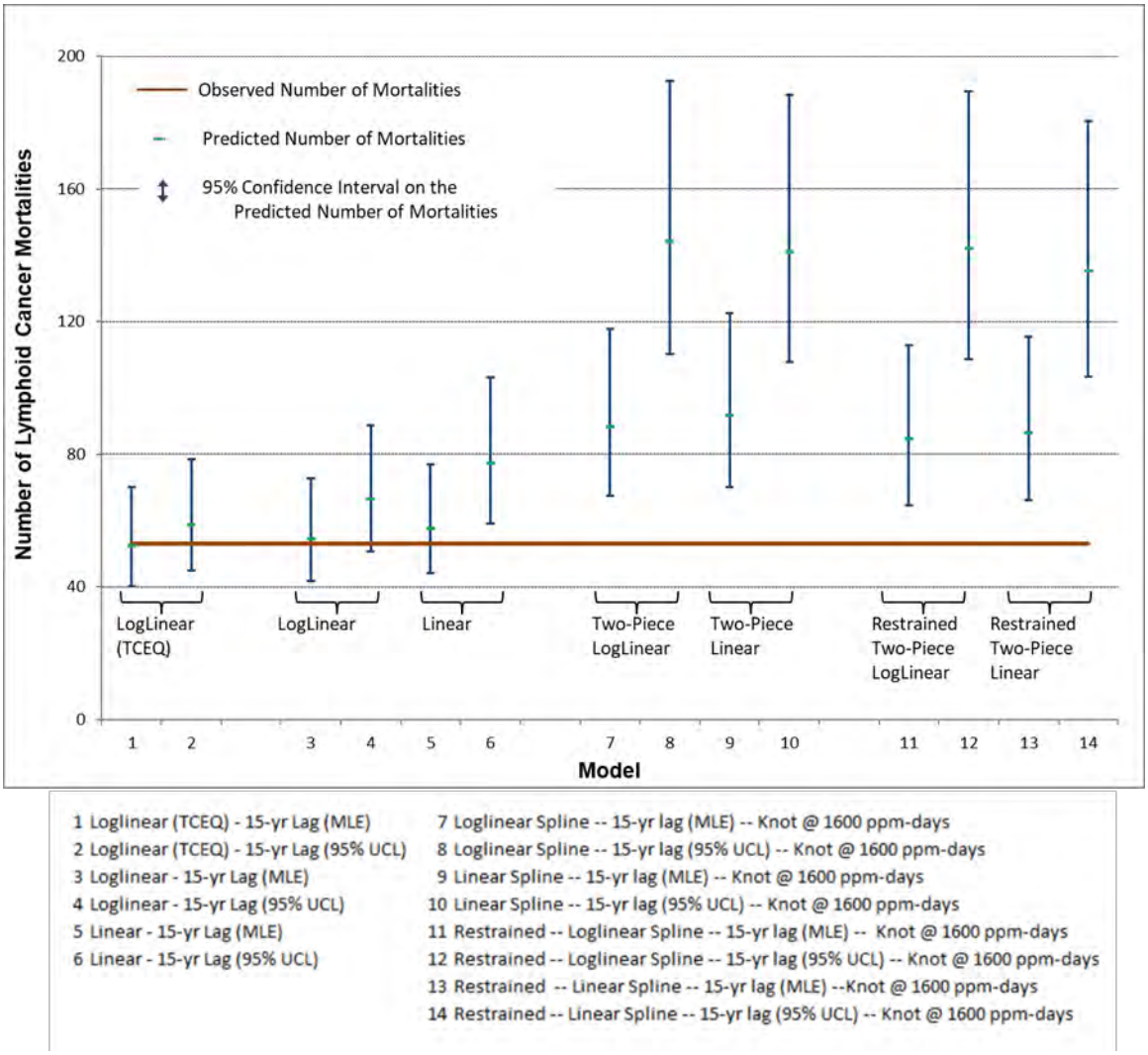


Figure 9: Total NIOSH cohort lymphoid cancer mortalities predicted by Sielken & Associates (S&A) and USEPA loglinear, linear, and two-piece spline models

A3.2 Predicted Versus Observed Number of Lymphoid Cancer Deaths in the NIOSH Cohort by Quintiles

Table 30 expands on the results presented in Table 29 to calculate the observed and expected number of lymphoid cancer deaths in each of the NIOSH cohort's five exposure quintiles. A total of 53 lymphoid cancer deaths were observed in the NIOSH cohort. The first quintile included the nine NIOSH workers who died with lymphoid cancer and whose cumulative exposure to EtO (with an exposure duration of 15 years) was equal to zero. Cumulative exposures to EtO lagged 15 years were defined so that quintiles 2 to 5 included the same number of lymphoid cancer deaths (11) in each quintile.

Only the best estimates of the log-linear (Cox proportional hazards) model (models 1 and 3), the linear model (model 5), and the 95% upper confidence limit of the log-linear (Cox proportional hazards) model (model 2; TCEQ's preferred model) predict a number of lymphoid

cancer mortalities that is consistent with the number of observed deaths in each of five quintiles. USEPA's 95% UCL of the log-linear (model 4) and linear model (model 6) statistically significantly over-predict the number of the lymphoid cancer deaths in the highest exposure group.

The two-piece spline models (both the fitted models 7-10 and the restrained models 11-14) significantly over-predict the number of observed lymphoid cancer deaths in multiple exposure quintiles, including the lowest exposure quintile. The 95% UCL of the two-piece spline models (for both the fitted models and the restrained models - models 8, 10, 12, and 14) significantly over-predict the number of observed lymphoid cancer deaths at every exposure quintile. More specifically: (1) the best estimate of the linear two-piece spline model (model used by USEPA 2016) significantly over-predicts the number of observed lymphoid cancer deaths in every exposure quintile except quintile 3 (models 9 and 10); and (2) the upper bound of this two-piece spline model (used by USEPA 2016 for their URF) statistically significantly over-predicts lymphoid cancer deaths for every quintile, even if the slope of the upper spline is set to zero (models 13 and 14).

In summary, the log-linear model preferred by the TCEQ (i.e., Cox proportional hazards model) is reasonably accurate for the cohort as a whole and for every exposure quintile, neither significantly over- or under-estimating lymphoid cancer deaths for the NIOSH cohort as a whole or any cumulative exposure quintile. This is true regardless of whether the MLE or upper bound is used for the Cox model. By contrast, the MLE for the linear two-piece spline model (used by USEPA 2016) statistically significantly over-estimates the total number of observed lymphoid cancer deaths for the NIOSH cohort as a whole and for every exposure quintile except quintile 3. Moreover, the upper bound of that model (used by USEPA 2016 for their URF) statistically significantly over-predicts lymphoid cancer deaths for the cohort as a whole and for every cumulative exposure group, including the lowest exposure group (quintile 2), even if the slope of the upper spline is set to zero.

Table 30: Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities per Exposure Quintile using Cox, Linear, and Two-Piece Spline Models

Model [a]	Quintile 2 [b]	Quintile 3	Quintile 4	Quintile 5
Observed	*11*	*11*	*11*	*11*
Background (No Model)	14.4 (8.0, 28.9)	7.9 (4.4, 15.9)	9.1 (5.1, 18.3)	7.4 (4.2, 14.9)
1. S&A – Loglinear – 15-yr lag (MLE) – **Model Preferred by TCEQ**	14.4 (8.1, 28.9)	8.0 (4.5, 16.1)	9.4 (5.2, 18.8)	9.1 (5.1, 18.3)
2. S&A – Loglinear – 15-yr lag (95% UCL)	14.5 (8.1, 29.0)	8.1 (4.5, 16.2)	9.8 (5.5, 19.6)	15.0 (8.4, 30.0)
3. USEPA - Loglinear - 15-yr Lag (MLE) USEPA Table 4-2	14.4 (8.1, 29.0)	8.0 (4.5, 16.1)	9.5 (5.3, 19.1)	11.0 (6.2, 22.1)
4. USEPA - Loglinear - 15-yr Lag (95% UCL) USEPA Table 4-2	14.5 (8.1, 29.1)	8.2 (4.6, 16.4)	10.0 (5.6, 20.1)	**22.2 (12.4, 44.6)**

Model [a]	Quintile 2 [b]	Quintile 3	Quintile 4	Quintile 5
5. USEPA - Linear - 15-yr Lag (MLE) USEPA Table D-36	14.5 (8.1, 29.1)	8.2 (4.6, 16.5)	10.2 (5.7, 20.4)	13.2 (7.4, 26.5)
6. USEPA - Linear - 15-yr Lag (95% UCL) USEPA Table D-36	14.8 (8.3, 29.7)	9.0 (5.0, 18.0)	13.1 (7.3, 26.3)	**28.9 (16.2, 58.0)**
EPA Spline Model with Knot at 1,600 ppm-days				
7. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**19.8 (11.1, 39.7)**	17.3 (9.7, 34.7)	**20.3 (11.3, 40.7)**	19.4 (10.8, 38.9)
8. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**27.0 (15.1, 54.2)**	**33.5 (18.7, 67.3)**	**38.8 (21.7, 77.9)**	**33.3 (18.6, 66.7)**
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model Preferred by USEPA	**20.9 (11.7, 42.0)**	17.6 (9.8, 35.2)	**20.8 (11.6, 41.7)**	**20.9 (11.7, 41.9)**
10. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**29.9 (16.7, 60.0)**	**30.5 (17.1, 61.2)**	**35.8 (20.0, 71.7)**	**33.4 (18.7, 67.1)**
Results using above USEPA two-piece spline models but assuming that slope for RR is zero after the "knot"				
11. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**19.8 (11.1, 39.7)**	17.3 (9.6, 34.6)	**19.9 (11.1, 39.9)**	16.2 (9.0, 32.5)
12. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**27.0 (15.1, 54.2)**	**33.5 (18.7, 67.2)**	**38.6 (21.6, 77.4)**	**31.3 (17.5, 62.8)**
13. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**20.9 (11.7, 42.0)**	17.5 (9.8, 35.0)	**20.1 (11.2, 40.3)**	16.4 (9.1, 32.8)
14. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**29.9 (16.7, 60.0)**	**30.4 (17.0, 61.0)**	**35.0 (19.5, 70.2)**	**28.4 (15.9, 57.0)**

MLE – maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, RR – rate ratio, S&A – Sielken & Associates, UCL – upper confidence limit

[**Boldface** values indicate that the model over-prediction of lymphoid cancer deaths for the quintile is statistically significant.]

[a] The models used to calculate the estimated number of lymphoid deaths are the same as those listed in Table 31 and the footnotes to Table 29 apply here also. Except that the assumption of perfect negative correlation of the slopes before and after the knot in Models 8 and 10 (EPA's 95% UCL for the two-piece spline models) do not affect the predictions in quintile 2.

[b] Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted by all models with a 95% confidence interval of (6.0, 25.2).

A3.3 Calculation of the Expected Number of Case-Specific Deaths in a Cohort Using US Background Hazard Rates

The SMR is a measure that compares the number of observed cause-specific deaths in a study population (e.g., the NIOSH study) with the number of cause-specific deaths expected in the study population (e.g., the NIOSH study) with known cause-specific background death rates of a reference population (e.g., the US population). The cause-specific background death rates of the reference population are published for specific calendar year, age group, sex, race, and other relevant variables that influence the cause-specific death rates. The SMR is calculated using the following equation:

$$SMR = \frac{Observed}{Expected}$$

with

$$Observed = \sum_i y_{oi} \qquad and \qquad Expected = \sum_i p_{oi} \frac{y_{ri}}{p_{ri}}$$

where *Observed* is the number of the cause-specific deaths observed in the study group and *Expected* is expected number of cause-specific deaths if the reference population background rates were applied to the individuals in the study group. In addition, *i* is the stratum (the stratum is calendar year-, age-, sex-, and race-specific), y_{oi} is the number of observed deaths in the *i*-th stratum of the study group, p_{oi} is the observed number of person-years in the *i*-th stratum of the study group, y_{ri} is the number of deaths in the *i*-th stratum of the reference population, and p_{ri} is the number of person-years in the *i*-th stratum of the reference population.

The ratios $\frac{y_{ri}}{p_{ri}}$ are the stratum- and cause-specific mortality rates in the reference population. The SMR is then the ratio of the *Observed* number of cause-specific deaths in the study population $(\sum_i y_{oi})$ to the *Expected* number of cause-specific deaths in the study group $(\sum_i p_{oi} \frac{y_{ri}}{p_{ri}})$ estimated using the background cause-specific death rates of the reference population. Several references have a more in-depth discussion of SMRs (e.g., Rothman 1986, Breslow and Day 1987, Checkoway et al 1989).

Herein, the numerator in the SMR calculation is the sum of the calendar year, sex, race, and age-specific lymphoid cancer deaths in the NIOSH study $(\sum_i y_{oi})$ and is equal to the number of observed lymphoid cancer deaths. The denominator in the SMR calculation is the expected number of lymphoid cancer deaths in the NIOSH workers assuming that lymphoid was the only cause of death by using the US background lymphoid cancer mortality rates. The calendar year, sex, race, and age-specific lymphoid cancer mortality rates (y_{ri}/p_{ri}) for the US populations and

the calendar year, sex, race, and age-specific person-years in the NIOSH study (p_{oi}) were used to calculate the expected number of the lymphoid cancer deaths in NIOSH workers. A numerical example of how to calculate the *Expected* number of lymphoid cancer deaths in the NIOSH study is in Section A3.5.1. Similar examples for other endpoints and other studies are shown elsewhere (e.g., Breslow and Day 1987).

An SMR greater than 1 (or 100%) implies that the number of observed deaths in the cohort is greater than would be expected in a population with the same demographic characteristics as the study group, except for potential exposures on the job. In contrast, an SMR less than 1 (or 100%) implies that the number of observed deaths in the study group is less than would be expected in a population with the same demographic characteristics as the study group, except for potential exposures on the job. The point estimate of the SMR, though informative, cannot be used to determine whether the hypothesis that the SMR is 100% (*Observed = Expected*) is rejected. In order to get a sense of the precision of the SMR estimate and to determine whether the hypothesis is rejected, a confidence interval on the SMR can be constructed (Breslow and Day 1987). Rothman and Boice (1979) use the following equations to derive 100(1-α)% confidence intervals for the SMR.

$$SMR_{LCL} = \frac{Observed}{Expected} \times \left(1 - \frac{1}{9 \times Observed} - \frac{Z_{\alpha/2}}{3 \times \sqrt{Observed}}\right)^3$$

and

$$SMR_{UCL} = \frac{(Observed + 1)}{Expected} \times \left(1 - \frac{1}{9 \times (Observed + 1)} + \frac{Z_{\alpha/2}}{3 \times \sqrt{Observed + 1}}\right)^3$$

where SMR_{LCL} is the 100(1-α/2)% lower confidence limit on the SMR, SMR_{UCL} is the 100(1-α/2)% upper confidence limit on the SMR, *Observed* is the number of observed cause-specific deaths (e.g., lymphoid cancer deaths) in the study $(i.e.,\ Observed = \sum_i y_{oi})$, *Expected* is the expected cause-specific deaths (e.g., lymphoid cancer deaths) derived from the reference population background rates $\left(i.e.,\ Expected = \sum_i p_{oi} \frac{y_{ri}}{p_{ri}}\right)$, and $Z_{\alpha/2}$ is the 100(1- α/2)% percentile of the standard normal distribution.

The 100(1-α)% confidence interval for an SMR is given by the interval (SMR_{LCL}, SMR_{UCL}). Thus, if the SMR_{LCL} of a 100(1-α)% confidence interval is greater than 1 (or 100%), then the SMR is statistically significantly different (greater) than 1 (or 100%), implying that the number of *Observed* cause-specific deaths (e.g., lymphoid cancer deaths) in the study group is more than the *Expected* number of cause-specific deaths (e.g., lymphoid cancer deaths) in the general population with similar demographics as the study group. On the contrary, if the SMR_{UCL} of a 100(1-α)% confidence interval is less than 1 (or 100%), then the SMR is statistically significantly different (less) than 1 (or 100%), implying that the number of *Observed* cause-specific deaths (e.g., lymphoid cancer deaths) in the study group is less than the E*xpected* number of cause-

specific deaths (e.g., lymphoid cancer deaths) in the general population with similar demographics as the study group.

The US lymphoid cancer mortality rates used for the calculations of the expected number of lymphoid cancer deaths are in Tables 34 to 38.

A3.3.1 US Background Hazard Rates are Appropriate for Calculating the Expected Number of Lymphoid Cancer Deaths in the NIOSH Cohort due to Absence of a Healthy Worker Effect for Lymphoid Cancer Mortality

The models used by TCEQ were derived using internal comparisons and did not rely on the general U.S. population standard mortality rates. However, national rates can be used to predict the specific cancers in the NIOSH worker cohort. This is because: (1) the approach for calculating SMRs is well established and documented and has been used extensively by regulatory agencies and researchers to compare mortality rates in target populations to mortality rates in reference populations; and (2) importantly, the healthy worker effect is absent for the candidate cancer endpoints of interest for the NIOSH cohort (e.g., lymphoid cancers, breast cancer), including the key cancer endpoint (i.e., lymphoid cancer), negating the potential need for internal comparisons for these particular endpoints (see below, also discussed in Section 3.1.1.2).

Regarding these points, though opinions vary about using general population background rates for evaluating cause-specific mortality rates of occupational studies, it is standard practice to use general population background rates because there is often no scientific evaluation of the magnitude of the “healthy worker effect” in a given cohort. In general, the healthy worker effect (if any) is cause-specific and often cannot be easily ascertained. However, Kirkeleit et al. (2013) researched the healthy worker effect in a large study of 366,114 randomly selected workers and compared the incidence of numerous endpoints with the general population. Their findings indicate that there is a potential for the healthy worker effect for some endpoints while there is an increased incidence (i.e., an “unhealthy” worker effect) for other endpoints. Relevant to the EtO assessment, Kirkeleit et al. (2013) did not find a healthy worker effect for lymphoid and hematopoietic cancer incidence, with SIRs and 95% confidence intervals of 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27) for male and female workers, respectively. The lack of a healthy worker effect was also true for breast cancer with an SIR and 95% confidence interval of 1.02 (0.95, 1.09).

Even more specifically, the lymphoid cancer mortality rate in unexposed workers in the NIOSH study is not statistically significantly different from the mortality rate of the general U.S. population. Footnote “*” to Table 34 indicates that for Quintile 1, the control (unexposed lagged-out) group, the 9 lymphoid cancer mortalities observed is well within the 95% confidence interval (6.0, 25.2) for all models. That is, the 9 lymphoid cancer deaths observed in the unexposed male and female workers of the NIOSH cohort is consistent with the number of lymphoid cancer deaths in the general U.S. population (i.e., during the same period of time after accounting for age, sex, and calendar year). Expressed in terms of SMRs, the SMR for

lymphoid cancer deaths in the unexposed male and female NIOSH workers is equal to 0.78 (9/11.5) with a 95% confidence interval (CI) equal to (0.36, 1.50). The 95% CI on the SMR for unexposed workers includes the value of one, which indicates that the mortality rate in the unexposed workers in the NIOSH study and the U.S. population mortality rate are not statistically significantly different at the 5% significance level. Similar results are obtained for the male NIOSH workers that drive lymphoid cancer risk and upon which TCEQ's URF is conservatively based. More specifically, the SMR for lymphoid cancer deaths in the unexposed male NIOSH workers is equal to 1.03 (6/5.8) with a 95% CI of (0.38, 2.25). Thus, the lymphoid cancer mortality rate in unexposed male workers in the NIOSH cohort, the gender that drives the URF, is not statistically significantly different than that in the U.S. population.

In summary, these results demonstrate that there is no healthy worker effect for this critical endpoint in this key group (i.e., male workers, who drive lymphoid cancer risk in the NIOSH cohort and the TCEQ's URF). Similarly, no healthy worker effect for lymphoid cancer mortality is demonstrated in NIOSH male and female workers combined. These results based on the NIOSH cohort are consistent with the findings of Kirkeleit et al. (2013) that there is no difference in lymphohematopoietic tumor incidence in workers compared to the general population.

A3.3.2 Sensitivity Analysis Assuming a Healthy Worker Effect for Lymphoid Cancer Mortality

Although there is a lack of evidence for a healthy worker effect for lymphohematopoietic tumor incidence in general (Kirkeleit et al. 2013) and in the NIOSH cohort population in particular (Steenland et al. 2004), the TCEQ conducted a sensitivity analysis of the model fit validation assuming a healthy worker effect for cancer. For purposes of this sensitivity analysis, the TCEQ assumed that the overall cancer SMR of 0.85 and 0.84 for male and female workers, respectively, from Kirkeleit et al. (2013) applies to lymphoid cancers. That is, the TCEQ sensitivity analysis assumes NIOSH workers were 15-16% "healthier" than the general population as to cancer mortality by multiplying the U.S. male and female background hazard rates by 0.85 and 0.84, respectively, to account for the assumed healthy worker effect. The results did not change significantly. Using these values, the standard Cox proportional hazards model still estimates the observed number (53) of lymphoid deaths in the NIOSH study with a 95% confidence: 44.3 with a 95% CI of (33.9, 59.2). By contrast, even assuming a healthy worker effect, the MLE of the linear two-piece spline model still statistically significantly overestimates the number of observed (53) lymphoid deaths in the NIOSH study: 77.5 with a 95% CI of (59.3, 103.6).

A3.3.3 Using UCC Study Data to Validate the Cox Proportional Hazards Model Fit to the NIOSH Study Data

In Section A3.1, exposure-response models fit to lymphoid cancer deaths in the NIOSH study were used to compare the observed and the expected number of lymphoid cancer deaths in the NIOSH cohort predicted by various exposure-response models. Because the models were fit to the NIOSH data, it would be expected that the observed number of lymphoid cancer mortalities in the NIOSH cohort and the number of lymphoid cancer mortalities predicted by

the models would not be statistically significantly different. However, the results indicated that all spline models statistically significantly over-predicted the number of lymphoid cancer deaths in the NIOSH cohort. By contrast, the TCEQ-preferred dose-response model (i.e., the standard Cox proportional hazards model) was reasonably accurate at predicting the number of lymphoid cancer mortalities in the NIOSH cohort, neither statistically significantly over- nor under-predicting the number that was actually observed.

The exposure-response models can be further evaluated by applying the models obtained for the NIOSH cohort to an independent epidemiological data set that was not used to fit the model. Accordingly, a model that uses the parameters estimated using the lymphoid cancer mortality data from the NIOSH cohort can be validated by predicting the number of lymphoid cancer deaths in the 2013 update of the UCC study. Such a demonstration for a model supports its robustness for predicting lymphoid cancer deaths for other populations and exposure scenarios.

