Response to MON Comments Related to TCEQ's Risk Assessment Approach

Ciriaco Valdez-Flores, Ph.D., P.E.
Professor of Practice
Department of Industrial and Systems Engineering
4073 Emerging Technologies Building
3131 TAMU
College Station, TX 77843-3131
Tel. (979) 458-2366 Fax: (979) 458-4299
e-mail: ciriacov@tamu.edu

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In the document "Reconsideration of the National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review" (FR 12/21/2022) the EPA (2022a) made several claims about TCEQ's DSD published in May 2020. Following are clarifications in response to comments made by EPA regarding TCEQ's request for reconsideration of EPA's risk assessment of ethylene oxide (EtO). In the following paragraphs, page numbers and comments were extracted from EPA (2022a) and/or the more detailed public comments and responses published in EPA (2022b).

There were four issues raised by EPA:

Number 1. TCEQ shows EPA's model implausibility using the variability of endogenously produced ethylene oxide (EtO)
Number 2. TCEQ weight of evidence found that breast cancer was not associated with EtO exposures
Number 3. TCEQ model was allegedly not consistent with the epidemiological data; and
Number 4. TCEQ reality check is purportedly flawed.

Issues 1 and 2 are addressed shortly at the beginning of this document, with most of the responses focused on issues 3 and 4.

Issue 3 was divided in two points where EPA critiqued TCEQ:

3.a. TCEQ inconsistency with EPA's quintiles
3.b. TCEQ inconsistency with attenuation

Issue 4 was divided into four points where EPA critiqued TCEQ:

4.a. TCEQ did not consider the healthy worker effect
4.b. TCEQ calculations did not include lagged exposures
4.c. TCEQ confidence interval calculation is flawed
4.d. TCEQ is not consistent with low-exposure risks

The document addresses all six EPA criticisms for issues 3 and 4 and offers both an executive (high-level) summary response and a more extensive response indicating how TCEQ has addressed the issues raised.

The following is an outline of the document.

1. TCEQ Shows EPA's Model Implausibility given the Variability of Endogenously Produced Ethylene Oxide (EtO)

1.a. EPA's Model is Inconsistent with Cancer Risks of Endogenous EtO

1.a.1. EPA comments about their Model in EPA (2022a)

Page 16: "It is important to recognize that the IRIS [unit] risk estimate for EtO represents the increased cancer risk due to exposure to ethylene oxide emissions – above any potential existing risks from endogenous or ambient background levels of EtO exposure. The occupational exposures in the NIOSH study represent workplace EtO levels these workers experienced – and are in addition to any endogenous or broad population background exposures to which the workers may also have been exposed."

1.a.2. Response to EPA Comments

The TCEQ DSD (2020) clearly states in Section A5.1.1 that "endogenous levels did not play a role in model selection for the EtO carcinogenic dose-response assessment." This statement does not contradict or question EPA's claim. However, TCEQ points out that EPA's model would produce unacceptable increased cancer risks for individuals on the upper percentiles of the distribution of endogenously produced EtO when compared with the risks of the individuals producing the mean of endogenous EtO. In other words, even if EPA's model was fit to the NIOSH study with workers that produce the mean endogenous EtO, EPA's unit risk estimate would suggest that the fraction of the population producing endogenous EtO in the higher percentiles of endogenous EtO production would result in cancer rates in the general population that are higher than the rates that are actually observed. Although it did not play any role in model selection, Section A6.4.2 of the DSD contains some example predictions of background lymphoid cancer rates based on endogenous/background internal EtO levels. Results suggest that USEPA's selected model assessment overestimates observable lymphoid cancer risk based on endogenous/background levels of EtO alone.

2. TCEQ Weight of Evidence found that Breast Cancer was not Associated with EtO Exposures

2.a. Meta-analysis supporting the exclusion of breast cancer is supported by dose-response models that use internal comparisons

2.a.1. EPA (2002a) comments about the TCEQ meta-analysis of breast cancer

Pages 25-26: "Comments against the inclusion of breast cancer cite two meta-analyses addressing ethylene oxide breast cancer studies that were published after the completion of the 2016 IRIS assessment (Marsh et al. (2019). Both reviews included five breast cancer studies, all of which were examined in the IRIS assessment (Coggon, 2004; Mikoczy, 2011; Norman, 1995; Steenland, 2003; and Steenland, 2004). The conclusions of these meta-analyses are flawed for two major reasons: (1) the authors did not consider findings of increased cancer incidence or mortality in highly exposed study subgroups, and (2) the authors excluded published findings

using internal comparison groups within the worker populations, which goes against best practice in epidemiology. Consequently, the meta-analyses inappropriately omitted all positive findings from the Steenland et al. (2003 and 2004) and Mikoczy et al. (2011) studies for breast cancer mortality and incidence and treated these studies as providing negative evidence of an effect of ethylene oxide on breast cancer. These flawed re-analyses of data (data that had been previously reviewed in the IRIS assessment and found to provide positive evidence) led the authors to conclude that the weight of evidence does not support breast cancer as an endpoint."

2.a.1. Response to EPA Comments on Meta-Analysis

The TCEQ DSD (2020) discusses the weight of evidence of breast cancer by presenting the Marsh et al. 2019 and Vincent et al. 2019 results. Both meta-analyses include the Steenland 2003 and 2004 results on breast cancer. Steenland et al. 2003 clearly states in the abstract that the results are not conclusive when they state, "Our data suggest that EtO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment." The meta-analyses reported by Marsh et al. 2019 and Vincent et al. 2019 are consistent with Steenland et al. 2003 in that there is no sufficient evidence to link exposures to EtO with breast cancer incidence. Steenland et al. 2004 do not contradict the findings in the meta-analyses when they conclude, "There was also some evidence of a positive exposure-response for breast cancer mortality." These results in Steenland et al. 2004 refer to the Cox model using cumulative exposure lagged 20 years. This "significant" result may not have been significant had Steenland et al. 2004 used unlagged cumulative exposure. For Steenland et al. 2004 breast cancer model to be statistically significantly different than the null model, they would have to account for the fact that the "significant" result was for a model with exposure lag (20 years) chosen so that the model likelihood would be maximized. In summary, neither Steenland et al. 2003 or 2004 publications conclusively relate exposure to EtO and increasing breast cancer incidence or mortality. The purpose of the meta-analyses is to aggregate the evidence or lack of evidence and reach a conclusion. In this case, both the meta-analyses and Steenland et al. 2003 and 2004 reached the same conclusion; that is, there is no sufficient evidence to relate cancer incidence or mortality with exposures to EtO.

2.b.1. EPA (2002a) comments about Jain (2020) study

Pages 26: "There are three major issues that call into question the interpretation of the results from this study. First, it appears that Jain misleadingly interpreted a biomarker of exposure as "[ethylene oxide] levels in the blood". Importantly, since NHANES did not measure ethylene oxide levels in the blood, this suggests a misunderstanding of the NHANES data consistent with Jain's overinterpretation of the results. Second, Jain failed to note the large number of unaccounted-for variables that may contribute to one's lifetime breast cancer risk, such as lifestyle, a history of breast cancer in relatives, co-exposures, and cumulative exposure to ethylene oxide and other chemicals. NHANES provides cross-sectional data representing a snapshot in time of exposure and health outcome and is not designed to establish temporal causality between chemical exposure and cancer outcomes. For this reason, NHANES data cannot be used to reliably rule out causation between chemical exposure and breast cancer. Third, biomarker measurements that offer a snapshot in time of one's exposure to chemicals are

not necessarily representative of continuous, lifetime exposure leading to the development of breast cancer. Taken together, the Jain study results do not support the author's conclusion."