Using the same methodology as the reality check of the models for the NIOSH cohort (described in Section A3.3), the same models were validated using the UCC epidemiological study data. The UCC cohort includes a set of different workers than those in the NIOSH study and the exposure concentrations to EtO were estimated using a completely different method. Table 31 and Figure 10 show the predicted number of lymphoid cancer deaths in the UCC cohort using the EtO exposure-response models derived from the NIOSH study. There are 25 lymphoid cancer deaths in the most recent update of the UCC study (brown horizontal line in Figure 10). The 95% confidence intervals for the number of lymphoid cancer deaths predicted by the log-linear (Cox proportional hazards) model and its upper bound (Models 1, 2, 3, and 4) include the number of lymphoid cancer deaths observed (25) in the UCC cohort. The 95% confidence interval for the number of lymphoid cancer deaths predicted by the linear model (Model 5) also include the 25 lymphoid cancer deaths observed in the UCC study, however, the upper bound of the linear model (Model 6) statistically significantly over-predicts the 25 observed lymphoid cancer deaths at the 5% significance level.

Models 7, 8, 9, and 10 are the two-piece spline models derived by USEPA (2016). Every two-piece spline model statistically significantly over-predicts the 25 observed lymphoid cancer deaths in the UCC cohort. Furthermore, even the restrained two-piece spline models with the slope of the upper spline set to zero (Models 11, 12, 13, and 14) statistically significantly over-predict the number of lymphoid cancer deaths observed in the UCC cohort.

The fact that the model predictions/over-predictions for the NIOSH and UCC cohorts behave remarkably similar is not surprising. These results corroborate the findings in Valdez-Flores et al. (2010), who tested for the homogeneity of the Cox proportional hazards model in the NIOSH study and the 2003 update of the UCC study. Their findings are summarized in the following:

> “Potential heterogeneity between dose-response models of different studies and pooled studies was tested using DerSimonian and Laird’s Q Test (also known as Cochran’s Test) which found no statistically significant differences at the 5%

> significance level (Cochran 1954; DerSimonian and Laird 1986; Takkouche et al. 1999). Because we had the individual worker data available and not just the summary results of the modeling, we also tested for potential heterogeneity among dose-response models of different studies using the more powerful likelihood ratio tests. Although there were some statistically significant differences among the endpoints with negative slopes using the likelihood ratio tests, there were no statistically significant heterogeneity among dose-response models for different studies for the endpoints with positive slopes."

In summary, results of this model validation analysis show that both the MLE and upper bound of the Cox proportional hazards model (preferred by the TCEQ) are reasonably accurate, predicting 28 (95% CI of 19, 43) and 32 (95% CI of 22, 50) lymphoid cancer deaths for the cohort, respectively, compared to the 25 actually observed. By contrast, the linear two-piece spline model used by USEPA (2016) statistically significantly over-predicts the number of lymphoid cancer mortalities in the UCC cohort. More specifically, the MLE and upper bound of the linear two-piece spline model predict 57 (95% CI of 39, 89) and 92 (95% CI of 62, 143) lymphoid cancer mortalities, respectively, compared to the 25 actually observed in the UCC cohort. Thus, these validation results are wholly consistent with those for the NIOSH cohort itself (Section A3.1) and support the robustness of TCEQ's preferred model (the Cox proportional hazards model) for predicting lymphoid cancer deaths for other populations and exposure scenarios.

Table 31: Predicted Number of UCC Cohort Lymphoid Cancer Mortalities using the NIOSH Cohort-based Cox, Linear, and Two-Piece Spline Models

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
Background (No Model)	n/a	26.20	104.8%	(17.7, 40.5)
1. S&A – Loglinear – 15-yr lag (MLE) [a] **– Model Preferred by TCEQ**	2.81E-06	28.09	112.4%	(19.0, 43.4)
2. S&A – Loglinear – 15-yr lag (95% UCL) [a]	7.17E-06	32.28	129.1%	(21.9, 49.9)
3. USEPA - Loglinear - 15-yr Lag (MLE) [a] USEPA Table 4-2	4.74E-06 [b]	29.70	118.8%	(20.1, 45.9)
4. USEPA - Loglinear - 15-yr Lag (95% UCL) [a] USEPA Table 4-2	1.03E-05 [c]	36.78	147.1%	(24.9, 56.9)
5. USEPA - Linear - 15-yr Lag (MLE) USEPA Table D-36	1.23E-05 [d]	33.45	133.8%	(22.7, 51.7)
6. USEPA - Linear - 15-yr Lag (95% UCL) USEPA Table D-36	**4.71E-05** [e]	**53.27**	**213.1%**	**(36.1, 82.3)**
USEPA Spline Model with Knot at 1,600 ppm-days				
7. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**4.89E-04** [f]	**54.64**	**218.6%**	**(37.0, 84.5)**

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% CI on Predicted if the Model were True
8. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**9.08E-04** [g]	**95.33**	**381.3%**	**(64.6, 147.4)**
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model Preferred by USEPA	**7.58E-04** [h]	**57.43**	**229.7%**	**(38.9, 88.8)**
10. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**1.80E-03** [i]	**92.27**	**369.1%**	**(62.5, 142.6)**
Results using above USEPA models but assuming that slope for RR is zero after the "knot"				
11. USEPA – Loglinear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**4.89E-04**	**51.16**	**204.7%**	**(34.7, 79.1)**
12. USEPA – Loglinear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**9.08E-04**	**93.11**	**372.4%**	**(63.1, 143.9)**
13. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**7.58E-04**	**52.00**	**208.0%**	**(35.2, 80.4)**
14. USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days	**1.80E-03**	**86.35**	**345.4%**	**(58.5, 133.5)**

MLE – maximum likelihood estimate, NIOSH - National Institute for Occupational Safety and Health, RR – rate ratio, S&A – Sielken & Associates, UCC – Union Carbide Corporation, UCL – upper confidence limit
[**Boldface** values indicate that the model over-prediction of lymphoid cancer deaths is statistically significant.]
[a] The models used by Sielken & Associates (S&A) and USEPA [appearing as an appendix in USEPA (2016)] are the same models; however, USEPA did not use all of the individual data – Steenland et al. (2004) and USEPA (2016) only used a subsample of the individual data as discussed in Section 4.3.
[b] The best estimate and standard error of the slope are 4.74E-06 and 3.35E-06, respectively.
[c] The 95% upper confidence limit on the slope is 1.03E-05 (4.74E-06 + 1.645×3.35E-06).
[d] The best estimate and standard error of the slope are 1.23E-05 and 2.12E-05, respectively. The standard error (2.12E-05) of the slopes was inferred from the upper bound on the slope (4.75E-05) given in Table D-36; that is 1.23E-0-5 = (4.71E-05 – 1.23E-05)/1.645.
[e] The 95% upper confidence limit on the slope is 4.71E-05 from Table D-36.
[f] The best estimate and standard error of the slope below the knot are 4.89E-04 and 2.55E-04, respectively. The slope and corresponding standard error after the knot are -4.86E-04 and 2.56E-04, respectively, from Tables 4-4 and D-33 log-linear with knot @ 1600 ppm-days.
[g] The slope after the knot for the 95% upper confidence limit for the model is -9.07E-04 (-4.86E-04 - 1.645×2.56E-04, which a 95% LCL on the slope above the knot). This conservatively assumes perfect negative correlation of the

slope below and after the knot. **Thus, the over-prediction may be larger than what is shown in the table.** The assumption of perfect negative correlation is consistent with the covariance values obtained by USEPA for linear two-piece spline model; e.g., see footnote to Table D-36 in the appendices of USEPA's report.

[h] The best estimate and standard error of the slope below the knot are 7.58E-04 and 6.32E-04, respectively. The slope and corresponding standard error after the knot are -7.48E-04 and 6.31E-04, respectively, from footnote to Table D-36.

[i] The slope after the knot for the 95% upper confidence limit for the model is -1.79E-03 (-7.48E-04 - 1.645×6.32E-04, which a 95% LCL on the slope above the knot). This conservatively assumes perfect negative correlation of the slope below and after the knot. **Thus, the over-prediction may be larger than what is shown in the table.** The assumption of perfect negative correlation is consistent with the covariance values obtained by USEPA (see footnote to Table D-36 in the appendices of USEPA's report where the covariance is approximately equal to the negative of the variances for the slopes above and below the knot; i.e., covariance=-3.99E-07, Var1=3.99E-07, and Var2=3.98E-07).

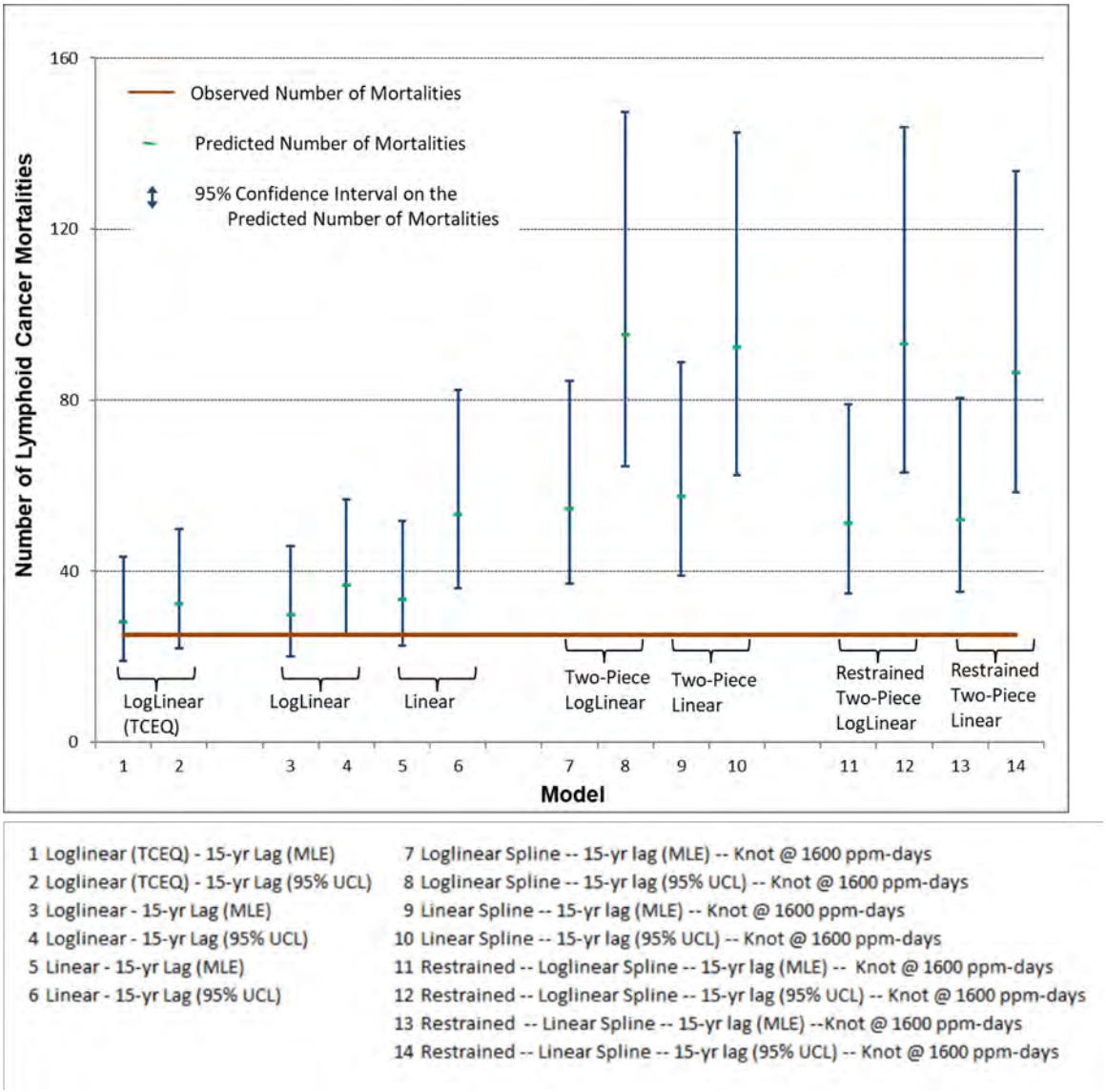


Figure 10: Total UCC cohort lymphoid cancer mortalities predicted by Sielken & Associates (S&A) and USEPA loglinear, linear, and two-piece spline models based on NIOSH cohort data

A3.4 Calculating the Expected Number of Cause-Specific Deaths in a Cohort Assuming that the Death Rate in the Cohort Increases with Cumulative Exposure*

The SMR is the ratio of observed to expected number of cause-specific deaths in a cohort. The expected number of deaths is calculated assuming that the hazard rate is equal to the background hazard rate of the reference population. However, if the background hazard rate is assumed to be adjusted by exposure to a carcinogen via a multiplicative function (which is the assumption made by the hazards models used to analyze the NIOSH data), then the *Expected** number of deaths can be calculated assuming that the hazard rate is equal to the product of the background hazard rate of the reference population multiplied by the exposure-response (rate ratio) function that adjusts the background hazard rates. That is, the *Expected** number of cause-specific deaths in a cohort exposed to a carcinogen can be calculated as follows:

$$Expected^* = \sum_i p_{oi} \times RR(d_i) \times \frac{y_{ri}}{p_{ri}}$$

where p_{oi} is the number of observed person-years in the *i*-th stratum of the study group, y_{ri} is the number of *Observed* deaths in the *i*-th stratum of the reference population, p_{ri} is the number of person-years in the *i*-th stratum of the reference population, and $RR(d_i)$ is the exposure-response function (rate ratio function) evaluated at cumulative exposure d_i.

Using this *Expected** number of cause-specific deaths in a cohort, an SMR* and bounds on the SMR* are as follows:

$$SMR^* = \frac{Observed}{Expected^*}$$

A numerical example of how to calculate the *Expected** number of lymphoid cancer deaths in the NIOSH study is given in Section A.3.5.2.

Similar to the standard *SMR*, the lower and upper limits of the 100(1-α)% confidence interval on the *SMR** are calculated as follows:

$$SMR^*_{LCL} = \frac{Observed}{Expected^*} \times \left(1 - \frac{1}{9 \times Observed} - \frac{Z_{\alpha/2}}{3 \times \sqrt{Observed}}\right)^3$$

and

$$SMR^*_{UCL} = \frac{(Observed + 1)}{Expected^*} \times \left(1 - \frac{1}{9 \times (Observed + 1)} + \frac{Z_{\alpha/2}}{3 \times \sqrt{Observed + 1}}\right)^3$$

where SMR^*_{LCL} is the 100(1-α/2)% lower confidence limit on the *SMR**, SMR^*_{UCL} is the 100(1-α/2)% upper confidence limit on the *SMR**, *Observed* is the number of observed cause-specific deaths (e.g., lymphoid cancer deaths) in the study ($i.e.,\ Observed = \sum_i y_{oi}$), *Expected** is the expected cause-specific deaths (e.g., lymphoid cancer deaths) derived from the reference population background rates multiplied by the exposure response function $RR(d_i)$ $\left(i.e.,\ Expected^* = \sum_i p_{oi} \times RR(d_i) \times \frac{y_{ri}}{p_{ri}}\right)$, and $Z_{\alpha/2}$ is the 100(1- α/2)% percentile of the standard normal distribution.

A3.5 Sample Calculations of the Expected and Expected used in the Derivation of SMR and SMR**

The SMR calculation is a well-known measure used by epidemiologists that compares the mortality observed in a study and the mortality expected in the same study assuming the mortality rate in a reference population (Rothman 1986, Breslow and Day 1987, and Checkoway et al., 1989). The SMR is usually derived for a specific cause of death. The reference population is usually a population with similar demographic characteristics as the individuals in the study.

The SMR (*SMR**) is calculated as the ratio of the *Observed* cause-specific deaths in the study and the *Expected* (*Expected**) number of cause-specific deaths using a reference population mortality rates. The *Observed* cause-specific deaths in the study is the cause-specific death count through the end of the study.

The *Expected* number of cause-specific deaths, on the other hand, involves an actuarial approach that cumulates the hazard rate in the reference population for every day of follow up of individuals in the study. Calculations of the *Expected* number of cause-specific deaths are well-documented elsewhere (e.g., Section 2.1 in Breslow and Day 1987). Herein, however, a hypothetical individual job history is used to calculate their contribution to the *Expected* number of deaths (Section A3.5.1).

The *Expected** number of cause-specific deaths, similarly, involves an actuarial approach that cumulates the product of the hazard rate in the reference population and a hazard rate ratio function of the cumulative exposure for every day of follow up of the individual in the study. Although calculations of the *Expected* number of cause-specific deaths are well-documented elsewhere (e.g., Section 2.1 in Breslow and Day 1987), calculations of the *Expected** number are not, but follow a very similar approach. A hypothetical individual's job and exposure histories are used to calculate their contribution to the *Expected** number of deaths (Section A3.5.2).

The hypothetical worker used in Sections A3.5.1 and A3.5.2 was born on March 15, 1943 and died on January 10, 2008. The hypothetical worker was a white male. The worker was followed from June 22, 1964 through his death date on January 10, 2008. The hypothetical worker was hypothetically exposed to 15 ppm of EtO from 6/22/1964 through 9/11/1964. From 9/12/1964 through 12/31/1964, the worker was not exposed to the EtO. Then, from 1/1/1965 through 12/31/1968 the hypothetical worker was hypothetically exposed to 20 ppm of EtO. From 1/1/1969 through his death, the hypothetical worker was not exposed to EtO.

A3.5.1 Expected Number of Cause-Specific Deaths in a Study Group

The calculations for the contribution of the hypothetical worker to the *Expected* number of lymphoid cancer deaths in the study group are in Table 32. The period of follow up is split into intervals of time that accommodate changes in the follow up history and the calendar-year- and age-specific population hazard rates. (Herein, the first five observation intervals were split because the worker changed jobs and to simplify presentation.) Thus, for the observation period 6/22/1964 to 9/11/1964 (81 days), the workers age went from 21.27 to 21.49 years and the cause-specific hazard rate available at that time was for the year 1960. Because the age of the worker was within the range 20 to 24 years of age, the hazard rate (1.2269088) corresponding to that age group is taken from the corresponding cell (Table 33, Calendar Year 1960, White Males, Age Group 20-24). This same hazard rate is applicable to the following four intervals between 9/12/1964 to 12/31/1967) because during that period the worker was between 20 and 24 years of age and the most recent hazard data available through 12/31/1967 was that for 1960. (Note that the age group in Tables 33 to 37 includes ages from the first day of the age interval through the last day of the age interval.)

Because hazard rates were available for the year 1968, the interval 1/1/1968 to 3/15/1968 use the hazard rate (1.8538885) reported in 1968 for the same 20-24 age group in white males. However, starting on 3/16/1968 the worker is 25 years old and the background rates for this age group (25-34) is 1.9489378. From year 1968 on, there were yearly tables with the sex-, race-, and age-specific background hazard rates (Tables 34 to 38). Thus, the observation intervals in Table 32 are split by calendar year with occasional intervals defined to accommodate observation intervals corresponding to different age groups. In order to help the reader follow the calculations, the applicable hazard rates are boldfaced in Tables 34 to 38.

The last column in Table 32 is the hazard rate accumulated over the time interval specified in the first two columns of the table. That is, the accumulated hazard rate over the observation interval is the number of days in the observation interval multiplied by the hazard rate applicable during that observation interval (second to last column in Table 32). The sum of all values on the last column (146250.21) is the total hazard rate accumulated by the hypothetical worker in the calculations. This cumulative hazard rate per 100,000 individuals is accumulated over the follow up period in days. Thus, the total accumulated hazard rate for the entire period of follow up is equal to 0.004004 (=146250.21/(100000 × 365.25)). The division by 100,000 is to convert it to an individual cumulative hazard and the division by 365.25 is to convert the hazard rate accumulated over days to a hazard accumulated over years. Although this accumulated hazard is often used as the contribution of the individual worker to the *Expected* number of lymphoid cancer deaths, a more accurate estimation would use the cumulative probability using the expression (Breslow and Day, 1987)

$$CumulativeProbability = 1 - e^{-CumulativeHazard}$$

Even though *CumulativeProbability* is approximately equal to the *CumulativeHazard* for small values of the *CumulativeHazard* (which is usually the case in SMR analyses, Breslow and Day, 1987), the *CumulativeProbability* was used by TCEQ. In the example shown in Table 32 the *CumulativeProbability* is equal to 0.003996.

The *Expected* number of cause-specific deaths is calculated as the sum over all workers in the study of their *CumulativeProbability*. That is, *Expected* number of cause-specific deaths in the NIOSH study it is the sum over all 17,493 workers of their cause-specific *CumulativeProbability* of death.