2.b.1. Response to EPA Comments on Jain (2020) study

The TCEQ DSD (2020) uses the conclusion of Jain (2020) as a supporting study of other studies that did not find a relationship between EtO exposures and breast cancer. EPA's first concern is that Jain (2020) may have misinterpreted the measures reported in the NHANES study. TCEQ (2020) did not confirm EPA's concern and relied on the peer-reviewed conclusions in Jain (2020). The second concern of EPA, that Jain "failed to note the large number of unaccounted-for variables that may contribute to one's lifetime breast cancer risk", is a concern for any epidemiology study results. That is, Jain (2020) results may have excluded some variables that could have affected breast cancer, but as is almost always the case the available data were not sufficient to account for all potential variables influencing the outcome (breast cancer in this instance). Furthermore, because Jain (2020) analyses are based on aggregate data, adjustment for individual-specific variables is not possible. EPA's third concern, although valid, is a standard assumption made in predicting risks. For example, dose-response models are used to estimate the risks of cancer assuming a hypothetical constant exposure level 24 hours a day, 7 days a week, from birth until the end of life. The TCEQ added the Jain (2020) study to their document as just one more study (albeit just a snapshot) that does not show an association between EtO and breast cancer. The TCEQ did not rely on it in any substantive way.

3. TCEQ Model is Supported by the Underlying Epidemiological Data

3.a. TCEQ Model is Consistent with the Observed Epidemiological Study

3.a.1. EPA comments about TCEQ Model in EPA (2022a)

Page 23: "1) the dose-response model selected by TCEQ is unsupported by the underlying epidemiological data"

Page 28 and 29: "For their model selection, TCEQ chose a model that is inconsistent with the underlying epidemiological data, particularly for ethylene oxide levels in the range of general population exposure (where the general population would include children and other potentially vulnerable groups), which is of most relevance for the CAA section 112 risk assessments.

The epidemiological data indicate that cancer risk rises more rapidly with increasing exposure in the lower exposure range and more gradually in the higher exposure range. TCEQ selected a model that is unable to fit the shape of the data throughout the exposure range. The slope of TCEQ's model is more representative of higher, occupational exposures. By using a single slope (a line) to project risks, TCEQ's model predicts risks at lower exposure ranges that are inconsistent with the underlying epidemiological dose-response data. EPA rejects TCEQ's model because it is inconsistent with the underlying epidemiological dose-response data and mischaracterizes risk at the lower exposure range (i.e., the range representing potential general population exposures)."

3.a.2. Executive Summary of Response to EPA Comments about TCEQ Model

Due to misinterpretations of exposure-response modeling for epidemiological data, EPA has been misled to believe that estimates of a few categorical RRs are "the data." The real data for epidemiological studies is the number of individuals who died from specific causes of death, measures of exposures to ethylene oxide (EtO), and demographic characteristics. TCEQ showed (TCEQ Table 30) that TCEQ's model can accurately estimate, with 95% confidence, the number of lymphoid cancer deaths for every level of cumulative exposures to EtO (low and high exposure ranges). EPA's model (two-piece spline model) on the other hand, statistically significantly over-estimates, at the 5% significance level, the observed number of lymphoid cancer deaths in the low and high cumulative exposure ranges, and also statistically significantly overestimates the overall number of observed lymphoid cancer deaths in the NIOSH study and the UCC study. That is, EPA's model fails the most basic statistical test for any model fit to observed data; that is, a model should, at a minimum, estimate the observed data used to fit the model parameters. TCEQ's model not only predicts the overall lymphoid cancer mortality in the NIOSH study, but also accurately predicts the number of lymphoid cancer deaths at every level of EtO exposure quintiles (TCEQ Table 30). TCEQ's accuracy and EPA's overestimation were corroborated using an independent epidemiological study of workers exposed to EtO (TCEQ Table 31).

3.a.3. Detailed Discussion of EPA Misunderstandings about TCEQ Model

Lack of understanding of exposure-response modeling using Cox proportional hazards models can easily lead to incorrect interpretations of model results. EPA's misinterpretations have led them to draw incorrect conclusions due to the following four misunderstandings.

3.a.3.1. Epidemiological data. The underlying epidemiological data do not include measures of cancer risks with cumulative exposures. The underlying epidemiological data, at best, measure the number of cancer-specific deaths by cumulative exposure intervals. So, it is not clear what EPA means by, "The epidemiological data indicate that cancer risk rises more rapidly with increasing exposure in the lower exposure range and more gradually in the higher exposure range." However, that statement could be the result of a second misunderstanding.

3.a.3.2. Categorical rate ratios (RRs) are not the observed data. Categorical RR models are non-parametric (do not conform to a continuous functional relationship between cumulative exposure and RRs) Cox proportional hazards models, but they are not the observed data. The number of RRs and pattern of the non-parametric (categorical) RRs depend on the size of the cumulative exposure intervals chosen and the specific cutoffs of such intervals. EPA, however, uses non-parametric estimates of the RRs as a yardstick to visually judge whether a parametric model conforms to the non-parametric RR estimates. In the IRIS 2016 appendices EPA states, "For these endpoints, a simple linear model, where the log RR (for the log-linear model) or the RR increases linearly with cumulative exposure, does not fit the data well, based on simple visual inspection of the categorical data." EPA used this flawed visual fit logic as a criterion for selecting their model (e.g., EPA Table 4-6). EPA used the visual fit criterion in contradiction to their own warnings (e.g., footnote to EPA Figure 4-3: "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."). EPA's emphasis on visual fit to non-parametric estimates of RRs and poor use of the more objective and robust statistical measures of model fit led them to a third misunderstanding.

3.a.3.3. Overlooking model fit statistics and relying on visual fit. The following EPA statement is evidence of the poor understanding of statistical measures of model fit: "EPA rejects TCEQ's model because it is inconsistent with the underlying epidemiological dose-response data and mischaracterizes risk at the lower exposure range (i.e., the range representing potential general population exposures)." The first two misunderstandings have led EPA to believe that their model conforms to the data significantly better than TCEQ's model. EPA reliance on visual fit to some non-parametric estimates of the RRs and the belief that the non-parametric RRs are the observed data led them to overlook statistical measures of model fit to the actual epidemiological data. Probably, this misunderstanding and over-reliance on visual fit of their model to non-parametric estimates of the RRs was driven in part by a fourth misunderstanding on how to account for parameter estimation using scientifically-sound statistical measures of model significance.

3.a.3.4. Inappropriate consideration of the knot parameter. EPA selected a two-piece spline model for RRs whereby a steep slope is estimated for cumulative exposures to EtO below a cumulative exposure level ("knot") where the slope for higher cumulative exposures is shallower. EPA determined the "knot" as the point that maximized the likelihood of the two-piece spline model. On page 4-13 of the IRIS assessment, they state "For this assessment, the knot was generally selected by evaluating different knots in increments of 100 ppm × days over some range of cumulative exposures starting at 0 and then choosing the one that resulted in the best (largest) model likelihood." When evaluating statistical significance of a model, ALL parameters estimated using the data should be included to determine the appropriate measure of significance of the model. EPA, however, failed to include the "knot" of the two-piece spline models in their statistical analyses resulting in a biased significance level of their model.

3.a.4. How TCEQ addressed EPA's Four Misunderstandings about the TCEQ Model

The four misunderstandings discussed in Section 3.a.3 "supported" each other, leading EPA to believe that their two-spline linear model was superior to other models. TCEQ, on the other hand, used valid statistical procedures to show that the model selected by EPA is not statistically significantly, at the 5% significance level, better than a model with no increasing relationship between RRs and cumulative exposure to EtO. The TCEQ DSD discusses all of the four misunderstandings. The following discusses how TCEQ has addressed those misunderstandings.