Table 32: Sample Calculations of the Contribution of a Hypothetical Worker to the Expected Number of Lymphoid Cancer Deaths in the Study Group

Specific Worker Information [a]					Reference Population Information [b]			Hazard Rate for Period: Days*Hazard Rate per 100,000 per day [c]
Start Date	End Date	Start Age (yrs)	End Age (yrs)	Days Start-End	Year with Spec. Rates	Age Group	Hazard Rate: Lymphoid deaths per 100,000 per year	
6/22/1964	9/11/1964	21.27	21.49	81	1960	20-24	1.2269088	99.37961
9/12/1964	12/31/1964	21.50	21.80	111	1960	20-24	1.2269088	136.18688
1/1/1965	12/31/1965	21.80	22.80	365	1960	20-24	1.2269088	447.82172
1/1/1966	12/31/1966	22.80	23.80	365	1960	20-24	1.2269088	447.82172
1/1/1967	12/31/1967	23.80	24.80	365	1960	20-24	1.2269088	447.82172
1/1/1968	3/15/1968	24.80	25.00	74	1968	20-24	1.8538885	137.18775
3/16/1968	12/31/1968	25.01	25.80	292	1968	25-34	1.9489378	569.08985
1/1/1969	12/31/1969	25.80	26.80	365	1969	25-34	1.8260952	666.52474
1/1/1970	12/31/1970	26.80	27.80	365	1970	25-34	1.6427126	599.59010
1/1/1971	12/31/1971	27.80	28.80	365	1971	25-34	1.8667381	681.35941
1/1/1972	12/31/1972	28.80	29.80	366	1972	25-34	1.4360858	525.60741
1/1/1973	12/31/1973	29.80	30.80	365	1973	25-34	1.5596403	569.26872
1/1/1974	12/31/1974	30.80	31.80	365	1974	25-34	1.6393443	598.36066
1/1/1975	12/31/1975	31.80	32.80	365	1975	25-34	1.4671362	535.50469
1/1/1976	12/31/1976	32.80	33.80	366	1976	25-34	1.4321998	524.18513
1/1/1977	12/31/1977	33.80	34.80	365	1977	25-34	1.4560795	531.46901
1/1/1978	3/15/1978	34.80	35.00	74	1978	25-34	1.5788775	116.83694
3/16/1978	12/31/1978	35.01	35.80	291	1978	35-44	3.4144950	993.61803
1/1/1979	12/31/1979	35.80	36.80	365	1979	35-44	3.1564375	1152.09968
1/1/1980	12/31/1980	36.80	37.80	366	1980	35-44	3.5059257	1283.16880
1/1/1981	12/31/1981	37.80	38.80	365	1981	35-44	3.0052751	1096.92543
1/1/1982	12/31/1982	38.80	39.80	365	1982	35-44	3.6074238	1316.70970
1/1/1983	12/31/1983	39.80	40.80	365	1983	35-44	3.2109072	1171.98113
1/1/1984	12/31/1984	40.80	41.80	366	1984	35-44	3.6075915	1320.37848
1/1/1985	12/31/1985	41.80	42.80	365	1985	35-44	3.9000177	1423.50647

Specific Worker Information [a]					Reference Population Information [b]			Hazard Rate for Period: Days*Hazard Rate per 100,000 per day [c]
Start Date	End Date	Start Age (yrs)	End Age (yrs)	Days Start-End	Year with Spec. Rates	Age Group	Hazard Rate: Lymphoid deaths per 100,000 per year	
1/1/1986	12/31/1986	42.80	43.80	365	1986	35-44	3.9074933	1426.23505
1/1/1987	12/31/1987	43.80	44.80	365	1987	35-44	3.7333094	1362.65793
1/1/1988	3/14/1988	44.80	45.00	74	1988	35-44	3.7443317	277.08054
3/15/1988	12/31/1988	45.00	45.80	292	1988	45-54	10.1212315	2955.39960
1/1/1989	12/31/1989	45.80	46.80	365	1989	45-54	10.4543571	3815.84033
1/1/1990	12/31/1990	46.80	47.80	365	1990	45-54	11.3420080	4139.83293
1/1/1991	12/31/1991	47.80	48.80	365	1991	45-54	11.2991321	4124.18323
1/1/1992	12/31/1992	48.80	49.80	366	1992	45-54	10.7658867	3940.31454
1/1/1993	12/31/1993	49.80	50.80	365	1993	45-54	10.4984713	3831.94204
1/1/1994	12/31/1994	50.80	51.80	365	1994	45-54	11.2407277	4102.86560
1/1/1995	12/31/1995	51.80	52.80	365	1995	45-54	10.9565184	3999.12920
1/1/1996	12/31/1996	52.80	53.80	366	1996	45-54	10.3848722	3800.86323
1/1/1997	12/31/1997	53.80	54.80	365	1997	45-54	10.9412591	3993.55957
1/1/1998	3/15/1998	54.80	55.00	74	1998	45-54	10.0855678	746.33202
3/16/1998	12/31/1998	55.01	55.80	291	1998	55-64	28.2780557	8228.91421
1/1/1999	12/31/1999	55.80	56.80	365	1999	55-64	27.7683602	10135.45149
1/1/2000	12/31/2000	56.80	57.80	366	2000	55-64	26.0245994	9525.00338
1/1/2001	12/31/2001	57.80	58.80	365	2001	55-64	25.7682490	9405.41087
1/1/2002	12/31/2002	58.80	59.80	365	2002	55-64	24.6020452	8979.74651
1/1/2003	12/31/2003	59.80	60.80	365	2003	55-64	24.3376112	8883.22809
1/1/2004	12/31/2004	60.80	61.80	366	2004	55-64	22.2903793	8158.27884
1/1/2005	12/31/2005	61.80	62.80	365	2005	55-64	21.4439484	7827.04116
1/1/2006	12/31/2006	62.80	63.80	365	2006	55-64	20.8159028	7597.80451
1/1/2007	12/31/2007	63.80	64.80	365	2007	55-64	20.2182691	7379.66823
1/1/2008	1/10/2008	64.80	64.82	11	2008	55-64	20.0930161	221.02318

[a] The worker specific information is split in the coarsest observation time intervals possible that accommodate worker and reference population time-interval cut points.

[b] The reference population information column includes three items that are applicable to the specific observation time interval of the worker: i) the "Year with Spec. Rates" is the calendar year which had the most recent, at the

observation time, sex-, age-, and race-specific background hazard rates; ii) the "Age Group" is the age group in the background hazard rate tables that includes the ages of the worker during the observation time interval; and iii) the "Hazard Rate: Lymphoid deaths per 100,000 per year" is the hazard rate for lymphoid mortality reported in the table for the ""Year with Spec. Rates" and the "Age Group" in units of number of deaths in one year per 100,000 individuals (numbers have been rounded to seven significant digits).
[c] The column "Hazard Rate for Period: Days*Hazard Rate per 100,000 per day" is the hazard rate per 100,000 cumulated over the days during the observation time of the worker.

A3.5.2 Expected* Number of Cause-Specific Deaths in a Study Group

The calculations for the contribution of the hypothetical worker to the *Expected** number of lymphoid cancer deaths in the study group are shown in Table 33. The period of follow up is split into intervals of time that accommodate changes in the follow up history, exposure history, and the calendar-year- and age-specific population hazard rates. As discussed above, this worker was hypothetically exposed to an EtO concentration of 15 ppm from 6/22/1964 through 9/11/1964. The worker was not exposed from 9/12/1964 through 12/31/1964 and then he was exposed to a concentration of 20 ppm from 1/1/1965 through 12/31/1968. From 1/1/1969 through his death on 1/10/2008 the worker was not exposed to EtO at his workplace.

Cumulative exposures (ppm-days) are calculated as follows. For the observation period 6/22/1964 to 9/11/1964 (81 days), the worker accumulated 1215 ppm-days (=81×15) of exposure to EtO. Because the worker was unexposed from 9/12/1964 to 12/31/1964, his cumulative exposure to EtO remained at 1215 ppm-days throughout this period. From 1/1/1965 through 12/31/1965, the worker was exposed to a concentration of 20 ppm and accumulated a total of 7300 ppm-days (=365×30) during the interval to end the period with 8515 ppm-days (=1215+7300). During 1966 (1/1/1966 through 12/31/1966) the worker accumulated another 7300 ppm-days to end the period with 15815 ppm-days (=8515+7300). Similarly, in 1967 the worker accumulated another 7300 ppm-days to end the year with 23115 ppm-days (=15815+7300). The next interval, 1/1/1968 to 3/14/1968 (74 days) the worker was exposed to 20 ppm and accumulated 1480 ppm-days (=74×20) and ended the period with 24595 ppm-days (=23115+1480). The remainder of 1968 (3/15/1968 through 12/31/1968, or 292 days), the worker accumulated 5840 (=292×20) ppm-days and ended the year with 30435 (=24595+5840) ppm-days. Because the worker was not occupationally exposed to EtO starting on 1/1/1969 his cumulative EtO exposure remained at 30345 ppm-days thereafter.

The reference population lymphoid mortality rates are taken from Tables 34 to 38 as follows. For the observation period 6/22/1964 to 9/11/1964 (81 days), the hazard rate available for the period was for the year 1960. Because the age of the worker was within the range 20 to 24 years of age, the hazard rate (1.2269088) corresponding to that age group is taken from the corresponding cell (Table 34, Calendar Year 1960, White Males, Age Group 20-24). This same hazard rate is applicable to the following four intervals between 9/12/1964 to 12/31/1967 because during that period the worker was between 20 and 24 years of age and the most recent hazard data available through 12/31/1967 was for 1960. (Note that the age group in Tables 34 to 38 includes ages from the first day of the age interval through the last day of the age interval.)

Because hazard rates were available for the year 1968, the interval 1/1/1968 to 3/15/1968 use the hazard rate (1.8538885) reported in 1968 for the same 20-24 age group in white males. However, starting on 3/16/1968 the worker is 25 years old and the background rates for this age group (25-34) is 1.9489378. From year 1968 on, there were yearly tables with the sex-, race-, and age-specific background hazard rates. Thus, the observation intervals in Table 33 are split by calendar year with occasional intervals defined to accommodate observation intervals corresponding to different age groups. In order to help the reader follow the calculations, the applicable hazard rates are boldfaced in Tables 34 to 38.

The penultimate column in Table 33 is the rate ratio function that multiplies the reference population lymphoid mortality rates. This function describes the relationship between the cause-specific death rate ratio and cumulative exposure to EtO. For illustration purposes, the following function was used,

$$RR(d) = e^{4.74\times10^{-6}\times d}$$

where *d* is the cumulative exposure to EtO. In Table 33 the *RR(d)* is calculated at the midpoint of the cumulative exposure in the interval (the cumulative exposure at the beginning of the exposure history is zero). Thus, for the first interval in the table (6/22/1964 to 9/11/1964) the cumulative exposure is 1215 and the midpoint is 607.5 ppm-days (=(1215+0)/2) resulting in a *RR(d)* for this interval of 1.200288370 ($= e^{4.74\times10^{-6}\times607.5}$). For the second interval (9/12/1964 to 12/31/1964), there was no additional exposure and the midpoint of the cumulative exposure is 1215 ppm-days (=(1215+1215)/2) resulting in a RR(d) of 1.00577572. The third interval (1/1/1965 to 12/31/1965) was similarly calculated with a midpoint of 4865 ppm-days (=(8515+1215)/2) with a RR(d) of 1.02332804. Similar calculations were used to determine other values of the *RR(d)* function in the penultimate column of Table 33.

The last column in Table 33 is the RR-adjusted hazard rate accumulated over the time interval specified in the first two columns of the table. The RR-adjusted hazard rate is the product of the number of days in the observation interval (fifth column) multiplied by the *RR(d)* (second to last column) and the hazard rate (third to last column) applicable during that observation interval. The sum of all values on the last column (168768.7226) is the total RR-adjusted hazard rate accumulated by the hypothetical worker in the calculations. This cumulative RR-adjusted hazard rate per 100,000 individuals is accumulated over the follow up period in days. Thus, the total accumulated RR-adjusted hazard rate for the entire period of follow up is equal to 0.0046206 (=168768.7226/(100000×365.25)). The division by 100,000 is to convert it to an individual cumulative RR-adjusted hazard and the division by 365.25 is to convert the RR-adjusted hazard rate accumulated over days to a RR-adjusted hazard accumulated over years. Although this accumulated RR-adjusted hazard is often used as the contribution of the individual worker to the *Expected** number of lymphoid cancer deaths, a more accurate estimation would use the cumulative probability using the expression (Breslow and Day 1987)

$$CumulativeProbability^* = 1 - e^{-CumulativeRRadjustedHazard}$$

Even though *CumulativeProbability** is approximately equal to the *CumulativeRRadjustedHazard* for small values of the *CumulativeRRadjustedHazard* (which is usually the case in SMR analyses, Breslow and Day 1987), the *CumulativeProbability** was used by TCEQ. In the example shown in Table 33 the *CumulativeProbability** is equal to 0.00461.

The *Expected** number of cause-specific deaths is calculated as the sum over all workers in the study of their *CumulativeProbability**. That is, *Expected** number of cause-specific deaths in the NIOSH study is the sum over all 17,493 workers of their cause-specific *CumulativeProbability** of death. The *Expected** number of cause-specific deaths in the NIOSH study is greater than the *Expected* number of cause-specific deaths in the NIOSH study because the *RR(d)* function increases with cumulative exposure *d*.

Table 33: Sample Calculations of the Contribution of a Hypothetical Worker to the Expected* Number of Lymphoid Cancer Deaths in the Study Group

Specific Worker Information [a]						Reference Population Information [b]			Rate Ratio Function Evaluated at Midpoint of Cumulative Exposure RR(d) = $e^{\beta \times (ppm-days)}$	RR-Adjusted Hazard Rate for Period: Days*RR(d)*Hazard Rate per 100,000 per day [c]
Start Date	End Date	Start Age (yrs)	End Age (yrs)	Days Start-End	Cum. Exposure (ppm-days)	Year with Spec. Rates	Age Group	Hazard Rate: Lymphoid deaths per 100,000 per year		
6/22/1964	9/11/1964	21.27	21.49	81	1215	1960	20-24	1.2269088	1.00288370	99.66620
9/12/1964	12/31/1964	21.50	21.80	111	1215	1960	20-24	1.2269088	1.00577572	136.97346
1/1/1965	12/31/1965	21.80	22.80	365	8515	1960	20-24	1.2269088	1.02332804	458.26852
1/1/1966	12/31/1966	22.80	23.80	365	15815	1960	20-24	1.2269088	1.05935698	474.40306
1/1/1967	12/31/1967	23.80	24.80	365	23115	1960	20-24	1.2269088	1.09665441	491.10566
1/1/1968	3/15/1968	24.80	25.00	74	24595	1968	20-24	1.8538885	1.11971333	153.61095
3/16/1968	12/31/1968	25.01	25.80	292	30435	1968	25-34	1.9489378	1.13930804	648.36864
1/1/1969	12/31/1969	25.80	26.80	365	30435	1969	25-34	1.8260952	1.15518661	769.96046
1/1/1970	12/31/1970	26.80	27.80	365	30435	1970	25-34	1.6427126	1.15518661	692.63846
1/1/1971	12/31/1971	27.80	28.80	365	30435	1971	25-34	1.8667381	1.15518661	787.09727
1/1/1972	12/31/1972	28.80	29.80	366	30435	1972	25-34	1.4360858	1.15518661	607.17465
1/1/1973	12/31/1973	29.80	30.80	365	30435	1973	25-34	1.5596403	1.15518661	657.61160
1/1/1974	12/31/1974	30.80	31.80	365	30435	1974	25-34	1.6393443	1.15518661	691.21822
1/1/1975	12/31/1975	31.80	32.80	365	30435	1975	25-34	1.4671362	1.15518661	618.60785
1/1/1976	12/31/1976	32.80	33.80	366	30435	1976	25-34	1.4321998	1.15518661	605.53164
1/1/1977	12/31/1977	33.80	34.80	365	30435	1977	25-34	1.4560795	1.15518661	613.94588
1/1/1978	3/15/1978	34.80	35.00	74	30435	1978	25-34	1.5788775	1.15518661	134.96847
3/16/1978	12/31/1978	35.01	35.80	291	30435	1978	35-44	3.4144950	1.15518661	1147.81425
1/1/1979	12/31/1979	35.80	36.80	365	30435	1979	35-44	3.1564375	1.15518661	1330.89012
1/1/1980	12/31/1980	36.80	37.80	366	30435	1980	35-44	3.5059257	1.15518661	1482.29942
1/1/1981	12/31/1981	37.80	38.80	365	30435	1981	35-44	3.0052751	1.15518661	1267.15357
1/1/1982	12/31/1982	38.80	39.80	365	30435	1982	35-44	3.6074238	1.15518661	1521.04542

Specific Worker Information [a]						Reference Population Information [b]			Rate Ratio Function Evaluated at Midpoint of Cumulative Exposure RR(d) = $e^{\beta \times (ppm-days)}$	RR-Adjusted Hazard Rate for Period: Days*RR(d)*Hazard Rate per 100,000 per day [c]
Start Date	End Date	Start Age (yrs)	End Age (yrs)	Days Start-End	Cum. Exposure (ppm-days)	Year with Spec. Rates	Age Group	Hazard Rate: Lymphoid deaths per 100,000 per year		
1/1/1983	12/31/1983	39.80	40.80	365	30435	1983	35-44	3.2109072	1.15518661	1353.85691
1/1/1984	12/31/1984	40.80	41.80	366	30435	1984	35-44	3.6075915	1.15518661	1525.28354
1/1/1985	12/31/1985	41.80	42.80	365	30435	1985	35-44	3.9000177	1.15518661	1644.41562
1/1/1986	12/31/1986	42.80	43.80	365	30435	1986	35-44	3.9074933	1.15518661	1647.56764
1/1/1987	12/31/1987	43.80	44.80	365	30435	1987	35-44	3.7333094	1.15518661	1574.12420
1/1/1988	3/14/1988	44.80	45.00	74	30435	1988	35-44	3.7443317	1.15518661	320.07973
3/15/1988	12/31/1988	45.00	45.80	292	30435	1988	45-54	10.1212315	1.15518661	3414.03805
1/1/1989	12/31/1989	45.80	46.80	365	30435	1989	45-54	10.4543571	1.15518661	4408.00766
1/1/1990	12/31/1990	46.80	47.80	365	30435	1990	45-54	11.3420080	1.15518661	4782.27958
1/1/1991	12/31/1991	47.80	48.80	365	30435	1991	45-54	11.2991321	1.15518661	4764.20125
1/1/1992	12/31/1992	48.80	49.80	366	30435	1992	45-54	10.7658867	1.15518661	4551.79861
1/1/1993	12/31/1993	49.80	50.80	365	30435	1993	45-54	10.4984713	1.15518661	4426.60814
1/1/1994	12/31/1994	50.80	51.80	365	30435	1994	45-54	11.2407277	1.15518661	4739.57541
1/1/1995	12/31/1995	51.80	52.80	365	30435	1995	45-54	10.9565184	1.15518661	4619.74051
1/1/1996	12/31/1996	52.80	53.80	366	30435	1996	45-54	10.3848722	1.15518661	4390.70632
1/1/1997	12/31/1997	53.80	54.80	365	30435	1997	45-54	10.9412591	1.15518661	4613.30655
1/1/1998	3/15/1998	54.80	55.00	74	30435	1998	45-54	10.0855678	1.15518661	862.15276
3/16/1998	12/31/1998	55.01	55.80	291	30435	1998	55-64	28.2780557	1.15518661	9505.93153
1/1/1999	12/31/1999	55.80	56.80	365	30435	1999	55-64	27.7683602	1.15518661	11708.33787
1/1/2000	12/31/2000	56.80	57.80	366	30435	2000	55-64	26.0245994	1.15518661	11003.15639
1/1/2001	12/31/2001	57.80	58.80	365	30435	2001	55-64	25.7682490	1.15518661	10865.00472
1/1/2002	12/31/2002	58.80	59.80	365	30435	2002	55-64	24.6020452	1.15518661	10373.28295
1/1/2003	12/31/2003	59.80	60.80	365	30435	2003	55-64	24.3376112	1.15518661	10261.78616
1/1/2004	12/31/2004	60.80	61.80	366	30435	2004	55-64	22.2903793	1.15518661	9424.33450
1/1/2005	12/31/2005	61.80	62.80	365	30435	2005	55-64	21.4439484	1.15518661	9041.69316

Specific Worker Information [a]						Reference Population Information [b]			Rate Ratio Function Evaluated at Midpoint of Cumulative Exposure RR(d) = $e^{\beta \times (ppm-days)}$	RR-Adjusted Hazard Rate for Period: Days*RR(d)*Hazard Rate per 100,000 per day [c]
Start Date	End Date	Start Age (yrs)	End Age (yrs)	Days Start-End	Cum. Exposure (ppm-days)	Year with Spec. Rates	Age Group	Hazard Rate: Lymphoid deaths per 100,000 per year		
1/1/2006	12/31/2006	62.80	63.80	365	30435	2006	55-64	20.8159028	1.15518661	8776.88205
1/1/2007	12/31/2007	63.80	64.80	365	30435	2007	55-64	20.2182691	1.15518661	8524.89394
1/1/2008	1/10/2008	64.80	64.82	11	30435	2008	55-64	20.0930161	1.15518661	255.32301

[a] The worker specific information is split in the coarsest observation time intervals possible that accommodate worker and reference population time-interval cut points.

[b] The reference population information column includes three items that are applicable to the specific observation time interval of the worker: i) the "Year with Spec. Rates" is the calendar year which had the most recent, at the observation time, sex-, age-, and race-specific background hazard rates; ii) the "Age Group" is the age group in the background hazard rate tables that includes the ages of the worker during the observation time interval; and iii) the "Hazard Rate: Lymphoid deaths per 100,000 per year" is the hazard rate for lymphoid mortality reported in the table for the ""Year with Spec. Rates" and the "Age Group" in units of number of deaths in one year per 100,000 individuals (numbers have been rounded to seven significant digits).

[c] The column "RR-adjusted Hazard Rate for Period: Days*RRD(d)*Hazard Rate per 100,000 per day" is the RR-adjusted hazard rate per 100,000 cumulated over the days during the observation time of the worker.