3.a.4.1. Addressing the epidemiology data. It is unclear what EPA meant by: "1) the dose-response model selected by TCEQ is unsupported by the underlying epidemiological data." EPA may have meant that the categorical RRs are "the underlying epidemiological data" because elsewhere they state, "The epidemiological data indicate that cancer risk rises more rapidly with increasing exposure in the lower exposure range and more gradually in the higher exposure range." EPA's claim that the categorical RRs are the epidemiological data is an incorrect statement and was addressed by TCEQ in subsection A.6.3.1.2.1.1 Non-parametric Rate Ratios

are Not the Observed Data. Alternatively, EPA may have meant that the number of cause-specific deaths is the observed data, in which case, TCEQ addressed the issue in the same subsection and this is discussed below in addressing EPA's second misunderstanding.

3.a.4.2. Addressing the categorical RRs. TCEQ addressed this misunderstanding in Appendix A.6 subsection A.6.3.1.2.1.1 Non-parametric Rate Ratios are Not the Observed Data. TCEQ clearly states that different models are ratios of hazards to model-dependent baseline hazard rates resulting in non-comparable rate ratios (rate ratio = hazard rate / baseline hazard rate). This is also what EPA meant in their footnote to graphs showing the RRs estimated by different models (e.g., footnote to EPA Figure 4-3: "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."). TCEQ offered a fairer alternative to EPA's visual comparison of RR models and observed data whereby the RR models and the exposure data in the NIOSH study were coupled with the US population background hazard rates to estimate the expected number of deaths predicted by the models. While the MLE of the standard Cox proportional hazards model used by TCEQ predicts, with 95% confidence, the number of lymphoid cancer deaths in every quintile and overall, the MLE of EPA's two-piece spline model statistically significantly, at the 5% significance level, overestimates the observed number of lymphoid cancer deaths in all but one quintile and overall (TCEQ Table 30).

3.a.4.3. Addressing model fit statistics and visual fit. EPA contradicts themselves when they use visual comparison of categorical RRs with parametric model RRs. The contradiction rests in the fact that, on one hand, footnotes to figures (e.g., EPA Figure 4-3) with several RR models caution readers to resist the temptation of comparing models with each other, and on the other hand, EPA emphasizes this comparative visual fit as a criterion for model selection. Categorical RRs for a few cumulative exposure intervals are not the epidemiological data, but rather, a model that does not conform to a functional form. TCEQ addressed the perils of using visual fit in subsection A.6.3.1.2 Visual Model Fit. In this section TCEQ discusses the visual non-comparability of RR models because of different baseline hazard rates that normalize the RRs to be 1 at zero cumulative exposures. In addition, TCEQ estimated the finest possible categorical RRs by creating cumulative exposure intervals that included exactly one cause-specific death in each non-zero exposure interval. These finest categorical RRs display the full variability of the RRs in the whole cohort, which is hidden in EPA's categorical RRs of five exposure groups with multiple cause-specific deaths per group. TCEQ then empirically adjusted the parametric models (TCEQ model and EPA's two-piece spline linear model) to account for the different baseline hazard rates between the parametric and the categorical (non-parametric) RR model. The results (in TCEQ Figure 14) show two conclusions: 1) when the parametric models are adjusted to account for the differences of baseline hazards rates implied by the parametric models versus the baseline hazard rate of categorical RRs, TCEQ and EPA models are much closer than what is shown in EPA's Figure 4-3; and 2) when the parametric models are compared to the finest categorical RRs (circles in TCEQ Figure 14), both models approximate the points equally. TCEQ Figure 14 corrects some of the shortcomings in EPA Figure 4-3 by showing more categorical RRs, adjusting the parametric RRs to account for differences in baseline hazard rates, and showing the full range of cumulative exposures.

3.a.4.4. Addressing the knot parameter. Cox proportional hazards models fit to epidemiological data are statistically compared to the null model (a model with no exposure-response relationship). These model comparisons take into account the complexity of the model by incorporating the number of parameters estimated using the Cox model in addition to the number of parameters estimated for the null model. Thus, for example, a model with just the slope parameter has one degree of freedom that can be adjusted to fit the data better than the null model that does not have a slope. The number of degrees of freedom in statistical testing is the number of parameters estimated above and beyond the number of parameters used in the null model. Not accounting for all the parameters (degrees of freedom) results in biased estimates of significance levels and incorrect statistical conclusions. EPA fit a two-piece linear spline model with an inflexion point ("knot"). These three parameters, (slope below the inflexion point, the slope above the inflexion point, and the inflexion point itself) were estimated in such a way that the likelihood of the model was maximized. However, when calculating the significance level of the two-piece linear spline model, EPA failed to account for the "knot" and assumed two degrees of freedom in their computations and calculated significance levels that were lower than the significance levels should have been if they had correctly used three degrees of freedom. This oversight led EPA to conclude that the two-spline linear model was significantly better than the standard Cox model. TCEQ addressed this EPA omission in Section A.6.3.1.1 p-Values and AIC values. TCEQ (TCEQ Table 5) showed that when the correct number of degrees of freedom are used in the calculation of significance levels, the p-value of EPA model is 0.144 (not significantly different than the null model at the 5% significance level). TCEQ's model has a comparable p-value that is also not statistically significantly different from the null model at the 5% significance level. EPA not only miscalculated the p-values by ignoring one degree of freedom but also miscalculated the Akaike information criterion (AIC) score. The AIC is a statistical score that compares models by explicitly incorporating the likelihood of the model and the number of parameters estimated. The correct AIC values for the TCEQ model and EPA model are listed in TCEQ Table 5. The AIC score for the TCEQ model is less than the AIC score for the EPA model, indicating that the more parsimonious TCEQ model is statistically preferable over the EPA model.

3.b. TCEQ Model is Consistent with the Observed Epidemiological Study Across All Exposures

3.b.1. EPA comments about Attenuation at Higher Cumulative Exposures in EPA (2022a)

In EPA (2022a), EPA states, "The dose-response model selected by TCEQ (a Cox proportional hazards model) is one of the models that was considered by the EPA as part of the IRIS assessment. EPA found that the linear curve selected by TCEQ was highly influenced by the uppermost 5% of the exposure range and did not fit the full range of epidemiological data points, leading to an underestimation of risk for points below the highest exposure levels. After considering all models, EPA found that the two-piece spline model best captured the initial increase in risk at lower doses followed by an attenuation at higher doses. Spline models are generally useful for exposure-response data in which risk increases with exposure at low doses but attenuates at higher exposures, as observed in the ethylene oxide lymphoid cancer data. The plateauing exposure-response relationship has been observed for other occupational carcinogens and may be explained by the depletion of susceptible subpopulations at high exposures,

mismeasurement of high exposures, or a healthy worker survivor effect (Stayner et al., 2003)." (pages 29-30).

3.b.2. Executive Summary of Response to EPA Comments about TCEQ Model and Attenuation

EPA's comments about the TCEQ model and their purportedly superior fit of the two-piece linear spline model is linked to the misunderstandings outlined and discussed in the response to comments on 3.a. EPA continues to ignore: 1) the statistical evidence and instead favors a visual comparison of parametric models with a few nonparametric (categorical) estimates of the RRs; 2) TCEQ's more appropriate visual comparison discussed in TCEQ section A.6.3.1.2 Visual Model Fit and presented in TCEQ Figure 14; and 3) the evidence that the TCEQ model can estimate the number of lymphoid cancer deaths in every cumulative exposure interval with 95% confidence while the EPA model statistically significantly overestimates, at the 5% significance level, the number of lymphoid cancer deaths in every (except one) cumulative exposure interval and overall (TCEQ Table 30). EPA's assumption that the parametric models should conform to the categorical RRs (e.g., EPA Figure 4-3) begs the question: why did EPA fit the parametric models to the individual epidemiological data, as was done in IRIS 2016 and strongly recommended by the 2007 EPA SAB, instead of fitting them to the categorical RRs, if EPA believes fit to the categorical RRs reveals the best dose-response model? The answer to this question was thoroughly answered by the 2007 EPA SAB when responding to EPA's question 2.b. Methods of Analysis on pages 31 to 41. The 2007 EPA SAB summarizes the inappropriateness of comparing or fitting parametric model RRs to categorical RRs when they state, "If categories of exposure (as opposed to individual exposure estimates) must be used, the crude rates should be computed for a **large number** of equally spaced exposure ranges and the Rothman and Greenland (1998) model fitted to these multiple points." [**emphasis added**]. TCEQ's suggested improved visual comparisons (TCEQ Figure 14) aligns with the 2007 EPA SAB recommendation.