Table 34: Lymphoid Cancer Mortality Rates in the U.S. Population for Each Calendar Year (1930-1972), Each Race, Each Sex, and Each Age Group (Number of Lymphoid Cancer Deaths per 100,000)

Age Group (Years)	Calendar Year								
	1930	1940	1950	1960	1968	1969	1970	1971	1972
White Males									
< 1	0.571574	0.571574	0.571574	0.952897	0.664582	0.193834	0.250050	0.264904	0.436483
1-4	0.889715	0.889715	0.889715	0.905855	2.716523	2.469136	2.639159	2.639196	1.416049
5-9	0.896007	0.896007	0.896007	0.792474	3.181767	3.222868	3.486584	3.365958	3.053435
10-14	0.808974	0.808974	0.808974	0.764426	1.743532	2.089818	1.892907	1.777729	1.573083
15-19	1.173753	1.173753	1.173753	1.302018	2.187854	2.304943	2.062410	1.853147	1.868520
20-24	0.779566	0.779566	0.779566	**1.226909**	**1.853888**	1.437771	2.074683	1.564349	1.969677
25-34	1.246367	1.246367	1.246367	1.348092	**1.948938**	**1.826095**	**1.642713**	**1.866738**	**1.436086**
35-44	2.822822	2.822822	2.822822	3.369977	4.096598	4.063587	3.427241	3.219945	3.996754
45-54	6.291235	6.291235	6.291235	8.459325	10.379543	10.326954	10.435895	10.292100	9.491327
55-64	13.704865	13.704865	13.704865	18.845992	25.093104	24.651811	25.357608	27.116973	25.569775
65-74	18.092659	18.092659	18.092659	32.706133	53.237410	51.595092	51.896786	51.955307	51.216641
75-84	18.992015	18.992015	18.992015	38.781214	82.331839	88.898757	86.483903	88.585069	91.555937
85+	11.917858	11.917858	11.917858	37.471858	104.761905	101.686747	87.071343	105.399568	117.052632
Other Race Males									
< 1	0.493869	0.493869	0.493869	0.000000	0.342912	0.334609	0.950275	0.958681	1.354541
1-4	0.506669	0.506669	0.506669	0.510781	1.218451	1.163832	1.553219	0.925069	0.722674
5-9	0.875629	0.875629	0.875629	0.460755	1.440733	1.962067	1.107201	1.724138	1.617251
10-14	0.419074	0.419074	0.419074	0.374631	1.760325	1.713909	1.412963	0.949367	1.501877
15-19	0.639471	0.639471	0.639471	0.878770	2.205882	1.334380	1.415189	1.505376	1.782042
20-24	1.159879	1.159879	1.159879	0.798062	2.016607	1.771872	1.024119	1.309635	0.886525
25-34	1.371643	1.371643	1.371643	1.371711	1.282051	1.747997	1.386486	1.828030	1.277139
35-44	2.362183	2.362183	2.362183	3.357051	3.718674	3.658537	4.072298	4.099678	5.229794
45-54	5.984989	5.984989	5.984989	9.095071	11.770245	10.925926	12.172295	10.151380	12.971078
55-64	11.279807	11.279807	11.279807	17.047913	29.750000	31.365314	28.395850	31.578947	26.004728
65-74	11.984811	11.984811	11.984811	22.473431	45.908184	51.185771	46.782908	52.000000	43.314501
75-84	11.892728	11.892728	11.892728	23.349211	61.827957	62.765957	67.857013	57.692308	68.202765
85+				15.943369	58.536585	52.272727	59.543142	80.851064	63.829787
White Females									
< 1	0.372830	0.372830	0.372830	0.466696	0.703416	0.752196	0.595918	0.419701	0.461215
1-4	0.589370	0.589370	0.589370	0.382623	2.033672	1.985371	1.976859	1.656868	1.449532
5-9	0.369624	0.369624	0.369624	0.240952	2.059308	2.331391	2.528940	2.320938	1.828012
10-14	0.231579	0.231579	0.231579	0.417692	1.185724	1.195589	1.110161	1.276644	1.255995
15-19	0.258359	0.258359	0.258359	0.242587	0.965624	0.882056	1.138742	1.116447	1.150775
20-24	0.521598	0.521598	0.521598	0.538865	0.859182	0.643897	0.830949	0.817682	0.823469
25-34	0.792567	0.792567	0.792567	0.695775	0.815707	0.811284	0.990505	0.730055	1.008598

Age Group (Years)	Calendar Year								
	1930	1940	1950	1960	1968	1969	1970	1971	1972
35-44	1.656499	1.656499	1.656499	2.209093	2.610084	2.225193	2.125844	2.257623	2.227040
45-54	3.927054	3.927054	3.927054	5.317963	7.310358	6.770297	6.805298	6.449242	6.650224
55-64	9.581633	9.581633	9.581633	13.184796	16.236934	16.778907	16.683520	16.793724	15.473466
65-74	13.471141	13.471141	13.471141	21.389945	33.714562	34.345683	35.204790	33.589547	36.741455
75-84	13.544646	13.544646	13.544646	28.303572	54.802432	54.652880	56.864558	57.238122	56.749460
85+	11.466575	11.466575	11.466575	23.163091	57.645467	65.772669	57.425086	62.057522	59.322034
Other Race Females									
< 1	0.490851	0.490851	0.490851	0.649642	0.000000	0.343348	0.327084	0.659039	0.695476
1-4	0.255302	0.255302	0.255302	0.425917	0.788782	1.171171	1.564646	1.022305	0.545455
5-9	0.373279	0.373279	0.373279	0.153607	0.524246	0.721311	1.050270	1.136364	0.814664
10-14	0.000000	0.000000	0.000000	0.281193	1.222826	0.991408	0.837986	1.144310	0.629327
15-19	0.302773	0.302773	0.302773	0.122783	0.642055	1.078582	0.663027	0.921986	0.679348
20-24	0.572140	0.572140	0.572140	0.142154	1.020408	0.287632	0.898678	0.583333	0.960769
25-34	0.686160	0.686160	0.686160	0.906197	1.654997	1.175015	0.652594	0.694444	0.986842
35-44	1.574455	1.574455	1.574455	3.092078	2.105978	2.642276	2.321355	2.675585	2.514891
45-54	4.516905	4.516905	4.516905	7.099807	9.083333	9.046455	8.699902	8.268934	8.308157
55-64	7.848951	7.848951	7.848951	10.717328	20.000000	16.902944	18.750576	20.582121	16.276704
65-74	5.746153	5.746153	5.746153	12.368748	30.629139	27.597403	28.920872	31.981279	33.027523
75-84	4.880954	4.880954	4.880954	16.111612	37.500000	33.333333	32.715935	35.000000	34.437086
85+				12.414341	29.508197	33.846154	22.881259	42.465753	36.842105

Table 35: Lymphoid Cancer Mortality Rates in the U.S. Population for Each Calendar Year (1973-1981), Each Race, Each Sex, and Each Age Group (Number of Lymphoid Cancer Deaths per 100,000)

Age Group (Years)	Calendar Year								
	1973	1974	1975	1976	1977	1978	1979	1980	1981
White Males									
< 1	0.908058	0.224475	0.528294	0.300067	0.500615	0.358533	0.273877	0.132507	0.132064
1-4	2.244898	1.937849	1.833031	1.491692	1.211771	1.370124	1.234337	0.999559	1.346066
5-9	3.192572	3.142184	2.786254	3.041926	2.701618	2.013605	2.703456	2.514574	2.153795
10-14	2.131166	2.046687	1.720841	1.787372	2.181993	1.920932	1.734473	1.758458	1.563759
15-19	1.934907	1.908439	1.957140	1.817788	1.691974	1.677743	1.720171	1.719677	1.542872
20-24	1.456249	1.256932	1.508621	1.205242	1.383173	1.537081	1.481645	1.646638	1.395948
25-34	**1.559640**	**1.639344**	**1.467136**	**1.432200**	**1.456079**	**1.578878**	1.322802	1.543315	1.499603
35-44	3.285860	3.206107	3.239279	2.932876	2.984485	**3.414495**	**3.156437**	**3.505926**	**3.005275**
45-54	9.415647	10.002913	9.567420	9.625196	9.086395	9.480337	9.692479	9.433185	9.489925
55-64	24.776732	24.812299	25.402042	24.272853	24.671202	24.745497	24.588897	25.549930	25.109082

Age Group (Years)	Calendar Year								
	1973	1974	1975	1976	1977	1978	1979	1980	1981
65-74	52.533589	52.720450	50.549249	52.758868	52.749171	53.199113	54.677339	54.513390	52.882396
75-84	91.595563	91.298812	90.050167	92.269737	90.846216	96.881248	98.868072	98.827567	99.726331
85+	109.183673	109.126214	119.074074	116.333938	119.789842	125.252525	135.008104	135.478217	128.314866
Other Race Males									
< 1	0.000000	0.350064	0.000000	0.686344	0.000000	0.952922	0.604677	0.000000	0.000000
1-4	0.890472	1.334520	1.432408	1.648352	0.925926	0.915751	0.896057	0.867085	1.145101
5-9	1.717033	1.670146	1.742160	1.098901	2.105978	1.683502	1.346801	0.799939	1.551788
10-14	1.607916	1.411909	0.973828	1.039755	1.363918	1.322418	0.890019	1.453699	1.239236
15-19	1.851852	1.726343	1.179392	1.390568	1.014925	1.410106	1.567034	1.377656	1.363956
20-24	1.528014	1.383238	1.242236	1.187825	1.275691	1.709986	1.058901	1.480282	1.175116
25-34	1.333333	1.145475	1.243243	1.379663	1.699854	1.661283	1.179554	1.310302	1.284428
35-44	3.903201	2.773498	3.506098	3.048327	3.537906	3.778866	3.653586	3.462009	4.639626
45-54	9.490940	13.356164	10.365336	10.867734	10.067114	9.468439	11.367381	10.689003	10.210284
55-64	27.570093	29.633867	29.319955	30.363036	28.862661	25.991649	29.183673	29.668996	26.891935
65-74	56.880734	54.821429	53.739130	53.962901	54.545455	58.582677	50.844854	58.720972	54.042417
75-84	73.991031	76.855895	66.115702	74.806202	81.992337	76.226415	78.651685	85.585907	93.874677
85+	64.583333	76.000000	75.925926	60.000000	82.142857	108.620690	106.779661	80.643834	104.987699
White Females									
< 1	0.559929	0.396269	0.479311	0.555150	0.302594	0.455050	0.361702	0.210232	0.139542
1-4	1.087926	1.337486	1.087164	1.130952	1.031553	1.022044	0.964947	0.643648	0.888346
5-9	2.089711	1.931242	1.779013	1.525870	1.558551	1.671667	1.377491	1.181182	1.282891
10-14	1.010913	1.042753	0.977275	0.935829	1.054746	0.896104	0.828655	0.922761	1.031858
15-19	1.049838	0.888990	0.972081	0.705803	0.887341	0.700328	0.797176	0.818234	0.945110
20-24	0.683717	0.843359	0.774256	0.900794	0.672464	0.716642	0.628578	0.724198	0.705556
25-34	0.861660	0.811775	0.928295	0.739332	0.837019	0.936504	0.798198	0.855556	0.724416
35-44	2.267551	2.112676	2.106728	1.792044	1.865996	1.696495	1.630139	1.887533	1.727053
45-54	6.246017	6.551095	6.287809	6.452209	6.487905	6.471816	6.256618	6.115654	5.936539
55-64	16.013353	16.622439	15.990803	16.423433	16.627989	16.348638	16.209867	16.803601	17.030421
65-74	34.125587	34.821812	32.178287	34.755847	34.549814	35.034501	35.199592	37.603777	35.889455
75-84	58.124174	58.643892	57.581864	61.363079	61.298077	61.771617	63.731992	67.535625	68.589388
85+	67.239636	66.761364	67.724868	67.617450	76.367962	76.519130	75.692964	84.172570	83.353422
Other Race Females									
< 1	0.718184	0.000000	0.000000	0.000000	0.000000	0.654986	0.311744	0.000000	0.000000
1-4	0.898473	0.450045	1.364877	0.372439	0.753296	0.279851	0.547445	0.795146	0.583260
5-9	0.966851	0.629811	1.190476	0.968188	0.959561	0.886767	0.752394	0.407426	1.169315
10-14	0.623053	0.992556	0.802965	0.745805	0.693569	0.960307	0.774693	0.642377	0.757866
15-19	0.786885	0.571429	0.803461	0.422705	0.774732	0.587544	0.815376	0.864307	0.402981
20-24	0.538462	0.591716	0.283487	0.683060	0.654879	0.758534	0.612745	0.654753	0.634340
25-34	0.677083	0.935961	0.836431	0.924296	0.962343	0.558659	0.833018	1.034294	0.828562

Age Group (Years)	Calendar Year								
	1973	1974	1975	1976	1977	1978	1979	1980	1981
35-44	2.156863	2.450032	1.977041	2.114428	2.238355	2.231356	2.103468	2.399917	2.864034
45-54	9.830007	6.540698	9.305655	6.770099	8.432056	6.662088	8.316430	8.035665	6.734315
55-64	18.818819	17.543860	19.038643	20.702403	19.516562	20.555074	18.891688	19.739761	18.660537
65-74	37.037037	34.240688	32.088520	34.087883	32.101911	32.885086	35.924617	32.425347	40.174421
75-84	31.761006	36.445783	44.067797	45.212766	48.041775	45.641026	47.727273	57.289609	57.167055
85+	46.250000	54.117647	41.935484	43.877551	45.192308	50.000000	63.157895	65.743449	70.517392

Table 36: Lymphoid Cancer Mortality Rates in the U.S. Population for Each Calendar Year (1982-1990), Each Race, Each Sex, and Each Age Group (Number of Lymphoid Cancer Deaths per 100,000)

Age Group (Years)	Calendar Year								
	1982	1983	1984	1985	1986	1987	1988	1989	1990
White Males									
< 1	0.000000	0.462407	0.000000	0.192266	0.064567	0.512302	0.000000	0.244261	0.118477
1-4	0.897367	1.310122	0.781290	0.830986	0.877404	0.739505	0.737235	0.663349	0.708275
5-9	2.366171	1.846937	1.510829	1.428039	1.366221	1.467699	1.225459	1.297239	0.913484
10-14	1.583212	1.360994	1.426616	1.285190	1.274476	1.210121	1.201909	1.428199	1.352777
15-19	1.796605	1.780555	1.689925	1.682906	1.512290	1.333880	1.353366	1.212178	1.409300
20-24	1.343823	1.284539	1.270779	1.324499	1.419361	1.497749	1.274751	1.514134	1.248516
25-34	1.527609	1.570647	1.584635	1.706365	2.154965	1.607166	1.992268	1.977337	2.268786
35-44	**3.607424**	**3.210907**	**3.607591**	**3.900018**	**3.907493**	**3.733309**	**3.744332**	4.073447	3.925666
45-54	10.320582	9.492029	9.475140	9.981628	10.353269	10.305775	**10.121232**	**10.454357**	**11.342008**
55-64	25.740401	25.933995	26.359149	27.642635	26.093181	28.162326	28.577168	29.628210	29.421239
65-74	55.446249	58.683266	58.006916	60.547081	63.379973	61.768858	60.894609	63.835855	64.680548
75-84	102.512985	103.269530	102.903810	113.797884	111.957418	110.325657	117.539257	121.572182	124.689270
85+	141.091466	154.657919	146.182157	158.545624	152.478016	146.762825	171.258407	163.709977	185.700410
Other Race Males									
< 1	0.282407	0.000000	0.560626	0.544009	0.265887	0.513383	0.243094	0.231537	0.000000
1-4	0.950552	0.843139	0.898864	0.815968	0.584038	0.359246	0.352241	0.545662	0.529965
5-9	1.544365	1.263091	1.035059	1.065461	1.635687	1.002256	0.802618	0.847424	0.838924
10-14	1.101152	1.094825	1.341328	1.465289	1.305275	0.991744	0.674730	1.075256	0.990555
15-19	1.544260	1.214203	1.108428	0.701977	0.978176	1.531826	1.121842	1.232062	0.892218
20-24	0.848498	1.603323	1.108261	1.322919	1.200467	0.919044	1.446631	1.389804	1.442548
25-34	1.840239	1.941467	1.637358	1.906600	1.752430	1.457848	1.865610	2.782049	2.290311
35-44	3.630473	3.495188	4.120332	4.426983	4.713920	4.554605	4.972986	4.699949	5.240313
45-54	12.753297	11.795082	11.153652	10.804774	11.090469	11.424834	12.745138	13.021074	13.059052
55-64	27.441584	33.281437	30.656579	29.982650	30.277039	26.602320	29.171684	30.098894	33.984171

Age Group (Years)	Calendar Year								
	1982	1983	1984	1985	1986	1987	1988	1989	1990
65-74	57.237298	55.381074	50.838187	61.469040	67.722773	64.142203	60.374990	60.402824	65.684984
75-84	99.028610	108.712639	94.311838	97.257155	112.593187	106.228728	99.871509	110.026091	109.071026
85+	110.976140	120.734757	82.336687	113.366296	106.579982	137.074874	121.273370	148.091471	159.703198
White Females									
< 1	0.412871	0.418804	0.207705	0.338393	0.204025	0.337325	0.397082	0.450230	0.062415
1-4	0.740887	0.943464	0.464971	0.714428	0.693092	0.601971	0.653006	0.419260	0.451249
5-9	1.294763	0.911457	0.835611	0.988693	0.757493	0.627520	0.559821	0.641137	0.623382
10-14	0.811883	0.631763	0.881446	0.834117	0.803605	0.716906	0.557631	0.640258	0.556603
15-19	0.816159	0.870140	0.723414	0.626600	0.838982	0.794999	0.644126	0.647127	0.788964
20-24	0.873275	0.679190	0.641055	0.778479	0.804127	0.708784	0.656806	0.791296	0.786603
25-34	0.743563	0.696736	0.814677	0.906247	0.940198	0.770082	0.829128	0.869329	0.884170
35-44	1.741456	1.859996	2.115381	1.992830	1.956782	1.717332	2.159311	1.856792	1.787279
45-54	6.734416	6.563147	6.457907	6.609959	6.253106	6.042936	6.355324	6.076045	6.084263
55-64	16.917034	17.085084	17.960658	18.684330	17.474939	17.735989	17.586514	18.798277	17.622023
65-74	37.596194	39.177268	39.824889	39.607408	41.121751	40.965889	41.342613	43.020215	43.082987
75-84	69.543091	70.552506	72.529403	71.315776	76.337351	76.845877	77.916555	80.989763	81.092049
85+	92.412534	89.912880	93.843998	94.727554	100.448726	104.084539	103.516519	109.816269	114.634887
Other Race Females									
< 1	0.292722	0.000000	0.868817	0.563369	0.553598	0.000000	0.252484	0.239977	0.468898
1-4	0.726035	0.546679	0.611366	0.454753	0.298587	0.515052	1.010791	0.699719	0.476427
5-9	0.548698	1.087145	0.198370	0.640049	0.804902	0.421807	0.645421	0.520951	0.458591
10-14	0.812410	0.622286	0.437587	0.752269	0.382603	0.509268	0.377932	0.490451	0.477840
15-19	0.580762	0.764674	0.593717	0.298791	0.471507	0.640464	0.461812	0.519634	0.748110
20-24	0.853074	0.561540	0.501356	0.221421	0.554927	0.671071	0.564213	0.510058	0.851649
25-34	0.731149	0.674739	0.950363	1.008959	0.926506	0.903771	1.071554	0.710502	0.963634
35-44	2.213313	2.192893	2.291606	2.543862	2.321505	2.242482	2.132750	2.326151	2.652870
45-54	7.298407	7.121108	7.312326	6.550464	8.025120	7.634042	7.331957	7.589449	8.253123
55-64	18.533248	17.381368	20.156957	19.876547	18.758072	18.216235	19.695708	19.588978	19.595873
65-74	37.355813	38.276541	36.088017	38.533843	40.391660	39.156632	40.894103	41.773392	41.612207
75-84	59.725264	61.003109	58.979590	72.662063	61.616938	61.855941	67.427820	70.322620	71.910686
85+	64.834220	66.926697	64.149876	77.144586	79.929917	83.506794	81.033922	81.645237	83.769867

Table 37: Lymphoid Cancer Mortality Rates in the U.S. Population for Each Calendar Year (1991-1999), Each Race, Each Sex, and Each Age Group (Number of Lymphoid Cancer Deaths per 100,000)

Age Group (Years)	Calendar Year								
	1991	1992	1993	1994	1995	1996	1997	1998	1999
White Males									
< 1	0.120549	0.304542	0.309342	0.250062	0.125911	0.126229	0.381286	0.313145	0.261647
1-4	0.598010	0.634873	0.641730	0.483114	0.597917	0.525628	0.322071	0.389179	0.520896
5-9	1.077332	1.046375	0.842215	0.869082	1.071523	0.627185	0.728541	0.635617	0.535847
10-14	1.069727	0.922609	1.018617	0.953443	0.855020	0.884591	0.804178	0.847763	0.589373
15-19	1.394160	1.411226	1.281312	1.131257	1.049657	1.046720	0.934061	1.187142	0.880738
20-24	1.486628	1.485252	1.049435	1.532901	1.098601	1.291260	1.508268	1.552742	1.398208
25-34	2.153514	2.230164	2.090814	2.252798	2.244475	2.011220	2.201578	1.773869	1.305571
35-44	4.716193	4.434700	4.386889	4.381832	4.635446	4.322717	3.891075	3.694620	2.936410
45-54	**11.299132**	**10.765887**	**10.498471**	**11.240728**	**10.956518**	**10.384872**	**10.941259**	**10.085568**	9.264970
55-64	28.990578	28.964490	28.869688	30.789233	30.267561	29.977605	29.599598	**28.278056**	**27.768360**
65-74	65.820142	67.437957	67.622686	70.574494	70.831434	69.983251	72.455585	71.013446	69.063573
75-84	123.244041	128.192453	129.169255	130.541394	132.139030	135.097298	134.542905	135.014407	136.039499
85+	184.620012	182.774888	186.482519	202.084388	203.049861	205.679170	195.813850	199.761637	200.496795
Other Race Males									
< 1	0.000000	0.000000	0.231198	0.000000	0.490283	0.492542	0.242734	0.476757	0.000000
1-4	0.251040	0.180786	0.291989	0.172394	0.286071	0.287824	0.233362	0.352567	0.176170
5-9	0.706327	0.689215	0.565082	0.492402	0.520381	0.819514	0.572628	0.430521	0.256131
10-14	0.775427	0.641820	0.568414	0.759836	1.047504	0.733418	0.767420	0.561479	0.813209
15-19	1.191880	1.185346	0.500675	0.864956	1.198790	0.553187	0.731660	0.662851	1.070727
20-24	1.124612	1.642354	1.785301	1.508855	0.972847	1.313934	2.015238	0.645289	0.993891
25-34	2.237519	2.484545	2.407845	2.206208	2.567098	2.425574	2.111731	1.761624	1.717844
35-44	5.264830	5.221627	4.846035	4.669117	5.130747	5.026924	5.259584	4.383872	3.907748
45-54	12.192547	12.871079	12.740362	12.099461	12.981341	12.574332	13.039173	11.972081	9.760551
55-64	31.597492	34.051901	28.743845	34.058142	31.510938	32.051830	30.667501	30.433409	31.292855
65-74	67.516141	61.893730	69.133246	62.181494	62.604246	67.819297	64.586214	62.510594	61.446247
75-84	118.346204	108.465272	111.503892	101.134128	110.952607	117.171986	116.895856	108.432653	108.149986
85+	131.534134	140.571056	164.607271	156.009507	161.524956	154.217709	152.287127	162.763360	161.416252
White Females									
< 1	0.189610	0.128216	0.260841	0.394373	0.198615	0.463996	0.600393	0.328510	0.206611
1-4	0.544654	0.484663	0.362290	0.393668	0.231834	0.268299	0.322384	0.375495	0.411102
5-9	0.617083	0.712038	0.651712	0.505619	0.510744	0.422820	0.559046	0.412139	0.282375
10-14	0.420396	0.650159	0.510683	0.558181	0.525734	0.507201	0.530655	0.539522	0.375783
15-19	0.791386	0.689823	0.563043	0.653104	0.495588	0.564889	0.605686	0.474534	0.521361
20-24	0.719853	0.647753	0.577305	0.783432	0.732804	0.840555	0.913694	0.930414	0.701500
25-34	0.928258	0.984040	0.944766	1.037638	0.882957	1.072279	0.822517	0.832823	0.824799