3.b.3. Detailed Response to EPA Comments about TCEQ Model and Attenuation

EPA's comments dismissing TCEQ's model stem from the misunderstandings outlined in response to 3.a. The observations made by EPA are not only countered by TCEQ but also by the 2007 EPA SAB. For example, EPA states, "… TCEQ was highly influenced by the uppermost 5% of the exposure range and did not fit the full range of epidemiological data points, leading to an underestimation of risk for points below the highest exposure levels. After considering all models, EPA found that the two-piece spline model best captured the initial increase in risk at lower doses followed by an attenuation at higher doses." This statement stems from the misunderstanding that the non-parametric (or categorical) RRs based on five categories are the observed data. The 2007 EPA SAB advised EPA to be careful with these comparisons when it stated, "If categories of exposure (as opposed to individual exposure estimates) must be used, the **crude rates** should be computed for a **large number** of equally spaced exposure ranges and the Rothman and Greenland (1998) model fitted to these multiple points." [**emphasis added**]. Following the EPA SAB 2007 recommendation of "a large number of exposure ranges" , TCEQ estimated the largest possible number of categorical RRs in order to compare the parametric models against the categorical RRs (TCEQ Figure 14) as opposed to EPA's comparison to five

categorical RRs (EPA Figure 4-3 and red dots in TCEQ Figure 14). In addition, TCEQ followed-up on the EPA SAB recommendation of using "crude rates" and adjusted the parametric models according to the Rothman (1986) and Rothman and Greenland (1998) model to account for discrepancies in the baseline background hazard rates (TCEQ Figure 14) as opposed to the raw model RRs presented by EPA (EPA Figure 4-3). Using the results in EPA Figure 4-3, EPA concludes that the TCEQ model "… did not fit the full range of epidemiological data points, leading to an underestimation of risk for points below the highest exposure levels." However, TCEQ Figure 14 (reproduced below) shows that the TCEQ model and the EPA model conformity to the finest possible number of categorical RRs is approximately the same. This subjective visual similarity of TCEQ and EPA models is corroborated by objective statistical results whereby neither model is statistically significantly different than the null model and the AIC favors the TCEQ model over EPA's two-piece linear spline model.

The TCEQ, in addition to providing an alternative analysis to compare parametric model RRs versus categorical RRs, presented an analysis that measured model predictability of observed data. That is, the models fit (TCEQ model and EPA model) to the NIOSH data were used to predict the number of lymphoid cancer deaths at every cumulative exposure quintile and overall (TCEQ Section A.3). TCEQ showed (TCEQ Table 30) that the TCEQ model predicted, with 95% confidence, the number of observed lymphoid cancer deaths in every exposure quintile of the NIOSH study while the EPA model statistically significantly overpredicted the number of observed lymphoid cancer deaths in the NIOSH study for all but one of the quintiles and overall. That is, TCEQ model predictability is not only on target overall but also at low and high exposure groups. In contrast, the EPA model statistically significantly overstates the number of lymphoid cancer deaths in low and high exposure groups and overall. TCEQ performed further analyses using an independent epidemiological study (UCC/DOW) of workers exposed to EtO (TCEQ Table 31). Results were similar; namely, the TCEQ model predicted, with 95% confidence level, the observed number of lymphoid cancer deaths in the UCC/DOW study, while the EPA model statistically significantly, at the 5% significance level, overestimated the observed number of lymphoid cancer deaths in the UCC/DOW study.

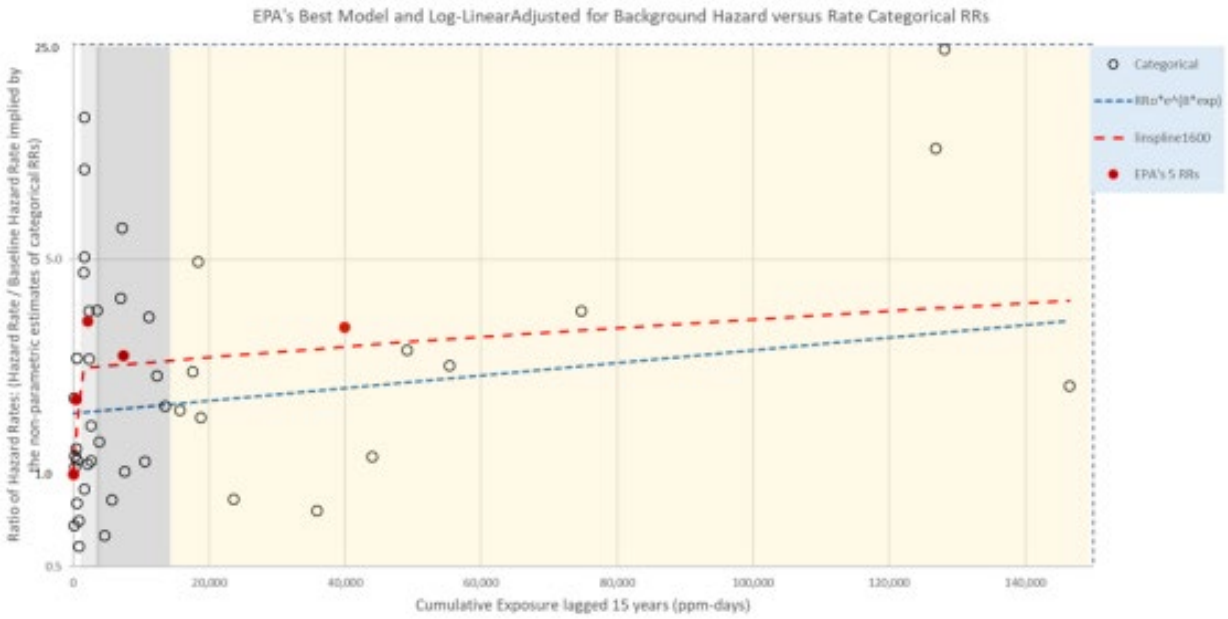

Figure 14 (from TCEQ 2020): Lymphoid cancer death ratios of hazard rates estimated by the standard Cox proportional hazards model after adjusting for differences in implied background hazard rates of categorical RRs and the linear two-piece spline ("knot" at 1,600 ppm-days) fitted models for 15-year 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.

4. TCEQ Reality Check Analyses are Correct and Based on Well-Established Statistical Procedures

4.a. TCEQ Used National Background Rates and the Sensitivity Analysis Included a Healthy Worker Effect

4.a.1. EPA comments about TCEQ Reality Check Using Population Hazard Rates

Page 23: "2) TCEQ's analyses to justify their model choice were erroneous and relied on flawed assumptions."

Page 31: "EPA has examined TCEQ's inferences and calculations and has identified problems with: 1) TCEQ's assumption that national lymphoid cancer mortality rates equal rates of cancer mortality for members of the NIOSH cohort in the absence of ethylene oxide exposures;"

Page 32: "For example, in making a claim that TCEQ's model more accurately predicts cancers attributable to ethylene oxide exposure, TCEQ incorrectly assumes that, in the absence of ethylene oxide exposure, cancer incidence rates in the worker cohort (the basis of the URE calculation in EPA's IRIS assessment) would be the same as national cancer mortality rates for the general population."