Age Group (Years)	Calendar Year								
	1991	1992	1993	1994	1995	1996	1997	1998	1999
35-44	1.920846	1.937426	1.865423	2.084310	2.097702	1.968226	1.983071	1.727557	1.672751
45-54	6.500862	5.997125	5.912764	6.459897	6.114375	6.139397	5.639134	5.577498	5.202266
55-64	19.178724	18.330817	19.220898	19.593339	19.239323	19.268723	19.531043	17.763069	17.363737
65-74	44.670651	45.063962	46.706389	46.334466	47.634353	46.662600	47.170072	45.873513	46.282577
75-84	85.652607	85.539274	87.768235	88.536784	89.289949	90.527655	89.550870	91.065418	91.226321
85+	118.035157	115.502420	120.620701	117.264248	125.040442	121.648591	124.871721	121.364315	122.155611
Other Race Females									
< 1	0.234086	0.000000	0.000000	0.000000	0.254598	0.254855	0.504694	0.000000	1.249619
1-4	0.193747	0.434289	0.180589	0.415097	0.472506	0.356208	0.300468	0.120879	0.181199
5-9	0.502308	0.109141	0.688359	0.355915	0.489020	0.376693	0.364674	0.178399	0.221088
10-14	0.340783	0.658581	0.265457	0.260343	0.718685	0.604677	0.148552	0.193467	0.420867
15-19	0.760147	0.290665	0.629617	0.667091	0.589240	0.516753	0.551219	0.243356	0.478619
20-24	0.552215	0.701958	0.744932	0.369962	0.529128	0.641656	0.371187	0.574389	0.811758
25-34	1.250760	1.161703	1.074879	0.969668	1.282122	1.191926	1.034714	1.221072	0.860489
35-44	2.631571	2.695297	2.201742	2.072282	2.737377	2.480527	2.904835	2.831665	2.114252
45-54	7.433460	7.524094	7.964662	7.841874	7.423539	6.577967	6.862564	6.910658	6.250333
55-64	20.877164	19.463921	21.271408	20.568934	23.617713	21.535597	20.943180	21.726642	21.037674
65-74	46.704315	41.136051	43.407193	39.603040	41.951707	46.011816	43.479905	44.474852	41.977259
75-84	81.049219	72.227947	77.173631	76.716888	75.573071	76.119672	72.954561	78.245435	76.115208
85+	87.337153	99.305842	94.501598	94.680398	94.904241	99.516750	98.701031	99.677092	95.995562

Table 38: Lymphoid Cancer Mortality Rates in the U.S. Population for Each Calendar Year (2000-2008), Each Race, Each Sex, and Each Age Group (Number of Lymphoid Cancer Deaths per 100,000)

Age Group (Years)	Calendar Year								
	2000	2001	2002	2003	2004	2005	2006	2007	2008
White Males									
< 1	0.524806	0.250750	0.381423	0.126342	0.125603	0.063462	0.378854	0.433816	0.375811
1-4	0.390715	0.311593	0.340849	0.547846	0.383588	0.428761	0.414535	0.207105	0.460199
5-9	0.647961	0.536133	0.544783	0.809098	0.738830	0.586288	0.440868	0.721561	0.485417
10-14	0.836564	0.644528	0.792704	0.683952	0.508571	0.705677	0.615860	0.597909	0.405742
15-19	1.143733	1.118192	1.005208	0.941732	1.015803	0.933706	0.867502	0.827787	0.838181
20-24	1.424321	1.262936	1.335348	1.160621	1.051160	1.247020	1.314343	1.043871	1.270049
25-34	1.207456	1.325997	1.292035	1.232081	1.287954	1.026088	1.180857	1.123533	1.249620
35-44	2.951331	2.947883	2.787913	2.719071	2.445056	2.470472	2.151277	2.365903	2.161794
45-54	8.736368	8.658735	8.160044	7.522465	7.274624	6.838794	6.861847	6.613099	6.164806
55-64	**26.024599**	**25.768249**	**24.602045**	**24.337611**	**22.290379**	**21.443948**	**20.815903**	**20.218269**	**20.093016**

Age Group (Years)	Calendar Year								
	2000	2001	2002	2003	2004	2005	2006	2007	2008
65-74	68.210725	66.846157	66.754466	63.724138	59.058038	59.772839	55.443301	55.225882	52.210701
75-84	137.861646	131.603614	132.026187	129.571266	125.750437	126.843740	126.655258	125.431566	123.714919
85+	202.953378	206.959834	212.138265	213.290538	201.174047	212.220517	195.502713	202.949122	202.726728
Other Race Males									
< 1	0.235491	0.000000	0.448970	0.000000	0.000000	0.211882	0.207428	0.000000	0.389636
1-4	0.232676	0.174487	0.114159	0.281887	0.388513	0.436998	0.324330	0.529700	0.359809
5-9	0.426663	0.433151	0.350934	0.177529	0.536648	0.669715	0.307361	0.432344	0.255016
10-14	0.352086	0.844244	0.697316	0.803100	0.437740	0.359507	0.481909	0.444312	0.486827
15-19	0.920683	1.076046	0.792248	0.602980	0.459569	0.604006	0.779758	0.720078	0.890076
20-24	1.679528	1.056120	0.877657	1.167735	1.357733	1.165263	1.232959	1.051449	0.744980
25-34	1.363152	1.404313	1.538684	1.551104	1.403061	1.602819	1.098655	1.126761	1.266334
35-44	2.835120	3.817562	3.392236	3.049851	2.553021	2.602693	3.074193	3.089058	2.116457
45-54	10.717689	9.866223	8.851983	9.939288	9.058168	9.391368	8.899028	8.540407	7.925244
55-64	26.363186	29.985785	26.175855	23.212888	23.481933	23.096876	24.894886	21.742272	21.917414
65-74	61.467682	61.255497	57.822519	52.268589	57.715894	54.302768	52.212361	49.404447	51.758535
75-84	102.947245	104.276589	99.069233	95.457067	100.239504	96.713415	94.921776	97.159675	93.011377
85+	145.308316	142.557723	134.973258	143.433958	145.190271	126.514193	152.502927	143.278205	131.946501
White Females									
< 1	0.483682	0.131239	0.332853	0.596126	0.263276	0.199731	0.198550	0.324862	0.327583
1-4	0.376789	0.310412	0.392293	0.388978	0.217928	0.199665	0.334287	0.317396	0.216318
5-9	0.425186	0.446824	0.547368	0.446350	0.436685	0.356507	0.299872	0.379088	0.375590
10-14	0.486294	0.377656	0.561295	0.397890	0.411565	0.441312	0.381939	0.540134	0.375560
15-19	0.492428	0.502412	0.435949	0.420339	0.629975	0.422781	0.479903	0.488373	0.438460
20-24	0.606969	0.729405	0.791141	0.676381	0.607536	0.555826	0.530911	0.682503	0.390786
25-34	0.751260	0.854954	0.782482	0.621166	0.630221	0.725255	0.731735	0.641508	0.582598
35-44	1.522875	1.588986	1.609632	1.453520	1.243847	1.286495	1.359781	1.251519	1.204327
45-54	5.326357	4.737304	4.630905	4.389539	4.295574	3.898529	3.933733	3.694953	3.534546
55-64	17.389128	16.335271	15.009996	13.676430	13.322191	13.352400	12.130725	11.797667	11.197640
65-74	44.010466	41.752191	40.585987	37.403030	36.937724	35.289786	35.434227	33.258375	31.591145
75-84	90.119912	87.396791	84.699781	84.711257	82.164651	81.038234	78.777329	78.024018	75.235482
85+	128.513697	128.834098	129.776449	128.647982	124.750168	125.342160	126.731086	123.320293	121.223154
Other Race Females									
< 1	0.244260	0.000000	0.464279	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
1-4	0.359362	0.179663	0.176290	0.232051	0.114423	0.000000	0.000000	0.164215	0.053145
5-9	0.309062	0.402679	0.271573	0.228525	0.459707	0.000000	0.135214	0.266130	0.261604
10-14	0.227928	0.174845	0.254859	0.499492	0.206140	0.289557	0.373864	0.083534	0.377093
15-19	0.520827	0.465908	0.824630	0.536728	0.260194	0.208961	0.283326	0.236140	0.231250
20-24	0.838657	0.702065	0.770675	0.398600	0.393036	0.650290	0.687329	0.466475	0.581676
25-34	1.000629	1.272210	1.020700	0.869944	0.899656	0.752461	0.696625	0.664100	0.611427

Age Group (Years)	Calendar Year								
	2000	2001	2002	2003	2004	2005	2006	2007	2008
35-44	2.317793	2.049276	1.899200	1.862371	1.737403	2.008196	1.872617	1.809375	1.348465
45-54	6.319216	6.213190	6.929462	5.666120	5.479445	5.300950	5.361658	5.400012	4.546107
55-64	17.592975	18.765077	17.788091	14.672254	15.503902	15.881942	14.640494	14.890397	13.472998
65-74	40.580024	41.223164	41.278055	41.797987	36.900825	36.086683	34.291068	34.010516	31.508649
75-84	74.119505	74.499069	70.453876	77.651645	71.641475	61.796102	62.880913	66.641937	62.963260
85+	115.616309	97.336673	86.333420	98.078476	99.450371	89.589566	92.445974	88.253258	86.059963

Appendix 4 PODs within the Observable Range of Key Cohort Data

For this DSD, the TCEQ evaluated the lower limit on the effective concentration (LEC; 95% LCL) at an extra risk of 1 in 100,000 consistent with USEPA cancer guidelines (2005a) on the selection of a POD at the low-end of the observable range of exposures. Regarding dose-response assessment using epidemiology data, the TCEQ (2015) guidelines state that the POD should be in the range of the observed data -- "near the lower end of the observed range, without significant extrapolation to lower doses" (USEPA 2005a, page 1-13).

The TCEQ used the standard Cox proportional hazards model to calculate the LEC for an extra risk of 1 in 100,000 (policy-based target risk per TCEQ 2015) because the effective concentration (EC) corresponding to this risk level is in the range of the observed data in the NIOSH study. That is, the EC for an extra risk of 1 in 100,000 of lymphoid cancer mortality in males is 9.67E-03 ppm for 70 years with an exposure lag of 15 years, which corresponds to a cumulative occupational exposure of 591 ppm-days. There are 7 male workers in the NIOSH cohort with cumulative exposures less than 591 ppm-days that died of lymphoid cancer. That is, 25.9% of the male workers in the NIOSH cohort that died with lymphoid cancer were exposed to cumulative exposures of less than the EC for 1 in 100,000 excess risk. A more detailed discussion is provided below.

Table 39 shows the EC corresponding to different excess risk levels and the corresponding cumulative exposures with the number of lymphoid mortality cases of the male workers in the NIOSH study, which conservatively serves as the basis for the TCEQ's URF for both males and females.

Table 39: Environmental and Equivalent Occupational Cumulative EtO Exposures for Different Potential PODs using TCEQ's Preferred Model for Lymphoid Cancer Mortality in the NIOSH Study (male workers)

Statistic	Extra Risk			
	1/100	1/1,000	1/10,000	1/100,000
Environmental EC (ppm) [a]	5.80E-0	8.99E-1	9.61E-2	9.67E-3
Equivalent Occupational EC (ppm-days) [b]	354,399	54,932	5,872	591
Lymphoid Deaths [c]	27	21	13	7
% Lymphoid Deaths [d]	100%	77.78%	48.15%	25.93%
% Male Workers [e]	99.84%	94.48%	66.45%	30.17%
LEC (ppm) [f]	2.44E-0	3.78E-1	4.04E-2	4.07E-3

Statistic	Extra Risk			
	1/100	1/1,000	1/10,000	1/100,000
URF (ppb^{-1}) [g]	4.09E-6	2.64E-6	2.47E-6	2.46E-6

EC – effective concentration, LEC – lower limit on the effective concentration, NIOSH - National Institute for Occupational Safety and Health, POD – point of departure, URF – unit risk factor

[a] Environmental concentration in ppm for 70-year lifetime with lag of 15 years corresponding to a specified extra risk

[b] Equivalent Occupational Exposure 70 years (ppm-days) = EC (ppm) × (365/240 days) × (20/10 m^3) × (365.25 days/year) × (70 years – lag in years)

[c] Number of male workers in the NIOSH cohort that died of lymphoid cancer with cumulative exposure less than the EC (i.e., EC in ppm-days at 1/100, 1/1,000, 1,10,000, or 1/100,000)

[d] Percentage of lymphoid cancer decedent male workers in the NIOSH cohort with cumulative exposures less than the EC (ppm-days)

[e] Percentage of male workers in the NIOSH cohort with cumulative exposures less than the EC (ppm-days)

[f] 95% lower bound on the EC (ppm)

[g] Unit risk estimate based on the LEC (ppm)

The results in Table 39 show that the EC for an extra risk of 1 in 100 (354,399 ppm-days) is outside the range of cumulative exposures for the male lymphoid mortalities observed in the NIOSH study (100% of lymphoid cancer decedent male workers in the NIOSH cohort had cumulative exposures less than this EC) and in the upper 1% of cumulative exposures for all male workers. That is, all males that died with lymphoid cancers and more than 99% of all male workers had cumulative exposures less than the EC (1/100). Thus, an excess risk of 1 in 100 is not within the NIOSH study data for lymphoid cancer mortalities.

The EC for an extra risk of 1 in 1,000 (54,932 ppm-days) is at the high end of cumulative exposures of male lymphoid mortalities observed in the NIOSH study. 77.78% of all males that died with lymphoid cancers and 94.48% of all male workers had cumulative exposures less than the EC (1/1,000). Thus, a POD of 1 in 1,000 is at the higher end of the cumulative exposures of male workers of the NIOSH study. The EC for an extra risk of 1 in 10,000 (5,872 ppm-days) includes 48.15% of the decedent men with lymphoid cancer and 66.45% of all men in the NIOSH cohort with lower cumulative exposures. Accordingly, a POD of 1 in 10,000 is close to the median of the cumulative exposures for decedent men with lymphoid cancer, with 2/3rd of all male workers having lower cumulative exposures.

The EC for an extra risk of 1 in 100,000 (591 ppm-days) includes 25.93% of male lymphoid decedents and 30.17% of all males in the NIOSH study with lower cumulative exposures. Thus, use of an extra risk of 1 in 100,000 is supported by the NIOSH observed data, being near the lower end of the observed range of cumulative exposures to EtO, and is consistent with TCEQ and USEPA guidelines (TCEQ 2015, USEPA 2005a) on the selection of a POD at the low-end of the observable range of exposures. The LEC on 1 in 100,000 extra risk is the POD utilized by the TCEQ to derive the URF.

Lastly, it is noted that use of the LEC for 1 in 10,000 extra risk would have resulted in the same rounded ADAF-unadjusted URF selected by the TCEQ (2.5E-06 per ppb) and the same 1 in 100,000 excess risk air concentration (i.e., 1E-05/2.47E-06 per ppb = 4.05 ppb, ADAF-unadjusted).

Appendix 5 Biological Context

A5.1 Normal Endogenous EtO Levels and Background Levels in Smokers

As mentioned in Section 2.2.1, EtO is produced endogenously in the body due to oxidation of ethylene, which is generated by intestinal bacteria, and lipid peroxidation of unsaturated fats, methionine, and hemoglobin. The analysis of Kirman and Hays (2017) reports endogenous EtO levels normally found within the body expressed in terms of exogenous EtO exposures. The study also documents background EtO levels in smokers. Such information can provide important context for chemicals such as EtO that have both endogenous and exogenous exposure pathways. Hemoglobin N-(2-hydroxyethyl)-valine (HEV) adducts are caused by the reaction of EtO with hemoglobin in erythrocytes. As EtO is widely distributed in the body, the levels of HEV in erythrocytes are expected to be proportional to levels of HEV in other tissues (including target tissues), which are further expected to be proportional to tissue exposures to free EtO (Kirman and Hays 2017). These HEV adducts provide a biomarker/molecular dosimeter of internal EtO dose that can be correlated with exogenous (i.e., ambient air) EtO exposure. USEPA (2005a) indicates that it may be informative to use such biomarkers of internal exposure for dose-response assessment or to provide insight into the potential shape of the dose-response curve at doses below those at which tumors are induced experimentally. As a biomarker/molecular dosimeter of internal EtO dose, data on endogenous and/or background internal levels of these adducts also provide biological context for risk-based results.

Kirman and Hays (2017) conducted a meta-analysis from the published literature characterizing the distribution of HEV adducts in EtO-unexposed populations (i.e., the background endogenous distribution) as well as in smokers (exposed to EtO in tobacco smoke). The relationship between EtO exposure and HEV adducts was linear with R^2=0.998 (see Figure 3 of the study). For HEV data from nonsmokers, the fixed and random effects models produced very similar results for the modeled mean (20.5 versus 21.1 pmol/g) and standard deviation (14.0 versus 14.6 pmol/g). Nearly all the total variation in the data was reported to be associated with within-study variation (i.e., very little between-study variation). For HEV data from smokers, the fixed and random effects models produced very different results (means of 29.9 versus 205 pmol/g, respectively). However, for smokers a large portion of the variation was associated with between-study variation, which may be expected given differences in smoking habits for different study populations. Because the data used for the meta-analyses came from studies of differing methods and diverse populations (across geographic region, age, sex), the results for the random effects model were considered by the study authors to be most appropriate for characterizing the distribution of HEV values.

In the meta-analysis for unexposed, non-smoking populations (n=661), the weighted mean of background endogenous HEV from the random effects model was 21.1 pmol/g hemoglobin (Hb). For smokers (n=379), the weighted mean of background HEV from the random effects

model was 205 pmol/g. These reported mean blood level meta-analysis estimates appear reasonable considering: (1) the geometric mean HEV levels reported for nonsmokers (≈31 pmol/g) and smokers (≈143 pmol/g) by Jain (2020) based on 2013-2016 NHANES data (see Table 3 of Jain 2020); and (2) the background HEV levels in control rats (≈42-50 pmol/g Hb) and mice (≈58-100 pmol/g Hb) (Walker et al. 1993, 2000)

The air concentrations corresponding to various endogenous level summary statistics (e.g., mean, 5th and 95th percentiles) from Kirman and Hays (2017) provide biological context for exogenous exposure concentrations. In particular, considering the normal range of endogenous levels informs the likelihood that the resulting internal doses (from exogenous + endogenous EtO) may be biologically distinguishable from normal endogenous levels. For example, ≈1.9 ppb is the continuous EtO air exposure concentration that corresponds to the endogenous EtO mean, and ≈0.56-4.5 ppb is the air concentration range that corresponds to the 5th-95th percentile range of the endogenous distribution (Table 4 of Kirman and Hays 2017). Additionally, ≈1.3 ppb is the continuous exposure level that corresponds to an endogenous EtO increase of 1 SD (corresponding to an HEV increase of 14.6 pmol/g Hb). Kirman and Hays (2017) indicate that, pragmatically speaking, the considerable variation in endogenous EtO exposure creates a signal-to-noise issue when exogenous exposures fall well below those consistent with endogenous exposures, and in such cases small exogenous exposures may not contribute to total exposure or to potential effects in a biologically meaningful way. Furthermore, exposure to typical environmental levels (i.e., background and environmental exposure means ≈0.0024-0.0034 ppb per USEPA 2016 or reported urban background levels of 0.1-0.2 ppb based on USEPA sampling from October 2018 through March 2019 available at https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-data-summary-national-air-toxics-trends) would not be expected to substantially affect Kirman and Hays (2017) estimates of endogenous levels since they are below the continuous air concentration corresponding to even the first percentile of the endogenous distribution (i.e., the 1st percentile of the distribution corresponds to a continuous air concentration of ≈0.37 ppb). Thus, for all practical purposes these data in the unexposed population (e.g., nonsmokers) can simply be referred to as endogenous.

A5.1.1 Comparison of Risk-Based EtO Doses and Normal Endogenous EtO Doses

Information on endogenous levels did not play a role in model selection for the EtO carcinogenic dose-response assessment described in Chapter 4. However, data on normal endogenous levels do provide biological context for risk-based results. For example, continuous exposure to 4.0 ppb EtO at 1 in 100,000 excess risk based on the ADAF-unadjusted URF would be predicted to result in an HEV burden (as a biomarker of internal exposure) of approximately 43.6 pmol/g Hb. This HEV level approximates the mean + 1.5 SD (21.1 + 21.9 pmol/g Hb = 43 pmol/g Hb) of the normal distribution in the non-smoking population that results from

endogenous EtO exposure (Table 4 of Kirman and Hays 2017). An additional ≈43.6 pmol/g Hb due to continuous exogenous exposure to 4.0 ppb would be predicted to:

- Increase the HEV level for the median non-smoker to between the 95th and 99th percentiles of normal endogenous background levels; and
- Increase the HEV level in 90th percentile non-smokers to over the 99th percentile.

Thus, continuous exposure to the ADAF-unadjusted 1 in 100,000 excess risk air concentration of 4.0 ppb would be predicted to result in total internal exposure (endogenous + exogenous) rising above the normal endogenous background range in some portion of the population.

Similarly, continuous exposure to the ADAF-adjusted $^{chronic}ESL_{nonthreshold(c)}$ of 2.4 ppb EtO would be predicted to result in an HEV burden (as a biomarker of internal exposure) of approximately 26.2 pmol/g Hb. This HEV level roughly approximates the 75th percentile (26.4 pmol/g Hb) of the normal distribution in the non-smoking population that results from endogenous EtO exposure.[h] An additional ≈26.2 pmol/g Hb due to continuous exogenous exposure to 2.4 ppb would be predicted to:

- Increase the HEV level for the median non-smoker (17.3 pmol/g Hb) to above the 90th percentile (38.8 pmol/g Hb) of normal endogenous background levels; and
- Increase the HEV level in 95th percentile non-smokers (48.7 pmol/g Hb) to the 99th percentile (74.9 pmol/g Hb).

Thus, continuous exposure to the ADAF-adjusted EtO $^{chronic}ESL_{nonthreshold(c)}$ of 2.4 ppb EtO would be predicted to result in total internal exposure increasing to the uppermost end of the range of normal endogenous levels for at least some appreciable percentage of the population (e.g., moving those at the 95th percentile to the 99th percentile). These results appear relatively consistent with the assessment of excess risk above and distinguishable from the background risk resulting from normal endogenous EtO levels. The calculated EtO $^{chronic}ESL_{nonthreshold(c)}$ (2.4

[h] USEPA's URF estimates that ambient concentrations of EtO > 0.01 ppb would produce an unacceptable increased cancer risk of greater than 1 in 10,000. This estimated ambient EtO concentration corresponds to an internal dose that is over 30 times lower than the 1st percentile of normal endogenous background levels (non-smokers). Similarly, USEPA's 1 in 100,000 excess air concentration (0.001 ppb) corresponds to an internal dose that is over 300 times lower than the 1st percentile of normal endogenous background levels. The total internal doses (from exogenous + endogenous) resulting from these USEPA risk-based exogenous exposures are therefore unlikely to be biologically distinguishable from the range of normal endogenous levels.

ppb) falls well within the range (0.13-6.9 ppb) supported by the approach in Kirman and Hays (2017) as protective of human health. Lastly, it is noted that the geometric mean internal EtO level reported by Jain (2020) based on NHANES data for nonsmokers (31.5 pmol/g Hb) would correspond to an equivalent exogenous continuous EtO air exposure of 2.9 ppb based on the HEV:EtO in air relationship reported in Kirman and Hays (2017), which is similar to the ADAF-adjusted EtO $^{chronic}ESL_{nonthreshold(c)}$ of 2.4 ppb EtO.

Appendix 6 Review of the USEPA (2016) Assessment

Consistent with TCEQ guidelines (TCEQ 2015), USEPA's recently completed Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (USEPA 2016) was reviewed to determine if it was suitable for adoption by the TCEQ. The USEPA derived a URF of 9.1E-3 per ppb (lymphoid and breast cancer, ADAF-adjusted), which corresponds to a 1 in 100,000 excess cancer risk air concentration of 0.001 ppb. The USEPA URF was based on the same key NIOSH cohort used by the TCEQ.

The USEPA ultimately chose to model EtO-induced lymphoid cancer, the key cancer endpoint used by the TCEQ, with a linear two-piece spline model. The linear two-piece spline model used by USEPA may be characterized as an overall supra-linear dose-response model that has a steep slope in the low-dose region with a "knot" as the point of an abrupt transition to the upper spline with a markedly reduced slope. The knot may be thought of as a more abrupt transition to the upper slope than the transitional curve in the example supra-linear dose-response shape shown in Figure 2.

As with TCEQ's own modeling choice (the Cox proportional hazards model), the TCEQ evaluated USEPA's modeling choice (the linear two-piece spline model) in the context of:

- Relevant guidance (TCEQ 2015);
- EtO's carcinogenic MOA;
- Standard model fit criteria; and
- Evaluation of the accuracy of model predictions for key underlying epidemiological cancer data.

Several substantial scientific issues with USEPA's assessment were identified by the TCEQ (e.g., model fit criteria calculations, visual misrepresentation of model fit, statistically significant model over-predictions). Consequently, the procedures used by USEPA (2016) are different than the standard procedures that the TCEQ would utilize and consistent with relevant guidelines (TCEQ 2015), the TCEQ did not adopt USEPA's URF. In the sections that follow, the TCEQ reviews the bulleted considerations above to document associated issues.

A6.1 Relevant Guidance

Cox regression is the preferred methodology for health endpoints of epidemiology studies under TCEQ guidelines (TCEQ 2015). The TCEQ (2015) guidelines require sufficient mechanistic or biological data to support the application of a supra-linear model like USEPA's linear two-piece spline model. In this context, the TCEQ defines a supra-linear model as a model with a dose-response curve above linear as illustrated in Figure 2 where the low-dose slope is steep beginning at zero dose and then transitions across the doses modeled to a greatly reduced higher-dose slope. The USEPA also refers to the shape of their linear two-piece spline model as

a dose-response model intended to address what the USEPA perceived as supra-linearity in the data (e.g., see p. 4-12 of USEPA 2016).

A6.2 MOA Considerations

Use of MOA data to inform the dose-response assessment is a main focus of the TCEQ (2015) and USEPA (2005a, b) guidelines. To the extent that the MOA for a chemical is understood, it informs the low-dose extrapolation procedure for that chemical. The MOA information discussed in Section 3.2 supports direct mutagenicity as the putative MOA for EtO carcinogenicity (USEPA 2016). As discussed in Section 4.2.1, EtO is a direct acting DNA-reactive chemical that is produced endogenously, and as such there are expected to be normal detoxification processes and baseline levels of DNA repair enzymes that have evolved to efficiently detoxify and/or repair substantial levels of endogenous EtO and associated adducts in the endogenous concentration range. This information suggests a no more than linear low-dose response component near the endogenous range with a transition to a steeper dose-response slope at some point above the endogenous range where the body can no longer effectively detoxify EtO and/or repair the EtO-induced DNA damage. Thus, across a complete range of doses from truly low (e.g., endogenous) to high (e.g., occupational exposures), the expected dose-response could be characterized as sublinear overall across doses (see Figure 2). However, if the low dose range in/near the endogenous range (that is expected to be responsible for overall sublinearity) is relatively narrow, and sufficient data are not available to reveal the full shape of the dose-response from truly low doses to high doses (e.g., endogenous to occupational), then the higher dose data that are available could simply appear as linear. Regulatory inhalation dose-response assessments that utilize human data are frequently based on occupational studies, which generally exclusively involve relatively high doses, as is the case here.

Kirman and Hays (2017) expressed this conclusion similarly. That is, based on relevant considerations, an overall sublinear dose-response would be expected over the range of possible exposures to EtO, from those that result in total body burdens (endogenous + exogenous) within the normal endogenous level range to those that result in a total body burden significantly greater than the normal range where the normally effective detoxification/repair processes are overwhelmed. This conclusion is reasonably consistent with that of the USEPA (2016), “EPA considers it highly plausible that the dose-response relationship over the endogenous range is sublinear (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases.”

For exogenous EtO exposures, USEPA cites direct mutagenic activity as mechanistic justification for default linear low-dose extrapolation (pp. 4-22 and 4-37 of USEPA 2016). In regard to the

shape of the EtO dose-response overall, Vincent et al. (2019) consider the MOA and dose-response analysis of the early effect data in humans/animals (as well as modeling results of relevant cancer endpoints in rodents; most notably, leukemia incidence in female F344 rats) to conclude that there is no evidence that a dose-response other than linear is justified. Since lymphoid cancer drove the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data was that in the bone marrow of mice exposed to 25-200 ppm EtO by inhalation *in vivo* (Recio et al. 2004, Figure 3). The TCEQ notes that the overall linear dose-response for mutagenicity in bone marrow is consistent with a linear dose-response (see C-17 of USEPA 2016) and did not plateau even at exposure concentrations as high as 200 ppm.

In contrast to direct acting mutagenic chemicals such as EtO, supra-linear responses are associated with an MOA that involves the saturation of metabolic activation where fewer electrophiles are formed per unit dose at higher exposures, which is not the case for EtO (Swenberg et al. 2008). Carcinogenic MOA data for EtO do not justify use of an overall supra-linear model (i.e., the linear two-piece spline model) under TCEQ guidelines (TCEQ 2015). USEPA (2016) acknowledged to the SAB that the MOA information for EtO does not support a supra-linear dose-response, stating “the EPA is not aware of a mechanistic explanation” (p. I-29 of USEPA 2016; also see pp. I-34 and 4-71). Similarly, the TCEQ is not aware of any MOA or mechanistic data for EtO that would suggest that a dose-response such as that represented by USEPA’s linear two-piece spline model (i.e., overall supra-linear) should be expected. Rather, MOA-relevant information for EtO suggests a no more than linear dose-response.

In conclusion, the consideration of MOA-relevant information for EtO suggests that an overall dose-response that is no more than linear is expected for EtO-induced carcinogenicity, and that linear low-dose extrapolation is appropriate and health-protective. The TCEQ’s evaluation of the MOA data has not revealed evidence that the exposure-response relationship for EtO is supra-linear that would be best represented by a linear two-piece spline model.

These MOA-based considerations are consistent with use of a POD from Cox proportional hazards modeling as the preferred methodology for low-dose extrapolation from epidemiology study data under TCEQ guidelines (TCEQ 2015). Cox proportional hazards modeling is indistinguishable from linear over the EtO dose range in the key epidemiological study, which is consistent with the expected dose-response for EtO-induced carcinogenicity based on the MOA.

A6.3 Standard Model Fit Criteria

Model fit is a topic of interest though not a deterministic consideration on its own when:

- MOA/mechanistic data for EtO must also be considered (TCEQ 2015); and

- The accuracy of models for predicting the underlying modeled cancer data differs significantly.

In this section, standard model fit criteria (i.e., p-values and AIC values) are used to evaluate dose-response model fit to the NIOSH lymphoid cancer data (TCEQ's key cohort and cancer endpoint, as well as the primary driver of USEPA's URF) for two dose-response models that have been put forward for EtO:

3) The Cox proportional hazards model preferred under TCEQ guidance (TCEQ 2015) and supported by MOA considerations (see discussions above); and
4) The linear two-piece spline model used by USEPA (2016) (linear two-piece spline model with knot at 1,600 ppm-days).

The consideration of visual fit of the models to the data is also addressed.

In summary, as discussed below, neither standard model fit criteria (p-values and AIC values) nor appropriate consideration of visual fit support deviation from the TCEQ's preferred and more standard dose-response model (i.e., the Cox proportional hazards model; TCEQ 2015), especially when considering supporting information on the MOA (see above) and the accuracy of Cox model predictions of lymphoid cancer for the key NIOSH cohort as well as the supporting UCC cohort (see Appendix 3 and below). Additionally, use of the standard Cox proportional hazards model is supported by considering the principle of parsimony (the USEPA SAB recommended that "the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered").

A6.3.1 USEPA's Consideration of Model Fit Criteria

A6.3.1.1 p-Values and AIC Values

An important issue with USEPA's consideration of model fit that the TCEQ must duly consider concerns the statistical optimization of "knot" values for the two-piece spline modeling approach. USEPA (2016) indicates that for this approach, the splines were "fit" to the EtO cancer exposure-response data, and that the knot was generally selected by evaluating different knots in increments (e.g., 100, 500, or 1,000 ppm-days) of cumulative exposure and then by choosing the one that resulted in the best (i.e., largest) model likelihood (pp. 4-13, 4-26, 4-36, and 4-45 of USEPA 2016). Thus, from the process described, it is readily apparent that:

- The "knot" was an iteratively fit model parameter and was not simply preselected (p. 4-52 of USEPA 2016); and
- The knot values, being statistically estimated/optimized based on the NIOSH data, clearly do not conform to the USEPA SAB's notion of potentially fixing some model

parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015).

For the spline models there were 3 parameters (k) estimated by USEPA: (1) the "knot" value; (2) the slope above the knot; and (3) the slope below the knot (k=3). However, USEPA (2016) did not account for statistically estimating the optimized knot value. Thus, it appears the degrees of freedom (df) were inappropriately reduced for the spline models (df=k, the number of additional parameters estimated for this model over the model with zero-slope with cumulative exposure).[i] This was not inconsequential. Among other consequences, this:

- Decreased the p-value for adequate statistical fit, incorrectly implying that the linear two-piece spline model with a knot at 1,600 ppm-days for lymphoid cancer fit the data statistically better than other models in Table 4-6 of USEPA (2016); and
- Decreased the AIC for the spline models, which did not allow for an appropriate comparison of model fit.

Thus, this appears to amount to an unfortunate statistical misevaluation of model fit in USEPA (2016).

A6.3.1.1.1 p-Values

Regarding the first bullet above, an example at the end of this section demonstrates that a p-value of 0.14 is the correct p-value for the likelihood ratio test (not 0.07 as in Table 4-6 of USEPA 2016) when appropriately using k=3 for the linear two-piece spline model with a knot at 1,600 ppm-days for lymphoid cancer. Thus, the correct p-values indicate that the likelihood of the linear two-piece spline models with a knot at 1,600 ppm-days is not different from the likelihood of the null model at the 5% significance level (i.e., the fitted two-piece spline models do not explain the variability in the data statistically significantly better than the null model). The log-linear (standard Cox regression) model has a similar p-value (0.22) and also does not explain the variability in the data statistically significantly better than the null model (Table 5). Thus, the appropriate calculation of p-values puts TCEQ's preferred model for lymphoid cancer (i.e., the Cox model) and the model used by USEPA (2016) (i.e., the linear two-piece spline model) on equal ground in this regard, although TCEQ's preferred model is more parsimonious

[i] Appendix D of USEPA (2016), a revised report of Dr. Kyle Steenland submitted in 2010 for the USEPA analysis, appears to acknowledge the df/p-value issue.

(i.e., uses fewer parameters). The section below contains additional information on p-value calculations for those interested and is followed by a section on AIC values.

A6.3.1.1.1.1 Recalculated p-Value for the Linear Two-Piece Spline Model

The likelihood ratio test is used to test whether a fitted model significantly improves the fit of the data by estimating parameters instead of just assuming a baseline (null) model for the data. The likelihood ratio test is evaluated by comparing the likelihood of the model with the estimated parameters and the likelihood of the null model. If the likelihood of the model with the estimated parameters is equal to the likelihood of the null model, then the natural logarithm of the ratio of these likelihoods multiplied by two follow a Chi-Square distribution with as many degrees of freedom as the number of parameters estimated for the fitted model (Checkoway et al. 1989). Thus, if the fit of the baseline (null) model and the model with estimated parameters are not different,

$$Chi - Square(k) = \chi_k^2 = -2\ln\left(\frac{likelihood\ for\ null\ model}{likelihood\ for\ fitted\ model}\right)$$

This can also be written as follows,

$$\chi_k^2 = -2LogL(null\ model) + 2LogL(fitted\ model)$$

Here *k* is the number of degrees of freedom (*k* is the number of parameters that were estimated in excess of the parameters estimated for the null model or nested model).

For the linear two-piece spline model with a knot at 1,600 ppm-days for lymphoid cancer (Table D-33 on page D-46 and Table D-36 on page D-49 of USEPA 2016), the χ_k^2 value was equal to 5.412 (463.912-(458.1+0.4))[j], and *k* was set to 2. This resulted in a p-value of 0.0668. That is, the fitted model was assumed to have two parameters; namely, the slope below the knot and the slope above the knot. The results are from a Statistical Analysis System (SAS) output for the model specified. The linear two-piece spline model specified included a knot. This knot was determined so that the likelihood of the spline model was maximized. That is, the knot is another parameter that was searched for outside SAS. Because the estimation of the knot was done outside SAS, the SAS program did not count the knot as a parameter and, consequently,

[j] 463.912 is the -2LL for the "null model" and was taken from Table D-33 (-2 Log L without covariates). 458.1 is the -2LL for the linear spline model with knot at 1,600 ppm-days and was taken from Table D-36. The factor of 0.4 was to adjust for the discrepancy between the procedures in calculating the -2LL, as described in footnote c in Table 4-6 of USEPA's (2016) risk assessment.

the Chi-Square test that SAS reported does not reflect the fact that the knot was also estimated. The Chi-Square that accounts for the fact that the knot was estimated outside SAS should then be 5.412, with *k* (the degrees of freedom) being three. This corrected calculation results in a p-value of 0.1440. That is, the p-value (0.14 in Table 5) indicates that the likelihood of the linear two-piece spline model with a knot at 1,600 ppm-days (preferred by USEPA 2016) is not different from the likelihood of the null model at the 5% significance level. In short, there is no evidence indicating that the fitted linear two-piece spline model explains the variability in the data any better than the null model.

A6.3.1.1.2 AIC Values

The USEPA SAB does not comment on or examine the AIC issue identified by the TCEQ in Appendix H of USEPA (2016). The SAB does recommend less reliance on the AIC (e.g., pp. I-2 and I-9 of USEPA 2016), particularly its naïve use without other scientific considerations (pp. I-17 and I-18 of USEPA 2016), and discusses the fixing of some model parameters (as opposed to statistical fitting/estimating parameter values from the data as USEPA did) in a more general discussion of model parsimony (p. I-16 of USEPA 2016). However, an example at the end of this section shows that an AIC of 464.5 is the correct AIC value (not 462.1 as in Table 4-6 of USEPA 2016) when appropriately using k=3 for the linear two-piece spline model with a knot at 1,600 ppm-days (lymphoid cancer). Consequently, not only does the linear two-piece spline model for lymphoid cancer preferred by USEPA (2016) not explain the variability in the data statistically significantly better than the null model, but the correct AIC values for the linear two-piece spline model (464.5) and the Cox regression model (464.4) are almost identical (Table 5), putting them on par with each other in this regard. The TCEQ-preferred Cox proportional hazards model is, however, more parsimonious, consistent with the USEPA SAB recommendation that "the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered." The section below contains additional information on AIC value calculations for those interested.

A6.3.1.1.2.1 Recalculated AIC Value for the Linear Two-Piece Spline Model

The AIC is equal to $2k - 2LogL$ where k is the number of parameters estimated for the model and LogL is the logarithm of the likelihood. Table D-36 in USEPA (2016) lists the $-2LogL$ as 458.1 and the AIC as 462.1. That is:

$$462.1 = 2k + 458.1$$

However, in order to compare AIC and -2LogL values for linear models and log-linear models, the AIC and -2LogL values need to be adjusted. The -2LogL and AIC values for the linear models are consistently 0.4 less than the -2LogL and AIC values for the log-linear models. This occurs because the log-linear models were fit using the PHREG SAS procedure while the linear models

were fit using the NLP SAS procedure (see footnote c in Table 4-6 of USEPA (2016) risk assessment). Thus, the comparable AIC and -2LogL values for the linear spline model are:

$$462.5 = 2k + 458.5$$

The comparable AIC and –2*LogL* implies that *k* equals 2. That is, the spline model was assumed to have estimated two parameters; namely, the slope below the knot and the slope above the knot. The results in Table D-36 (page D-49 of USEPA 2016) consist of SAS output for the linear two-piece spline model specified. The model specified included a knot. This knot was previously estimated using a separate optimization procedure outside the SAS run, so the likelihood of the model was maximized only conditional on the estimated knot-value used for that calculation. Consequently, the knot must be treated as an additional parameter that was estimated outside SAS. However, because the estimation of the knot was done outside SAS, the SAS run performed by USEPA (2016) did not count the knot as a model parameter and, consequently, the resulting AIC value obtained does not reflect that the knot was in fact estimated.

The AIC that correctly accounts for the fact that the knot was estimated outside SAS is calculated as

$$AIC = 464.5 = 2 \times 3 + 458.5$$

Thus, for the linear two-piece spline model with a knot at 1,600 ppm-days (lymphoid cancer) the correct AIC is 464.5 (not 462.1 as in Table 4-6 of USEPA 2016). This AIC value is almost identical to the AIC (464.4) for the Cox regression model preferred by the TCEQ (Table 5).

A6.3.1.2 Visual Model Fit

Visual fit to the data was also used by USEPA as a criterion for model selection (e.g., pp. 4-66 and 4-100 of USEPA 2016). Another important issue concerns the seeming visual misrepresentation of model fit in Figures 4-3 and 4-8 of USEPA (2016). This issue is discussed in detail below. Ultimately, appropriate consideration of visual fit to the underlying lymphoid cancer data reveals no readily apparent superior fit by either the linear two-piece spline or standard Cox proportional hazards model (Figure 14). Regardless, other considerations are considered more deterministic for model selection than visual fit (e.g., the MOA, accuracy of model predictions of lymphoid cancer in the key cohort), with visual fit being a less scientifically sophisticated consideration for model fit than standard statistical model fit criteria (discussed above) or the statistical evaluation of the accuracy of model predictions (Appendix 3).

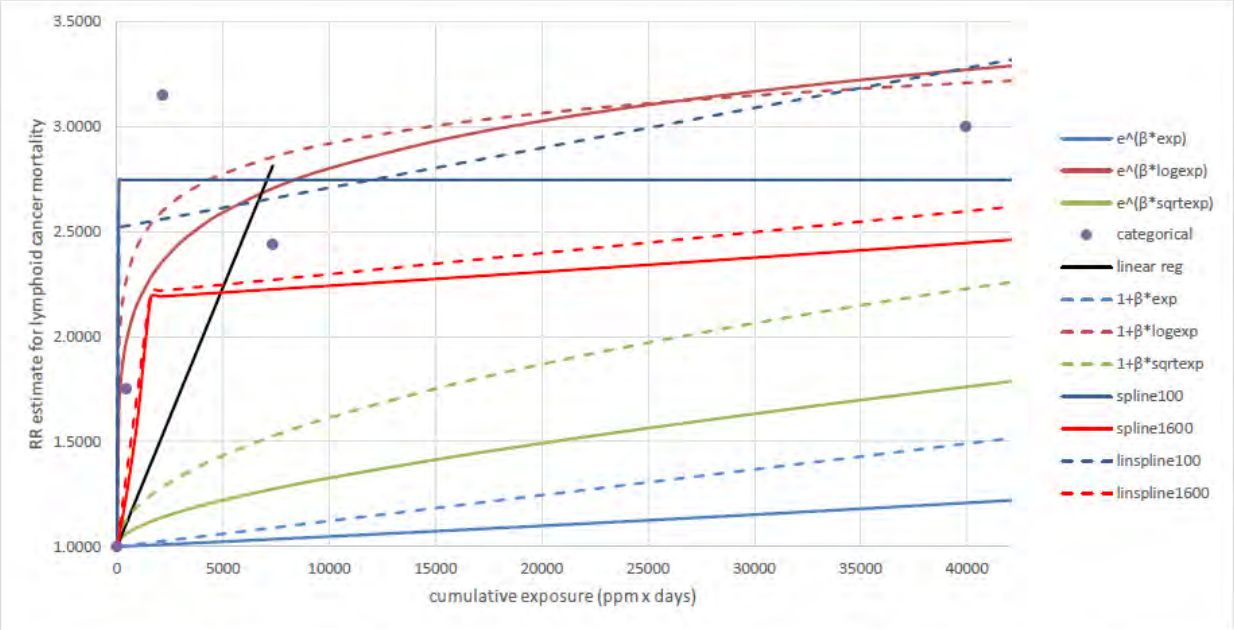
A6.3.1.2.1 USEPA's Representation of Visual Fit

Both USEPA (2016) models and the TCEQ Cox proportional hazards model were fit to the individual data from the NIOSH cohort. Section 4.2.3 of this DSD describes how well the models

can predict the original input data, as well as data from another cohort, and in doing so provides a measure of model validity.

In their 2016 assessment the USEPA used a different method of determining model validity, by assessing visual fit of the different EtO dose-response models (that were based on the individual data) to the cumulative exposure group data analysis (USEPA Figure 4-3 reproduced as Figure 11 below). Assessing model fit by visual inspection to the modeled datapoints is a commonly used technique (e.g., USEPA 2012). However, the method that USEPA (2016) used was not visual fit to the individual data modeled but rather visual fit to different, more crude data (i.e., rate ratios of cumulative exposure group data).[k] USEPA (2016) generated rate ratios (RR) for 4 exposure quintiles using a fifth non-exposed quintile as the referent (reproduced in Table 40) to assess visual fit with the dose-response models fit to the individual data. The TCEQ evaluated 1) whether there was a good apparent fit between the individual data and the dose-response models; and 2) whether the parametric dose-response models (i.e., those types of models discussed in Chapter 4) and the non-parametric model (i.e., categorical) imply similar baseline hazard rate values so that they can be directly compared.