4.a.2. Executive Summary of Response to EPA comments about TCEQ use of Population Hazard Rates

A statistical procedure cannot be judged incorrect just because it is poorly understood. EPA makes assertions that contradict themselves. First, EPA states that TCEQ analyses assume that "national lymphoid cancer mortality rates equal rates of cancer mortality for members of the NIOSH cohort", but then EPA states that "TCEQ incorrectly assumes that, in the absence of ethylene oxide exposure, cancer **incidence** rates in the worker cohort (the basis of the URE calculation in EPA's IRIS assessment) would be the same as national cancer **mortality** rates for the general population." [**emphasis added**]. If EPA believes that incidence rates and mortality rates are the same, that may be part of the problem. This misunderstanding may be derived from the fact that although EPA fit a model to lymphoid cancer mortality in the NIOSH study, EPA inappropriately applied US population lymphoid cancer incidence rates to calculate risks. The NIOSH study reports lymphoid cancer mortality but does not have information on lymphoid cancer incidence, as stated by EPA. Thus, TCEQ could not assume that the general population lymphoid cancer mortality rates were equal to the NIOSH lymphoid cancer incidence rates (because there are no data on lymphoid cancer incidence in the NIOSH study).

Assuming that EPA's assertion is a typographical error, and EPA meant mortality instead of incidence, the comment that TCEQ used general population lymphoid cancer mortality rates is true, but that does not make the approach flawed. In addition to performing the analyses using general population lymphoid cancer death rates, TCEQ performed sensitivity analyses assuming a healthy worker effect (i.e., that NIOSH workers lymphoid cancer mortality rates in the absence of EtO exposures were lower than the general population lymphoid cancer mortality rates). Results did not change even after assuming that NIOSH workers are healthier than the general population; namely, TCEQ's model still predicted the number of observed lymphoid cancer deaths with 95% confidence and EPA's model still statistically significantly, at the 5% significance level, overestimated the number of lymphoid cancer deaths in the NIOSH study. This sensitivity analysis is documented in TCEQ DSD section A.3.3.2 Sensitivity Analysis Assuming a Healthy Worker Effect for Lymphoid Cancer Mortality, and was conducted even though (as discussed in the DSD) the lymphoid mortality rate in unexposed NIOSH workers was not statistically different than that in the general U.S. population. Most specifically, for the male NIOSH workers that drive lymphoid cancer risk and serve as the basis of TCEQ's URF, the lymphoid cancer SMR in unexposed NIOSH males is 1.03 (6/5.8; with a 95% CI of 0.38, 2.25), which does not demonstrate a healthy worker effect for lymphoid cancer mortality.

4.a.3. Detailed Response to EPA comments about TCEQ use of Population Hazard Rates

EPA may have overlooked the well documented sensitivity analyses that TCEQ performed to account for any potential healthy worker effect. TCEQ discusses the issue of the healthy worker effect in Sections 3.1.1.2 Healthy Worker Effect, and 4.2.3 Model Accuracy Evaluation - Model Predictions versus Observed of the document. TCEQ then gave more details in the appendices in Sections A.3.3.1 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. TCEQ also documented a sensitivity analysis in A.3.3.2 Sensitivity Analysis Assuming a Healthy Worker Effect for Lymphoid Cancer Mortality. Kirkeleit et al. (2013) reports that the healthy worker effect for lymphoid cancer incidence is only 3% for male workers with no effect for female workers. However, TCEQ conservatively used 15% for males and 16% for females for the healthy worker effect, based on mortality from all malignant neoplasms (Kirkeleit et al. 2013). That is, TCEQ's sensitivity analysis used the

highest reasonable healthy worker effect in the published literature when estimating the expected number of lymphoid cancer deaths in the NIOSH study. The results, however, were the same. The TCEQ model still estimated within a 95% confidence interval the observed number of lymphoid cancer deaths in the NIOSH study while EPA's model statistically significantly, at the 5% significance level, overpredicted the observed number of lymphoid cancer deaths in the NIOSH study.

4.b. TCEQ Calculations are Correct and can be used with Lagged Cumulative Exposures

4.b.1. EPA's Comments about Predicted Number of Lymphoid Cancer Deaths

Page 23: "2) TCEQ's analyses to justify their model choice were erroneous and relied on flawed assumptions."

Page 31: "TCEQ made errors in their calculation of projected cancer rates and in the "reality check" calculations they used to justify their model choice. TCEQ's "reality check" calculations are not statistically appropriate and do not support TCEQ's claims."

EPA 2022b: Pages 90-91:
"(2) Calculation of projected cancer rates. TCEQ (Assessment, pg. 100) uses a numerical example to show their approach to calculate how to "calculate the expected number of lymphoid cancer deaths in the NIOSH study". EPA reviewed this information and in particular the calculations shown in Tables 32 and 33. EPA identified several concerns:

- These tables show expected mortality calculations extending until 2008. Follow-up of workers in the NIOSH cancer mortality study ended in 1998. This raises concerns regarding whether expected risks through the end of follow-up were correctly calculated in the TCEQ analysis.
- The calculations in Table 33 show no accounting for the 15-year lag between exposure and cancer risk as used in EPA modeling and also stated to be an assumption in modeling by TCEQ. Unless lag is addressed in this modeling, calculated risk estimates will again be inappropriately high.
- IRIS (Table D-26) tabulated the observed number of cases of lymphoid cancer in the exposure quintiles of the NIOSH cohort. In contrast with what is shown in TCEQ Table 30, the numbers of observed cases are not fixed at 11 per quintile, but vary, e.g., 13 deaths occurred in the top quintile. These results will affect reported comparisons between predicted and observed cancer mortality."

4.b.2. Executive Summary of Response to EPA comments about TCEQ Predicted Number of Lymphoid Cancer Deaths

The EPA's comments on pages 23 and 31 are vague. However, EPA's response to comments provided on pages 90 and 91 gives more information about what EPA considers erroneous about TCEQ's modeling. EPA's comments, however, are based on a draft of TCEQ's DSD and not on the final TCEQ DSD published on May 15, 2020. TCEQ's detailed description of the analyses is in Section A.3 in the final report. The numerical calculation EPA mentions are now part of the final TCEQ DSD Section A3.5 Sample Calculations of the Expected and Expected* used in the Derivation of SMR and SMR*. EPA is correct in that in Tables 32 and 33 "These tables show

expected mortality calculations extending until 2008. Follow-up of workers in the NIOSH cancer mortality study ended in 1998." EPA, however, failed to read that the calculations in Tables 32 and 33 are for a hypothetical (hypothetical means that it is "imagined for purposes of example") individual and not for one of the NIOSH workers. EPA's second concern is that "Table 33 show no accounting for the 15-year lag between exposure and cancer risk." The reason is the same; that is, the calculation was based on a model used for illustration purposes and assumed unlagged cumulative exposures to simplify the example. EPA's third concern is the comparison by quintiles. EPA's quintiles are not true quintiles, but rather have different number of lymphoid cancer deaths in each "quintile". TCEQ performed the analyses using true quintiles whereby each quintile has the same number of lymphoid cancer deaths. Although EPA is correct that using different exposure intervals would result in different comparisons, it is also true that no matter how the quintiles are defined, EPA's model statistically significantly overestimates the observed number of lymphoid cancer deaths in the NIOSH study at every quintile (except for one quintile when using the MLE) and overall, while TCEQ model estimates with 95% confidence the number of lymphoid cancer deaths in the NIOSH study for every quintile and overall. Furthermore, with the information given in the TCEQ DSD, EPA could do the calculations themselves and be more specific about the magnitude of the errors they purportedly found.

4.b.3. Detailed Response to EPA comments about TCEQ Reality Check

Although comments on pages 23 and 31 of the MON Final Rule regarding the correctness of the TCEQ reality check are vague, the EPA Response to Comments document offers a more detailed explanation of their concerns. Though the EPA's concerns in the Response to Comments are based on an earlier draft version of the final TCEQ DSD, their concerns can still be addressed and were documented in TCEQ Section A.3 of the appendices.