[k] In Appendix 3, the model used by USEPA (i.e., the linear two-piece spline model) is statistically shown not to accurately predict the underlying individual data modeled, while this section concerns fit to more crude categorical data that were not modeled.



e^(β*exp): $RR = e^{(\beta \times exposure)}$; e^(β*logexp): $RR = e^{(\beta \times \ln(exposure))}$; e^(β*sqrtexp): $RR = e^{(\beta \times sqrt(exposure))}$; categorical: $RR = e^{(\beta \times exposure)}$ with categorical exposures, plotted at the mean cumulative exposure; linear reg: weighted linear regression of categorical results, excluding highest exposure group (see text); 1 + β*exp: $RR = 1 + \beta \times exposure$; 1 + β*logexp: $RR = 1 + \beta \times \ln(exposure)$; 1 + β*sqrtexp: $RR = 1 + \beta \times sqrt(exposure)$; spline100(1,600): Two-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text); linspline100(1,600): Two-piece linear spline model with knot at 100 (1,600) ppm × days (see text). (Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the *y*-axis. They are, however, comparable in terms of general shape.)

Source: Steenland reanalyses for males and females combined; see Appendix D (except for linear regression of categorical results, which was done by EPA).

Figure 4-3. Exposure-response models for lymphoid cancer mortality vs. occupational cumulative exposure (with 15-year lag).

Figure 11: USEPA (2016) Figure 4-3.

A6.3.1.2.1.1 Non-parametric Rate Ratios are Not the Observed Data

Figure 11 reproduces Figure 4-3 in USEPA's 2016 risk assessment. This figure shows the rate ratios (RR) estimated by twelve models. The RR is the hazard rate at a cumulative exposure divided by the hazard rate at zero cumulative exposure implied by the model. That is, RRs are hazard rates relative to their own implicitly estimated baseline hazard rate at zero cumulative exposure. Each model, being different, implicitly estimates a different baseline hazard rate at zero cumulative exposure.

Eleven of those models in Figure 11 have a parametric functional form and one model (labeled here "categorical") estimates non-parametric RRs of the lymphoid mortality grouped by quintiles. Each quintile summarizes hazard rates for 11 lymphoid deaths (9 in the non-exposed quintile). As such, non-parametric RRs are not observed, they are estimated. And a RR is the

hazard rate at a cumulative exposure divided by the hazard rate at zero cumulative exposure implied by the model. Furthermore, the non-parametric RRs derived by USEPA and shown in Figure 11 do not show the full range of all possible RRs or the full range of cumulative exposures. Table D-28 of USEPA (2016) includes the uncertainty (i.e., 95% CIs) around USEPA's categorical odds ratios and is reproduced here as Table 40 for lymphoid cancer (males and females combined).

Table 40: Lymphoid Cancer Categorical Odds Ratios and 95% Confidence Limits (male and female)

Cumulative exposure range, 15-year lag (ppm-days)	Mean [a] Cumulative Exposure (ppm-days)	Odds Ratio	Lower Confidence Limit on the Rate Ratio	Upper Confidence Limit on the Rate Ratio
0 (lagged out) [b]	0	1.00	--	--
>0 – 1,200	446	1.75	0.59	5.25
1,201 – 3,680	2,143	3.15	1.04	9.49
3,681 – 13,500	7,335	2.44	0.80	7.50
>13,500	39,927	3.00	1.02	8.45

[a] Mean exposures for both male and female combined with 15-year lag for the categories in the table taken from the footnote to Table D-44 in the Appendices to USEPA (2016) Risk Assessment.
[b] Although all workers in the NIOSH study had cumulative exposures greater than zero at the end of follow up (last observation time), the lag-15 cumulative exposure is zero whenever exposures occur only within the last 15 years of follow-up. A lagged out group with 15-year lagged cumulative exposure is one that includes the cases whose exposure occurred only within the last 15 years of his/her lifetime (the end of his/her follow-up).

Categorical RRs should not be used for visually comparing models fit to individual data, particularly when appropriate statistical model fit criteria are available. More specifically, estimated non-parametric (categorical) RRs are calculated with respect to an underlying background hazard rate that is also estimated nonparametrically. The RRs of parametric models fit to the individual data are defined with respect to an underlying background hazard rate estimated by the model. However, the underlying background hazard rates estimated by the nonparametric RRs and the underlying background hazard rates estimated by the parametric models are generally different.

A better comparison of models fit to the observed data is to use the predictiveness of the model; that is, the capability of the model to estimate the observed number of deaths with a certain degree of confidence (see Appendix 3). Moreover, visual interpretation of the consistency of categorical RRs with the shape/slope of a modeled dose-response can change as the number of exposure categories changes. For example, Figures 1, 2, and 3 of Valdez-Flores

and Sielken (2013) demonstrate, among other things, how the dose-response (i.e., RR versus cumulative exposure) slope for breast cancer mortality in the NIOSH cohort appears very steep when compared to only four exposure categories, but seems more shallow when additional categories are added (20 and 61 categorical RRs). In the present case, the overall dose-response appears ill represented by only a few categorical RRs (see below and supplementary material for Valdez-Flores and Sielken 2013).

As evidenced by Valdez-Flores and Sielken (2013), the visual presentation of only a few non-parametric RRs prevent the reader from seeing the variability in the underlying dose-response data, and by corollary, preclude an appropriate visual assessment/comparison of model fit to the actual individual data. Figure 12 below shows the same models as Figure 11 with the superposition of the estimated individual RRs (open circles labeled as categorical in Figure 12 and USEPA's nonparametric estimates labeled as "EPA's 5 RRs" shown as red dots). Figure 12 uses a multiplicative scale for the vertical axis to increase resolution and to show the full range of RRs, while the x-axis displays the full range of exposure for lymphoid decedents in the NIOSH study. The square at the lower left-hand corner in Figure 12 is the range of the vertical and horizontal axes plotted in Figure 11 (USEPA's Figure 4-3). Figure 13 is an expansion of the marked lower left-hand corner of Figure 12 but restricted to the rate ratios (vertical scale) and to the cumulative exposures (x-axis) used by USEPA (2016) in their Figure 4-3, just to make the two figures more easily comparable. Paralleling the analyses reported by Valdez-Flores and Sielken (2013), Figures 12 and 13 also show a dotted line that fits an exponential model to the individual (categorical RRs shown as open circles). The intercept of this line can be used to approximate the ratio of the underlying background hazard rate implied by the standard Cox proportional hazards model to the underlying background hazard rate implied by the nonparametric estimates. Figure 14 shows the non-parametric RRs, the linear two-piece spline model (used by USEPA), and the standard Cox proportional hazards model (preferred by TCEQ) after adjusting the intercept of this model for the differences in the estimated baseline risks (using the same approach published by Valdez-Flores and Sielken 2013). As a consequence, the standard Cox proportional hazards model in Figure 14 (dashed blue line) is no longer a RR function, but rather a model that has been adjusted for discrepancies in the estimated baseline risks of two models so that they can be visually compared on the same graph.

Figure 15 shows the counterpart to Figure 14. That is, Figure 15 shows the standard Cox proportional hazards model (preferred by TCEQ), the non-parametric RRs (categorical), and the linear two-piece spline model (used by USEPA), after adjusting the intercept of the last two models for the discrepancies in the estimated baseline risks. As a consequence, the non-parametric estimates and the linear two-piece spline model in Figure 15 (red dots, open circles, and dashed red line) are no longer RR functions, but rather models that have been adjusted for discrepancies in the estimated baseline risks of those models and the standard Cox proportional hazards model so that they can be visually compared on the same graph. Thus,

Figures 14 and 15 account for the different implicit estimated baseline risks of the non-parametric RRs, the standard Cox proportional hazards, and linear two-piece spline models on the y-axis, respectively. Misinterpretation in the comparison of parametric and categorical (non-parametric) RRs used to judge model fit has been published in the peer-review literature (e.g., Valdez-Flores and Sielken 2013).

Examination of the model fits to the underlying data in Figures 12-15 reveals no readily apparent superior fit by any particular model. What is most readily apparent is the loss of visualized information that results from only using the five grouped RRs (represented by the red dots) as in Figure 4-3 of USEPA (2016). The nonparametric rate ratios for individual cases (categorical) represented by the open circles in Figures 14 and 15 below form no discernable pattern that appears most consistent with either model (i.e., visual fit alone cannot be used to readily identify either the linear two-piece spline model or standard Cox model as most representative of the actual data). In fact, multiple dose-response relationships appear equally plausible and/or consistent with these high-dose occupational data using this visual fit method.

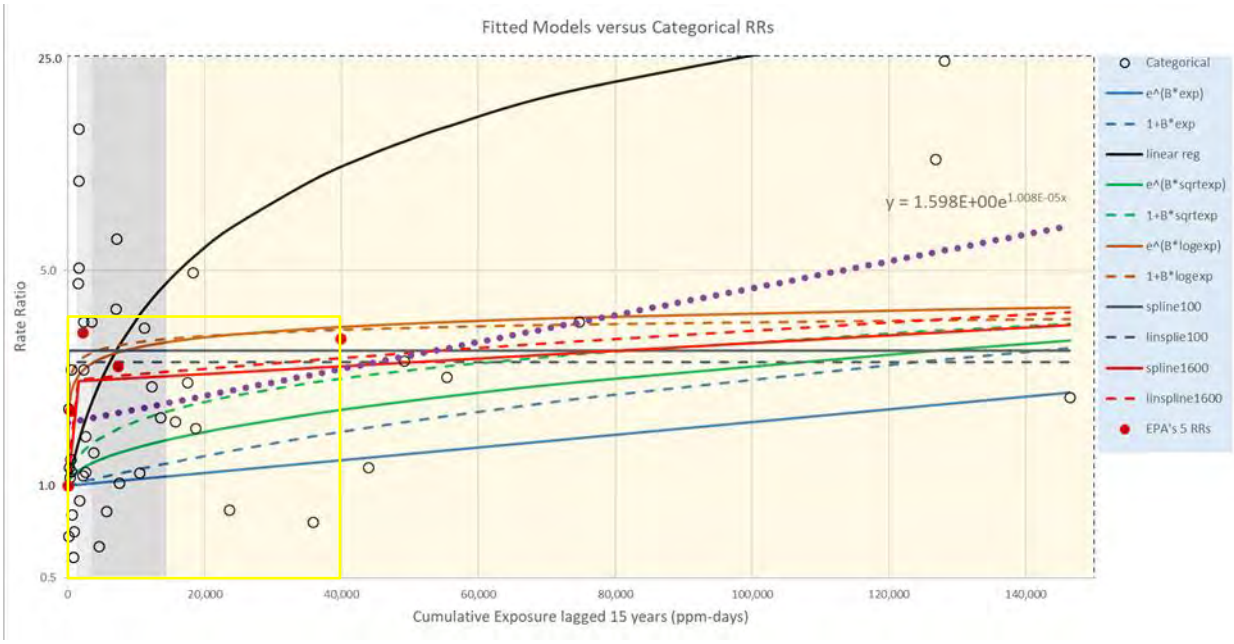


Figure 12: Lymphoid cancer death categorical rate ratios (RRs) and various fitted models for 15-year lagged occupational doses ≤150,000 ppm-days (NIOSH cohort). The square at the lower left-hand corner is the range of the vertical and horizontal axes plotted in Figure 11 (USEPA's Figure 4-3)

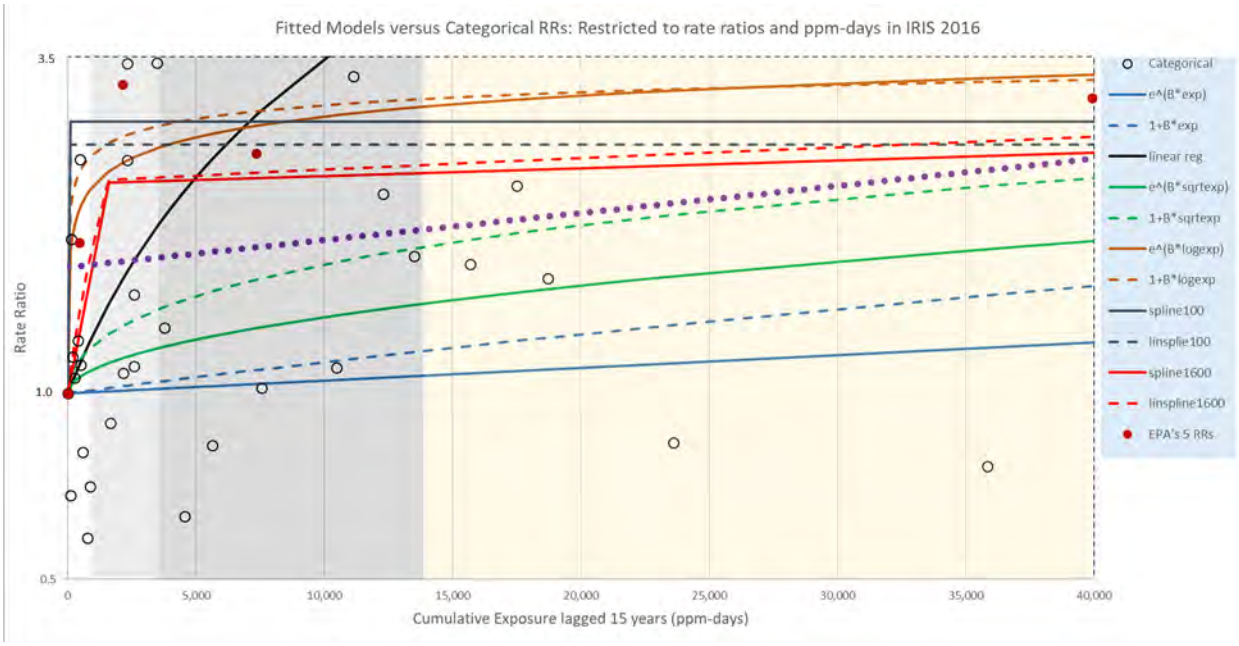


Figure 13: Lymphoid cancer death categorical RRs and various fitted models for 15-year lagged occupational doses ≤40,000 ppm-days (NIOSH cohort)

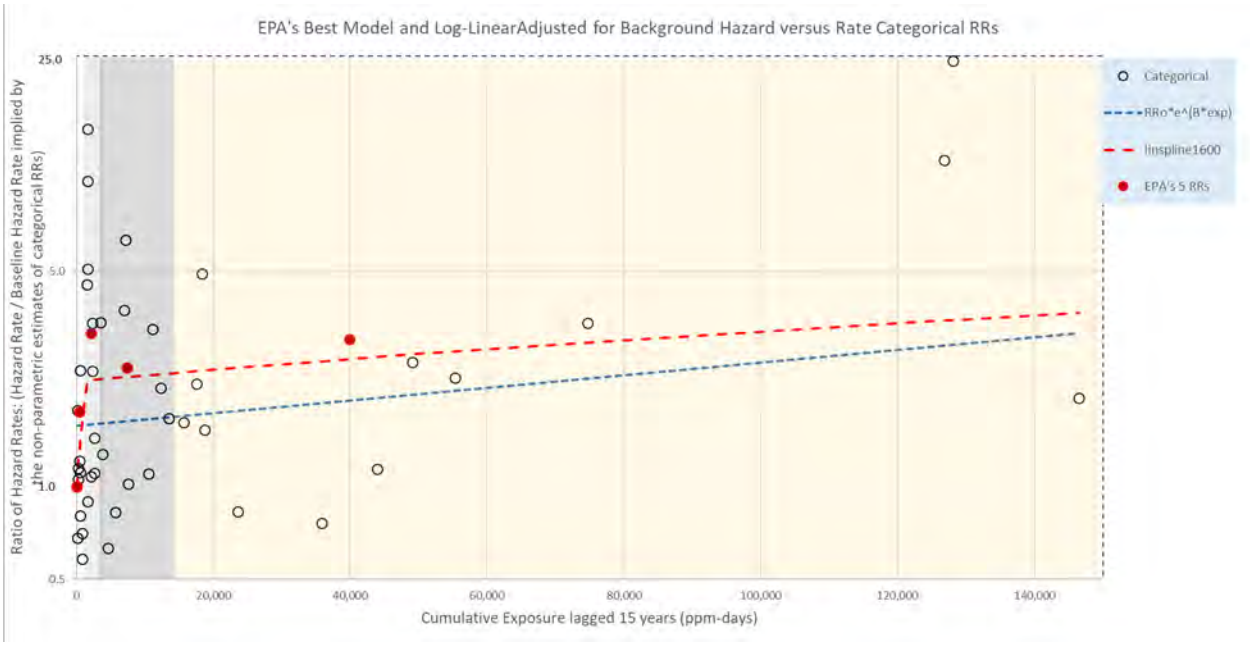


Figure 14: Lymphoid cancer death ratios of hazard rates estimated by the standard Cox proportional hazards model after adjusting for differences in implied background hazard rates of categorical RRs and the linear two-piece spline ("knot" at 1,600 ppm-days) fitted models for 15-year lagged occupational doses ≤150,000 ppm-days (NIOSH cohort) adjusting for the difference in baseline risks between the RRs and the Cox proportional hazards model

[Note: In Figure 14, the dashed blue line approximates a more appropriate visual representation of the log-linear model (standard proportional hazards model) fit to the full NIOSH dataset after adjusting for the difference in baseline risks between the non-parametric RRs and the log-linear model, thereby addressing USEPA's following footnote to Figure 4-3 (p. 4-21 of USEPA 2016) concerning the visual incomparability of model fit to the data, "Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis." The model "RRo* e^(B*exp)" is an approximation of the log-linear model (e^(B*exp)) adjusted through multiplying by RRo: the ratio of the underlying baseline hazard rate of the model to the underlying baseline hazard rate the nonparametric estimates.]

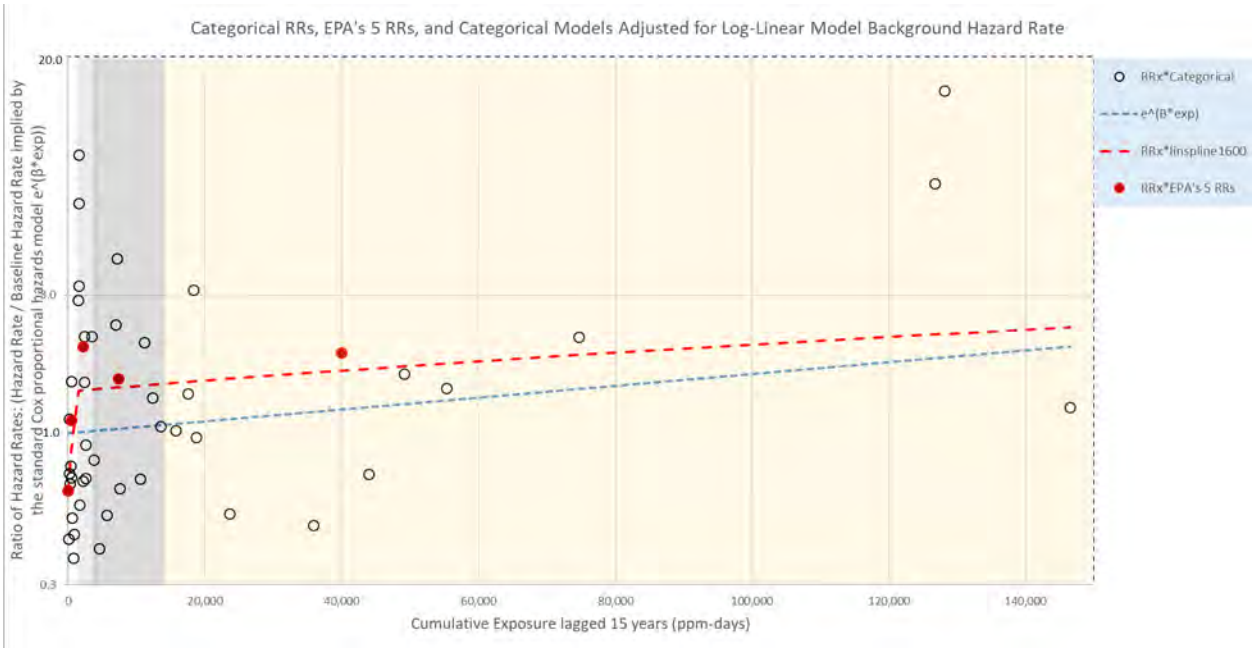


Figure 15: Lymphoid cancer death ratios of hazard rates estimated by the categorical RRs and the linear two-piece spline model ("knot" at 1,600 ppm-days) after adjusting them for differences in implied background hazard rates of the standard Cox proportional hazards fitted model for 15-year lagged occupational doses ≤150,000 ppm-days (NIOSH cohort) adjusting for the difference in baseline risks between the RRs and the linear two-piece spline model

[Note: In Figure 15, red dots, open circles, and the dashed red line approximates a more appropriate visual representation of the categorical model, EPA's 5 RRs, and the linear two-piece spline model fit to the full NIOSH dataset after adjusting them for the difference in baseline risks implied by these models and the baseline risk implied by the standard Cox proportional hazards model. This adjustment addresses USEPA's footnote to Figure 4-3 (p. 4-21 of USEPA 2016) concerning the visual incomparability of model fit to the data, "Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis." The models "RRx* Categorical", "RRx*linspline1600", and "RRx*EPAs 5 RRs" are an approximation of the "Categorical", "linspline1600", and "EPAs 5 RRs" adjusted through multiplying by RRx: the ratio of the underlying baseline hazard rate of the model to the underlying baseline hazard rate of the standard Cox proportional hazards model.]

In regard to the alleged sharp rise in excess risk that appears when using five categorical RRs as in Figure 4-3 of USEPA (2016) and Figures 12-15 above (represented by red dots): (1) visual

representation of summary statistics can be misleading when the summary statistics are believed to be observations; and (2) summarizing the RRs by using fewer grouped individual cases only masks the true variability in the underlying estimates of categorical RRs. Table 40 (Table 4-2 in the USEPA (2016) risk assessment) lists the estimates of the RRs (ratios of the hazard rate for each exposure quintile compared to the hazard rate for the unexposed workers). The quintile RRs (red dots) in Figures 12-15 are summary average approximations of the estimated individual RRs shown by open circles in Figures 12-15 and are approximately located in the center of the 11 individual RRs included in each quintile. Table 41 below shows USEPA's quintile RRs (USEPA calls them ORs) with their corresponding 95% CIs along with the average RR of the 11 individual RRs and the range of the individual RRs.