First concern. Referring to TCEQ Tables 32 and 33, EPA states, "These tables show expected mortality calculations extending until 2008. Follow-up of workers in the NIOSH cancer mortality study ended in 1998. This raises concerns regarding whether expected risks through the end of follow-up were correctly calculated in the TCEQ analysis."

Response to first concern: EPA is correct in stating that the calculations in Tables 32 and 33 extend through 2008, and that the NIOSH cohort was followed through 1998. EPA's concern, however, is unfounded. EPA may have overlooked the following statement that clearly states that the calculations in Tables 32 and 33 are based on a hypothetical individual and not for one of the NIOSH workers. Furthermore, TCEQ could not use the information of a NIOSH worker for illustration for two reasons: 1) NIOSH has custody of the data; and 2) NIOSH would not allow the use of worker data in order to protect the identity of the individual workers. Thus, TCEQ created a hypothetical individual (not associated with any real worker either in time or space).

TCEQ clearly states:

"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." [**emphasis added**].

Second Concern: "The calculations in Table 33 show no accounting for the 15-year lag between exposure and cancer risk as used in EPA modeling and also stated to be an assumption in modeling by TCEQ. Unless lag is addressed in this modeling, calculated risk estimates will again be inappropriately high"

Response to second concern: EPA's concern is again unfounded. The model used was for illustration purposes only and was not meant to imply that it is the EPA or TCEQ model or to imply that it was based on cumulative lagged exposure. Unlagged cumulative exposure was used to simplify the example. However, the calculations of the results presented by TCEQ do include the 15-year lag if the model fit used cumulative exposure lagged 15 years.

TCEQ clearly states:

"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." [**emphasis added**].

To help EPA see how calculations would be performed **if lagged cumulative exposure were assumed**, TCEQ recreates here TCEQ Tables 32 and 33 for the same **hypothetical** worker and the same model described in the final TCEQ DSD. The calculations in these tables follow the **hypothetical** worker only through 1998 (EPA's first concern) and uses cumulative exposures lagged 15 years (EPA's second concern) (See the appendix at the end of this report for results and details of these calculations.)

Third concern. EPA's third concern refers to the comparison of observed versus predicted number of lymphoid cancer deaths by quintile in TCEQ Table 30. EPA states, "IRIS (Table D-26) tabulated the observed number of cases of lymphoid cancer in the exposure quintiles of the NIOSH cohort. In contrast with what is shown in TCEQ Table 30, the numbers of observed cases are not fixed at 11 per quintile, but vary, e.g., 13 deaths occurred in the top quintile. These results will affect reported comparisons between predicted and observed cancer mortality."

Response to third concern: The most statistically efficient way to group the number of exposed cases into any number of quartiles is to create exposure intervals that have approximately the same number of cases in each quartile of exposed workers. TCEQ followed this statistical tenet and created four intervals of non-zero cumulative exposures lagged 15 years (in addition to the lagged-out unexposed group) to have five quintiles with exactly 11 lymphoid cancer deaths in each of the groups with non-zero cumulative exposure to EtO lagged 15 years. EPA, in contrast, used exposure intervals defined for four unlagged cumulative exposures to EtO for lymphohematopoietic cancers in the NIOSH study (Steenland et al., 2004), as if they were defined for cumulative exposures lagged 15 years and for quintiles of lymphoid cancer deaths in the NIOSH study. For this reason, EPA's "quintiles" do not have the same number of lymphoid cancer deaths in each group of cumulative exposures.

Although EPA is correct in stating that using different exposure intervals would result in different comparisons, it is also true that no matter how the quintiles are defined for the NOISH study, the EPA model statistically significantly overestimates the observed number of lymphoid cancer deaths in the NIOSH study at every quintile (except for one quintile using the MLE) and overall, while the TCEQ model estimates with 95% confidence the number of lymphoid cancer deaths in the NIOSH study for every quintile and overall (see Table 1 below). Furthermore, with the information given in the TCEQ DSD, EPA could do the calculations themselves and be more specific about the magnitude of the errors they purportedly found.

TCEQ calculated the observed and predicted number of lymphoid cancer deaths for each quintile for the TCEQ model and the EPA model using the definitions of quintiles by the TCEQ or the EPA. The results are as follows: (note that, regardless of how quintiles are defined, the TCEQ model predicts, with a 95% confidence interval, the observed number of lymphoid cancer deaths in every quintile and the EPA model statistically significantly, at the 5% significance level, overestimates the observed number of lymphoid cancer deaths observed in the NIOSH study in all but the third quintile).

TCEQ also calculated the 95% confidence intervals for the number of lymphoid deaths observed in the four exposure quintiles using the Poisson distribution as recommended by Breslow and Day (1987) "the observed number of deaths D is approximately Poisson distributed with mean and variance both equal to E*."

Table 1. Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities per Exposure Quintile using Cox Log-linear and Two-Piece Spline Models Using the TCEQ Quintiles, or the EPA Quintiles.

Quintile using Cox Log-Linear and Two-Piece Spline Models Model a	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**
Results from TCEQ Table 30 Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities per Exposure Quintile using Cox, Linear, and Two-Piece Spline Models				
Observed	*11*	*11*	*11*	*11*
1. S&A – Loglinear – 15-yr lag (MLE) – **Model Preferred by TCEQ**	14.4 (8.1, 28.9) (7.0, 21.8)[1]	8.0 (4.5, 16.1) (2.4, 13.5)	9.4 (5.2, 18.8) (3.3, 15.4)	9.1 (5.1, 18.3) (3.2, 15.0)
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)** **(11.9, 29.8)**	17.6 (9.8, 35.2) (9.3, 25.8)	**20.8 (11.6, 41.7)** **(11.8, 29.7)**	**20.9 (11.7, 41.9)** **(11.9, 29.8)**
Results parallel to TCEQ Table 30 Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities per Exposure Quintile using Cox Log-linear and Two-Piece Spline Models Using Quintiles with the same Number of Lymphoid Cancer Deaths Listed in EPA Table D-26				
Observed	*10*	*11*	*10*	*13*
1. S&A – Loglinear – 15-yr lag (MLE) – **Model Preferred by TCEQ**	14.1 (7.7, 29.5) (6.7, 21.5)	6.7 (3.7, 13.4) (1.6, 11.8)	9.3 (5.1, 19.5) (3.3, 15.3)	10.8 (6.3, 20.3) (4.3, 17.2)
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – **Model Preferred by USEPA**	**20.3 (11.1, 42.5)** **(11.4, 29.1)**	14.6 (8.2, 29.3) (7.1, 22.0)	**20.6 (11.2, 43.1)** **(11.7, 29.5)**	**24.6 (14.4, 46.3)** **(14.9, 34.3)**

[1]The 95% confidence intervals on the number of lymphoid deaths in each quintile (second row in each cell) were calculated using the Poisson distribution as suggested by Breslow and Day (1987) with the mean equal to the predicted number of lymphoid deaths in the quintile.
Results in bold are statistically-significantly higher than the observed cancers in the cohort.

4.c. TCEQ Used Well-Established Statistical Methods to Define Confidence Intervals

4.c.1. EPA comments about TCEQ Bounds on Number of Lymphoid Cancer Deaths

Page 23: "3) the statistical confidence intervals TCEQ developed for the "predicted" numbers of cancers."

EPA 2022b: Pages 91:
"(3) TCEQ's proposed confidence intervals on predicted cancer deaths.

TCEQ describes their analysis using a published formula for confidence limits on an SMR (ratio between cases observed in a cohort and predicted cases from the general population). They then take the inverse of this interval to represent a ratio of expected over observed. EPA notes that that step, while allowing for calculation of a confidence interval may not yield an interval with good statistical properties (e. g., expected length). However, the TCEQ then states (Assessment, pg. 92): "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." TCEQ, does not specify how they performed this "easy" step, but it appears that they multiplied the confidence interval for SMR-1 by the observed number of lymphoid cancer deaths in the cohort. EPA verified this calculation had been used in TCEQ's calculation for deaths in unexposed workers on page 101 where TCEQ presented both the original confidence interval on an SMR and their claimed confidence interval on expected deaths. Such an approach is not correct statistical practice and does not yield a statistical confidence interval on expected deaths. The confidence interval on the SMR (or its inverse) explicitly reflects expected variability in observed deaths. A calculation that combines an observed result (cancer deaths) and a confidence interval incorporating uncertainty in that result does not then yield a valid confidence interval. EPA concludes that TCEQ made an error in their math and the calculations utilized do not yield statistically valid (or useable) confidence intervals. The TCEQ proposal to calculate confidence intervals for expected values - which are not random variables - represents an error in statistical methodology.

EPA also notes that TCEQ had received strong comments from one of their peer reviewers regarding these so called "reality check" calculations. "Expert 5" (the comments from TCEQ reviewers were anonymized) stated:

"…, I do not understand how confidence bounds on the predicted numbers were derived. … TCEQ needs to clearly delineate and explain how these calculations were made and the rationale behind them. In conclusion, I find the arguments in the DSD to be neither clearly laid out nor scientifically appropriate."

While the length of the TCEQ Appendix on "reality checks" was expanded in their final assessment, the key language describing the calculation of a "confidence interval" on expected cases was not changed and remains vague and incomplete in both the draft and the final assessment (pg. 98 draft assessment and pg. 92 final assessment)."

4.c.2. Executive Summary of Response to EPA comments about TCEQ Bounds on Number of Lymphoid Cancer Deaths

EPA's claim that the confidence intervals presented by TCEQ "may not yield an interval with good statistical properties" is a moot point. TCEQ conclusions drawn comparing the number of lymphoid cancer deaths to the inverse of the SMRs and their confidence intervals multiplied by the actual number of lymphoid cancer deaths are the same conclusions drawn when comparing the SMRs and their confidence intervals with 1.0. That is, if the upper end on the confidence interval on SMRs is less than 1.0, then the lower end of the confidence interval on the expected number of lymphoid cancer deaths exceeds the observed number of lymphoid cancer deaths

(because SMR = Obs/Exp). On the other hand, if the confidence interval on SMRs includes 1.00, then the confidence interval on the expected number of lymphoid cancer deaths includes the observed number of lymphoid cancer deaths. TCEQ's presentation and discussion of confidence intervals with the observed number of lymphoid cancer deaths, rather that the confidence intervals on the SMRs, was done to provide clarity. Unfortunately, EPA quotes the comment of an expert who did not understand how confidence limits were created. Fortunately, EPA did understand how the confidence limits were calculated, although they did not agree with how the method by which this was done, which we address below. In addition, TCEQ went a step further and evaluated the models by building confidence intervals on the observed number of lymphoid deaths. Results were similar.

4.c.3. Detailed Response to EPA comments about TCEQ Bounds on Number of Lymphoid Cancer Deaths

Apparently, EPA mistyped "SMR-1" in the response to comments when quoting TCEQ's calculations on the bound of the expected number of lymphoid cancer deaths. It seems, though, that EPA did understand that TCEQ's original text reads SMR^{-1} (which is equivalent to 1/SMR) because the comments indicate that EPA meant to write SMR^{-1}.

EPA claims that the confidence intervals presented by TCEQ "may not yield an interval with good statistical properties", but this does not change the conclusions drawn by TCEQ using the confidence intervals developed to compare with the number of observed lymphoid cancer deaths. For clarity of presentation and discussion, TCEQ compared the expected number of lymphoid cancer deaths and its confidence interval with the observed number of lymphoid cancer deaths. These numbers, as discussed by TCEQ, and correctly interpreted by EPA, were derived by multiplying the number of observed lymphoid cancer deaths by the inverse of the SMR (SMR^{-1}) and the inverse of the confidence limits on the SMR. The conclusions drawn by TCEQ using these calculations are *identical* to the conclusions that would be reached had the SMRs with their confidence intervals been compared to 100% (the standard comparison when using SMRs). That is, Table 2 below (extracted from Table 29 in TCEQ DSD) lists the following for the TCEQ model and EPA model:

Table 2. Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities using Cox Log-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
1. S&A – Loglinear – 15-yr lag (MLE) a – Model Preferred by TCEQ	2.81E-06	52.42	98.9%	(40.1, 70.0)
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model used by USEPA	7.58E-04	91.69	173.0%	(70.1, 122.4)

Note: actual observed number of lymphoid cancer deaths was 53.

If SMRs were used to make the comparisons, then the following Table 3 (alternative Table 2 using SMRs) would be calculated.

Table 3. -SMR: Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities using Cox Log-linear and Two-Piece Spline Models

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × SMR = Observed /Predicted	95% CI on SMR if the Model were True
1. S&A – Loglinear – 15-yr lag (MLE) a – Model Preferred by TCEQ	2.81E-06	52.42	101.11%	(78.8%, 137.6%)
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model used by USEPA	7.58E-04	91.69	57.80%	(43.3%, 75.6%)

Note: actual observed number of lymphoid cancer deaths was 53.

The results in Table 2 (taken from TCEQ Table 29) indicate that the confidence interval on the expected number of lymphoid cancer deaths predicted by the TCEQ model includes the observed 53 lymphoid cancer deaths in the NIOSH study. Table 2 also indicates that the confidence interval on the expected number of lymphoid cancer deaths predicted by the EPA model statistically significantly overpredicts (the lower end of the confidence interval exceeds 53) the observed 53 lymphoid cancer deaths in the NIOSH study.

This same conclusion is drawn from Table 3 using SMRs and their confidence intervals. The results in Table 3 indicate that the confidence interval on the SMR for lymphoid cancer deaths, if the TCEQ model were used, includes 100% (that is, the predicted number of deaths by the TCEQ model is consistent with the observed 53 lymphoid cancer deaths in the NIOSH study). Table 3 also indicates that the confidence interval on the SMR for lymphoid cancer deaths, if the EPA model were used, is statistically significantly less than 100% because it excludes 100% (that is, the predicted number of deaths by the EPA model is statistically significantly greater than the observed 53 lymphoid cancer deaths in the NIOSH study). That is, an SMR (observed/expected) less than 100% means that observed number is less than the expected number.

The relationship between SMR and its bounds and SMR^{-1} and the reciprocal of the bounds can also be seen as a basic algebraic fact. If the following relationship for the SMR and its bounds is true,

$$SMR_{LCL} < SMR < SMR_{UCL}$$

then it follows that

$$1/SMR_{LCL} > 1/SMR > 1/SMR_{UCL}$$

and it also follows that if all the terms in the resulting inequalities are multiplied by a positive number (e.g., Q), the inequalities persist, i.e.,

$$Q/SMR_{LCL} > Q/SMR > Q/SMR_{UCL}$$

The above inequality relationships will hold for any number replacing the SMR (e.g., 100%) as long as it is between SMR_{LCL} and SMR_{UCL}. That means, if the confidence interval of an SMR includes 100% then the confidence interval formed by the reciprocal will include the reciprocal of 100%. Conversely, if the confidence interval of an SMR does not includes 100% then the confidence interval formed by the reciprocal of the SMR will not include the reciprocal of 100%.

To further address EPA's concern that "Such an approach is not correct statistical practice and does not yield a statistical confidence interval on expected deaths. The confidence interval on the SMR (or its inverse) explicitly reflects expected variability in observed deaths. A calculation that combines an observed result (cancer deaths) and a confidence interval incorporating uncertainty in that result does not then yield a valid confidence interval.", the TCEQ calculated the confidence interval on the observed number of cancer deaths and compared with expected number of cancer deaths predicted by EPA and TCEQ models (Table 4). This approach is recommended by Breslow and Day (1987) where they state, "the observed number of deaths D is approximately Poisson distributed with mean and variance both equal to E*."