Table 41: USEPA Quintile RRs and 95% Confidence Intervals versus Corresponding Quintile-Specific Individual RRs

Quintile	USEPA's Quintile RRs [a] (95% Confidence Interval)	Average of 11 [b] Individual RRs in the Quintile	Individual RRs Included in USEPA's Quintile RRs [c]
2	1.75 (0.59, 5.25)	1.46	0.58, 0.68, 0.71, 0.80, 1.06, 1.11, 1.15, 1.22, 1.77, 2.38, 4.55
3	3.15 (1.04, 9.49)	4.04	0.89, 1.08, 1.11, 1.28, 1.44, 2.38, 3.41, 3.42, 5.11, 9.82, 14.49
4	2.44 (0.80, 7.50)	2.22	0.63, 0.82, 1.02, 1.10, 1.62, 1.67, 2.10, 2.16, 3.25, 3.75, 6.34
5	3.00 (1.02, 8.45)	4.99	0.76, 0.83, 1.14, 1.53, 1.94, 2.26, 2.54, 3.40, 4.93, 11.50, 24.11

RR – Rate ratio

[a] Source: Table 4-2 of USEPA's (2016) risk assessment report.

[b] The average of the 11 individual RRs are not statistically significantly different than the quintile RRs estimated by USEPA.

[c] Most individual rate ratios are inside the 95% confidence interval of USEPA's RR corresponding to the quintile.

Figures 14-15 and this table show that the purported steep increase at low cumulative exposures and plateauing of the RRs at higher cumulative exposures is an artifact of summarizing the RRs into quintiles. The 95% CIs of the quintile RRs and the individual RRs based on each lymphoid decedent shown in the table characterize the variability in the NIOSH data for lymphoid cancer mortality. The apparent supra-linearity (steep increase for low cumulative exposures that becomes substantially shallower at higher cumulative exposures conjectured from the red dots in Figures 14-15) is not supported by the individual RRs (open circles) in Figures 14-15, which form no discernable dose-response pattern. These figures show that the two models fit the individual RRs about the same. This visual conclusion is corroborated by the similar p-values and AIC values for the two models in Table 5 once the correct degrees of freedom (*df*) for the linear two-piece spline model are accounted for.

A better comparison of models fit to the observed data is to use the predictiveness of the model; that is, the capability of the model to estimate the observed number of deaths with a certain degree of confidence (see Appendix 3).

A6.3.1.2.1.2 Model-Specific Implicitly Estimated Baseline Risks

USEPA's footnote to several figures indicates that the different models and the non-parametric RRs cannot be compared along the y-axis because "the different models have different implicitly estimated baseline risks." USEPA is correct. All models in Figure 4-3 of USEPA (2016) risk assessment (Figure 11 herein), with the exception of the "linear reg" model, are fit to hazard rates (not fit to RRs). The functional form of all the hazard models is

$$HR_i(d) = HR_i(0) \times f_i(d)$$

where $HR_i(d)$ is the hazard rate of model i at cumulative exposure *d,* $HR_i(0)$ is the "estimated baseline risk" by model i, and $f_i(d)$ is the function of the RR at cumulative exposure *d* for model i.

Note that by dividing $HR_i(d)$ by the "estimated baseline risk" $HR_i(0)$, the function $f_i(d)$ is the RR at cumulative exposure *d* for model i. Note also, that each model i could result in different estimates of the baseline risk, $HR_i(0)$. That means, all models would have RR ($f_i(0)$) equal to 1 at cumulative exposure equal to 0. However, the "estimated baseline risk" $HR_i(0)$, could be very different for different models. The model for USEPA's 5 categorical RRs, the linear two-piece linear spline model (USEPA preferred), and the standard Cox proportional hazards model (TCEQ preferred) have the following functional forms:

Model 1 ("EPA's 5 RRs" and "Individual RRs" in Figures 12 to 15): The non-parametric model fit to the data is given by the expression

$$HR_{NP,k}(d) = HR_{NP}(0) \times RR_{NP,k}(d)$$

where $HR_{NP,k}(d)$ is the hazard rate for the *k*-th group at mean cumulative exposure *d*, $HR_{NP}(0)$ is the "estimated baseline risk" for the nonparametric model, and $RR_{NP,k}(d)$ the RR for the *k*-th group. Although the function does not depend on the magnitude of the exposure *d,* the function is written with the *d* for the sake of consistency. (USEPA expresses the function $RR_{NP,k}(d) = e^{\beta_k}$ where "*d*" is a "categorical exposure." Using USEPA's expression guarantees $RR_{NP,k}(d)$ is non-negative when doing a search for the parameters β_k.)

Model 2 ("linspline1600" in Figures 12 to 15): The functional form of the USEPA-preferred two-piece linear model (linspline1600) is

$$HR_{spl}(d) = HR_{spl}(0) \times \begin{cases} 1 + \beta_1 \times d & d \leq knot \\ 1 + \beta_1 \times d + \beta_2 \times (d - knot) & d > knot \end{cases}$$

where $HR_{spl}(d)$ is the hazard rate at cumulative exposure *d*, $HR_{spl}(0)$ the "estimated baseline risk" by the two-piece linear model, $1 + \beta_1 \times d$ is the RR at cumulative exposures *d* below the *knot*, $1 + \beta_1 \times d + \beta_2 \times (d - knot)$ is the RR at cumulative exposures *d* above the *knot*, and *knot* is the cumulative exposure where the slope of the RR changes. USEPA estimated the *knot* at 1,600 ppm-days.

Model 3 ("e^(β*exp)" in Figures 12 to 15): The functional form of the TCEQ-preferred standard Cox proportional hazards model ($e^{\beta * exp}$) is

$$HR_{Cox}(d) = HR_{Cox}(0) \times e^{\beta \times d}$$

where $HR_{Cox}(d)$ the hazard rate at cumulative exposure *d*, $HR_{Cox}(0)$ the "estimated baseline risk" for the standard Cox proportional hazards model, $e^{\beta \times d}$ is the RR at cumulative exposure *d*.

The RRs from each of the models described above are, by definition, equal to one at zero cumulative exposures. However, as indicated by USEPA's 2016 assessment and shown above for Models 1, 2, and 3, the "implicitly estimated baseline risks" ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$, for Models 1, 2, and 3, respectively) are generally different. That is, the RRs for the models cannot be compared for non-zero cumulative exposures without accounting for the differences in the "implicitly estimated baseline risks" ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$). The partial likelihood methodology used by the proportional hazards models described above do not explicitly estimate the baseline risks ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$) and they are unknown. However, an approximation of the ratio of the "implicitly estimated baseline risks" for Models 2 and 3 to the "implicitly estimated baseline risks" for Model 1 ($HR_{spl}(0)/HR_{NP}(0)$ and $HR_{Cox}(0)/HR_{NP}(0)$, respectively) can be estimated from the non-parametric RRs based on the individual lymphoid decedents (open circles in Figure 12) and is approximately equal to 1.598 (the intercept of the dotted line in Figures 12 and 13).

A6.3.1.2.1.3 Adjusting Models for Differences in Implicitly Estimated Baseline Risks for More Appropriate Visual Comparison

The ratio $HR_{spl}(0)/\ HR_{NP}(0)$ for Model 2 and $HR_{Cox}(0)/\ HR_{NP}(0)$ for Model 3 were calculated using weighted least squares and the corresponding RR functions for models 2 and 3, respectively. The best intercepts (ratios of baseline risk for each of the models to the baseline risk implied by the non-parametric RR estimates) multiply the RR functions for Models 2 and 3. These adjusted Models 2 and 3 account for the differences in the baseline risks implied by the models and the implicitly estimated non-parametric baseline risks.

Figure 14 adjusts the standard Cox model (e^(β*exp)) by the estimated ratio $RRo = HR_{Cox}(0)/HR_{NP}(0)$. This adjusted plot is more appropriate for comparing models.

The y-axis in Figure 14 has been re-labeled to indicate that the models are normalized to the baseline risk implied by the non-parametric model rather than the models' own implied baseline risks. Figure 14 is divided into four regions using different colors. Each color shows the range of "individual RRs" and range of cumulative exposures that are summarized in each of "EPA's 5 RRs."

[That is, the RR for the highest quintile of "EPA's 5 RR" (red dots) is equal to 3 and is placed at a cumulative exposure of 39,927 ppm-days. Tables 40 and 41 above and Figure 13 show that the RR for the fifth quintile summarizes the individual RRs for the 11 lymphoid cancer decedents (open circles) that had cumulative exposures greater than 13,500 ppm-days. Similarly, the RR for the fourth quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative exposure between 3,681 and 13,500 ppm-days. The RR for the third quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative exposure between 1,201 and 3,680 ppm-days. Finally, the RR for the second quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative exposure greater than zero and less than or equal to 1,200 ppm-days.]

Figures 14 and 15 show that the model preferred by USEPA ("linspline1600") cannot be visually judged to provide better fit than the TCEQ-preferred model ("e^(β*exp)") when compared to the individual RRs (categorical).

In summary, although a secondary consideration to statistical analyses, appropriate visual comparison of the standard Cox proportional hazards model (TCEQ preferred) and the linear two-piece spline model (USEPA preferred) shows that the models appear to conform to the individual RRs approximately the same once differences in baseline risks of different RR models are reconciled. However, model performance in predicting the actual number of lymphoid cancers in the NIOSH cohort as a whole and in each quintile demonstrates the superiority of the Cox proportional hazards model, which is also confirmed in a validation analysis conducted using UCC cohort data (Appendix 3).

A6.4 Evaluation of the Accuracy of Model Predictions

A6.4.1 Predictions for the Key Underlying Epidemiological Cancer Data

The evaluation of the accuracy of model predictions for lymphoid cancer mortality in the key NIOSH cohort is documented in Appendix 3, where a validation analysis is also conducted using UCC cohort data (Section A3.3.3). Briefly, to determine whether the linear two-piece spline model (used by USEPA 2016) properly fits the original data, it was used to predict the expected

number of lymphoid cancer deaths based on the same NIOSH individual exposure data as USEPA used for modeling. The MLE for the linear two-piece spline model ("knot" at 1,600 ppm-days; 15-year exposure lag) statistically significantly over-estimated the total number of observed lymphoid cancer deaths for the NIOSH cohort as a whole and for every exposure quintile, except quintile 3. Moreover, the upper bound of the model statistically significantly over-predicted lymphoid cancer deaths for the cohort as a whole and for every cumulative exposure group (even if the slope of the upper spline was set to zero). By contrast, the log-linear model preferred by the TCEQ (i.e., the standard Cox proportional hazards model) was accurate for the cohort as a whole and for every exposure quintile, neither significantly over- nor under-estimating lymphoid cancer deaths for the cohort as a whole or for any cumulative exposure quintile. This was true regardless of whether the MLE or upper bound was used for the Cox model.

The TCEQ notes that the linear two-piece spline model best supported by USEPA criteria (Table 4-6 of USEPA 2016) was actually the linear two-piece spline model with the "knot" at 100 ppm-days (Figure 16). However, USEPA rejected that model as less biologically plausible even in the absence of relevant data, adopting the same model but with the "knot" at 1,600 ppm-days as relatively speaking, more biologically plausible/realistic (p. 4-16 of USEPA 2016). It is noted that had USEPA (2016) used the model best supported by their miscalculated model fit criteria (linear two-piece spline with the "knot" at 100 ppm-days), the statistically significant over-prediction for the NIOSH cohort would have been exacerbated (i.e., MLE estimates of 107.78 lymphoid cancers for the cohort (95% CI of 82.4, 143.9) compared to the 53 actually observed). Regardless, USEPA's second-best fitting model with the "knot" at 1,600 ppm-days is also statistically significantly over-predictive for the key NIOSH cohort (Appendix 3).

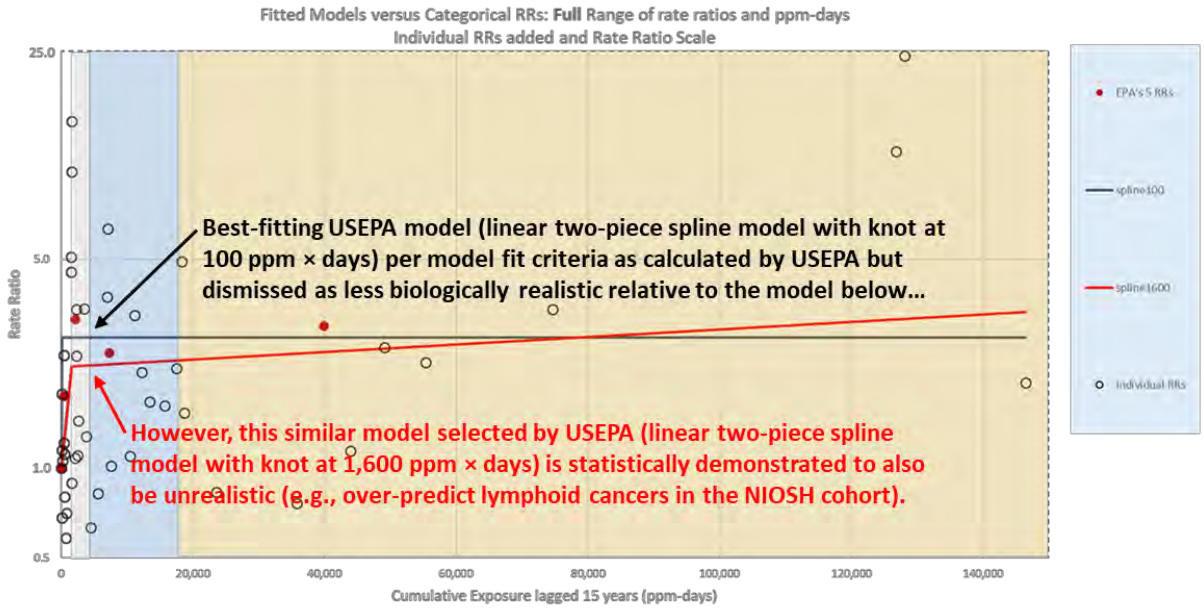


Figure 16: Best-fitting USEPA linear two-piece spline model for lymphoid cancer per USEPA model fit criteria compared to the model selected by USEPA

A sensitivity analysis assuming a healthy worker effect for overall cancer mortality (despite cancer endpoint-specific data to the contrary) also found that the linear two-piece spline model (MLE with the "knot" at 1,600 ppm-days; 15-year exposure lag) statistically significantly over-predicts the total number of lymphoid cancers for the NIOSH cohort. On the other hand, the Cox proportional hazards model remained reasonably accurate and neither statistically over- nor under-estimated the observed number of lymphoid mortalities in the NIOSH cohort (see Section A3.3.2 of Appendix 3).

Lastly, despite substantial differences in the exposure assessments for the NIOSH and UCC cohorts (see Section 3.1 of this DSD and Section 4.1 of USEPA 2016), the TCEQ conducted a validation analysis using the UCC cohort data (2013 update) to determine if the models derived based on the NIOSH cohort dose-response assessment would accurately predict the UCC cohort lymphoid cancer mortality data. The validation analysis is documented in Section A3.3.3 of Appendix 3. Results show that both the MLE and upper bound of the Cox proportional hazards model are reasonably accurate, predicting 28 (95% CI of 19, 43) and 32 (95% CI of 22, 50) lymphoid cancer mortalities for the cohort, respectively, compared to the 25 actually observed. For the linear two-piece spline model, however, the validation analysis shows that it statistically significantly over-predicts the number of lymphoid cancer mortalities in the UCC cohort. More specifically, the MLE and upper bound of the linear two-piece spline model predict 57 (95% CI of 39, 89) and 92 (95% CI of 62, 143) lymphoid cancer mortalities, respectively, compared to the

25 actually observed in the UCC cohort. Thus, these validation results are consistent with those for the NIOSH cohort itself.

In conclusion, the results discussed above demonstrate that the linear two-piece spline model (used by USEPA 2016) assessment overpredicted the key NIOSH data that were used to derive it (as well as the UCC data), whereas the standard Cox proportional hazards model were predictive of these two data sets. Therefore, the standard Cox proportional hazards model is preferred for estimates of population risk.

A6.4.2 Predictions of Background Lymphoid Cancer Rates based on Endogenous/Background Internal EtO Levels

For chemicals with adequate occupational dose-response data, regulatory dose-response assessments are based on exogenous occupational exposures. For chemicals that are also endogenously produced like EtO, background exposure for workers inherently includes exposure to endogenously produced levels in addition to background exposures outside the workplace such as environmental exposure to the chemical in ambient air and other exposures outside the workplace like smoking, etc. Accordingly, it should be recognized that the URFs developed for EtO based on the NIOSH cohort (e.g., by TCEQ and USEPA) are used to estimate excess risk for a source of exposure (i.e., EtO in ambient air) that was actually part of background exposure for the study population (i.e., occupationally-exposed workers), and not one for which the dose-response modeling was in fact conducted. This is commonly the case for regulatory dose-response assessments based on occupational data. However, a URF developed based solely on occupational exposure, where exposure to the chemical in ambient air outside the workplace was simply part of background, may be extrapolated and applied to environmental exposure from ambient air based on the toxicological principle that equal doses give rise to equal risk. Just as equal internal doses from occupational exposure (used for the EtO dose-response assessment) and environmental/ambient exposure (part of background for the NIOSH cohort) may be assumed to give rise to equal risk based on this toxicological principle, equal internal doses from exogenous exposure and endogenous production can be assumed to result in equivalent risk (i.e., the same risk per unit internal dose). This is consistent with the standard dose-response/risk assessment practice of considering equal internal doses as equipotent in producing carcinogenic effects (e.g., use of PBPK modeling to extrapolate between species and/or different exposure pathways).

Consistent with the standard practice of considering equal internal doses as equipotent in producing carcinogenic effects, endogenous EtO and background level data can be used for a reality check on EtO URFs. For example, use of the EtO air concentration corresponding to the mean of normal endogenous background levels in the unexposed population (equivalent to ≈1.9 ppb) evaluated by Kirman and Hays (2017) in conjunction with the USEPA (2016) ADAF-adjusted URF for lymphoid cancer (7.1E-03 per ppb) suggests a background incidence of ≈1.35%

in non-smokers due to endogenous EtO alone, which would be almost half (46%) of the lymphoid cancer background incidence of 3% in the general population (p. 4-95 of USEPA 2016). Based on a reasonable estimate of endogenous EtO (e.g., good agreement between the models in Kirman and Hays 2017 and with laboratory control animal data in Walker et al. 1993, 2000) and considering that contributions from other potential causes of lymphoid cancer are not accounted for, this reality check begins to suggest that the USEPA URF may be scientifically over-predictive of lymphoid cancer. However, the smoking population must also be considered as past EtO exposure from smoking would contribute to the background lymphoid cancer rate. Use of the EtO air concentration corresponding to the mean background in smokers evaluated by Kirman and Hays (2017) (18.8 ppb at an HEV of 205.4 pmol/g Hb; Tables 2 and 4 of the study) along with that for non-smokers (1.9 ppb) and USEPA's lymphoid cancer URF (4.8E-03 per ppb, ADAF-unadjusted) with ADAFs for early-life exposure (at 1.9 ppb) suggests an incidence of lymphoid cancer in smokers of ≈8% due to EtO alone. While the background EtO level for smokers is associated with greater between-study variability than that for nonsmokers (see Appendix 5), this background rate estimate for smokers appears particularly telling since: (1) the significant (i.e., 10-fold) increase in internal EtO dose is due to exogenous exposure (i.e., smoking), for which the URF was derived; and (2) this URF-predicted incidence would make lymphoid cancer (i.e., leukemia, non-Hodgkin's lymphoma, multiple myeloma) about as common as lung cancer in smokers (e.g., lifetime lung cancer risk for current smokers of ≈8-14%; Bruder et al. 2018). However, lymphoid cancer is not as common as lung cancer in smokers (e.g., see lung cancer versus myeloid leukemia results in Figures 3 and 4 of Gandini et al. 2008 and Table 1 of Doll et al. 2005; see lung/bronchus cancer versus lymphoma, multiple myeloma, and leukemia RRs in Jacob et al. 2018).

Weighting the URF-estimated lymphoid cancer incidence for smokers (8%) at above 25% of the population (e.g., for 1980-2005 (Wang et al. 2018) since current cancer rates would reflect contributions from past smoking, consistent with the USEPA 2016 exposure lag period of 15 years) with that for non-smokers (1.35%) results in a population estimate greater than the lymphoid cancer background incidence of 3% cited by USEPA (p. 4-95 of USEPA 2016) due to background EtO levels in the U.S. population alone; that is, without contributions from other potential causes of lymphoid cancer such as known chemical leukemogens, contributions from the endogenous conversion of ethylene to EtO, other risks factors such as genetic predispositions, etc. Because the population-wide lymphoid cancer incidence rate would have many contributing factors, not just a single chemical, this suggests that USEPA's selected model assessment overestimates observable lymphoid cancer risk based on endogenous/background levels of EtO alone.

The same conclusion can be drawn utilizing blood EtO (HEV) results from the Jain (2020) study, which evaluated 2013-2016 NHANES data for the general US population. More specifically, use of the time-weighted lifetime EtO air concentration (≈5.2 ppb) based on the geometric means

(see Table 3 of Jain 2020) for HEV in ages 6-11 (34.2 pmol/g Hb≈3.1 ppb EtO in air), ages 12-19 (38.3 pmol/g Hb≈3.5 ppb EtO in air), and ages ≥ 20 years (67.1 pmol/g Hb≈6.2 ppb EtO in air) in conjunction with the USEPA (2016) ADAF-adjusted URF for lymphoid cancer (7.1E-03 per ppb) suggests a background lymphoid cancer mortality of ≈3.7% for the general US population due to EtO alone.[l] This background estimate based on USEPA's assessment exceeds the actual lymphoid cancer background incidence of 3% cited by USEPA (2016). This over-prediction (3.7%) for lymphoid cancer background in the US population is based on 2013-2016 data that includes smokers. However, the over-prediction would be expected to be even higher if historical NHANES data on EtO in blood in the US population were available since smoking rates have declined appreciably over time (e.g., Wang et al. 2018).

Consistent with the statistically significant over-predictions by USEPA's preferred model (i.e., the linear two-piece spline model) documented in Appendix 3 for the key and supporting cohorts, the reality checks above based on endogenous/background levels of EtO alone suggest that USEPA's lymphoid cancer URF is scientifically unreasonable (i.e., leaving no room in the background rate for other causes of lymphoid cancer). Thus, while these calculations did not play a role in model selection (e.g., unlike information on MOA, the accuracy of model predictions of the key cohort data combined with statistical model fit criteria, and TCEQ guidance), they do provide additional important context relevant to the reasonableness of model predictions.

[l] The time-weighted air concentration is based on a duration of 70 years, conservatively utilizing the mean of 1.9 ppb from Kirman and Hays (2017) for ages 0<6 years since data for this age group were not available from Jain (2020).