Table 4. Predicted Number of NIOSH Cohort Lymphoid Cancer Mortalities using Cox Log-linear and Two-Piece Spline Models Compared with the 95% Confidence Interval of the Observed Number of Lymphoid Deaths

Model	Slope Parameter (per ppm-day)	Predicted if the Model were True	95% CI on the Observed Number of Lymphoid Deaths[1]
1. S&A – Loglinear – 15-yr lag (MLE) a – Model Preferred by TCEQ	2.81E-06	52.42	(38.2, 66.6)
9. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days – Model used by USEPA	7.58E-04	91.69	(72.9, 110.4)

[1]The 95% confidence interval on the number of lymphoid deaths was calculated using the Poisson distribution as suggested by Breslow and Day (1987) with the mean equal to the predicted number of lymphoid deaths.
Note: actual observed number of lymphoid cancer deaths was 53.

The conclusions are identical, regardless of what method is used to compare the predicted number of lymphoid cancer deaths with the number of lymphoid cancer deaths observed (Tables 2, 3, and 4). EPA's model statistically significantly overestimates the observed number of lymphoid cancer deaths observed in the NISOH study. The TCEQ model, on the other hand, estimates the number of lymphoid cancer deaths within the 95% confidence interval of the number of deaths observed in the NIOSH study.

EPA, unfortunately, quotes the opinion about the confidence interval of one of the experts who reviewed TCEQ DSD, but who lacked understanding of the statistics being used. The quote from this expert did not reflect the opinions of most experts. Had EPA reported all expert's opinions, they would have also quoted Expert 2 saying, "The checks on model predictiveness and so-called reality checks are reasonably done." Also, Expert 3 writing, "The use of these "reality checks" is well-justified and clearly presented. In general, modeling of this sort can generate implausible results given the many untestable assumptions underlying it, and seeking multiple approaches to judging whether or not they are sensible is critically important. Relating predicted effects of EtO on disease occurrence to the predicted impact of endogenous exposure levels, occupational exposures, and community exposures is very helpful to judging the general reasonableness of the model. While such exercises cannot confirm that the model is correct in an absolute sense, it can raise a red flag to indicate when something is clearly erroneous." Expert 4 added, "I appreciated TCEQ's attempts to "reality check", "benchmark" or "ground truth" their estimates of risk, based on the selected model." Expert 6 stated, "I agree that accurate predictions of cancers over the entire dose range are a desirable feature of a model." Expert 1 did not comment on the topic because it was out of his/her area of expertise. That is, one expert acknowledged that it was out of his/her area of expertise, four experts had a positive opinion of the exercise, and one expert (Expert 5 quoted by EPA) did not understand how it was done and EPA unfairly emphasizes that opinion.

4.d. TCEQ's Model is Consistent with Categorical Rate Ratios at Low and High Exposures to EtO

4.d.1. EPA's Comments about TCEQ model

EPA 2022b: Pages 49-50:
"This model predicts notably lower risks than all other models under consideration. It is important to note that both the EPA and TCEQ models are linear in the low dose range, a general property recommended for assessing mutagenic carcinogens. Where the two models differ is in their ability to represent dose-response over the observed range of elevated EtO doses seen in the NIOSH study. While the log-linear Cox model has been a useful tool in many epidemiological studies, it has a specific limitation in regard to its application for EtO. The NIOSH workers have a very broad range of exposure. However, the reported exposure group average results (categorical rates as calculated using the standard Cox procedure) found elevated risks of lymphoid tumors at relatively low levels of exposure (e.g., for exposures less than several thousand "ppm-days" as reported in Steenland, 2004). The log-linear Cox model has the property that if it predicts an elevated risk at a given dose, it then becomes extremely steep for doses that are substantially higher. Given the broad range of doses in the NIOSH study, the log-linear Cox model is incapable of providing estimates of risk that are consistent with the categorical findings in the lower dose ranges of the NIOSH study without "exploding" upward at the high doses received by some other workers in the study. That is this model is incapable of representing the increased cancer risk estimated with the categorical analyses at lower dose ranges without making entirely unreasonable risk predictions at high doses. The graph below shows relative risk levels versus dose as predicted by a range of log-linear model forms, each drawn to be consistent with the estimated risk for one of the categorical exposure groups. All of these log-linear model realizations predict unreasonably high risks for the highly exposed workers in the cohort (in

which maximum individual exposures exceed 500,000 ppm-days)."

4.d.2. TCEQ Executive Summary of Response

First, TCEQ did not fit individual categorical RRs as the examples given by EPA in their figures on page 51. Second, EPA's criticism of TCEQ's model would apply to any statistical model, including EPA's model. (It is one of the basic tenets of statistical model fitting that regression models are valid only within the range of the explanatory variable used to fit the model, e.g., the range of cumulative exposures to EtO used to fit the model.) The analysis EPA presented in this section does not make any sense from a statistical modeling point of view. Essentially, EPA formed four pairs of categorical RRs (RR at zero dose (RR=1) and every RR for the other four quintiles). EPA then fit the log-linear model (solving the equation for the log-linear model because a pair of points can be fit perfectly with a model with one parameter) to every pair and then they extrapolated the fit of those models to much higher cumulative exposures. Any model will fail miserably when "tested" the way EPA tested the log-linear model. Below, TCEQ applied the same "test" to EPA's model and showed that it fails in the same way. Third, when the prediction or RRs from the EPA and TCEQ models are compared, the EPA model-estimated RRs are always greater than the TCEQ model-estimated RRs for cumulative exposures in the range of exposures experienced by NIOSH workers. The RRs from the EPA model go from 1 at zero ppm-days to 8.6 at 642,925 ppm-days (the maximum cumulative exposure in the NIOSH study). The RRs from the TCEQ model, on the other hand, go from 1 at zero ppm-days to 6.1 at 642,925 ppm-days. The log-linear model used by TCEQ results in more realistic RRs as demonstrated by the superiority of this model in estimating the actual number of lymphoid cancer deaths.

4.d.3. TCEQ Detailed Response

This comment again demonstrates that EPA believes that the categorical RRs estimated for five exposure groups (quintiles) are the data and that any good model should conform to these categorical RRs. Hopefully this has been clarified in the response to EPA's other misunderstandings. Neither TCEQ nor EPA fit their models to the RRs of the five quintiles; they were fitted to the individual NIOSH epidemiological data. Neither TCEQ nor EPA fit models to each quintile RR as EPA has done in their criticism of TCEQ model. Had TCEQ or EPA fit their models to each quintile RR, both models would have failed in predicting any reasonable categorical RRs for other quintiles. That is, EPA's exercise to "prove" that the TCEQ model could result in unreasonable estimates of RRs for higher cumulative exposures would also be true for EPA's two-piece spline model (EPA's two-piece spline model will default to a linear model when fitting only two points) because EPA's model also "explodes" upwards when fit to RRs in the lower quintiles.

EPA's criticism about TCEQ's model exploding upwards (which applies to EPAs model also) violates one of the standard assumptions of regression modeling; that is, predictions based on regression models are valid only within the range of the independent variable (cumulative exposure) fit by the model. In other words, if the model is fit only to the unexposed and the first quintile, the model is valid only for exposures between zero and the cumulative exposure for the first quintile. In such a case, any extrapolation beyond the cumulative exposure for the first

quintile is subject to excessive uncertainty. Although TCEQ disagrees with the model extrapolation done by EPA in the figure on page 51 of EPA 2022b, TCEQ used EPA's inappropriate methodology to illustrate that EPA's model would have the same problem when EPA's flawed logic is used. The following is analogous to the figure on page 51 of EPA 2022b but using EPA's model.

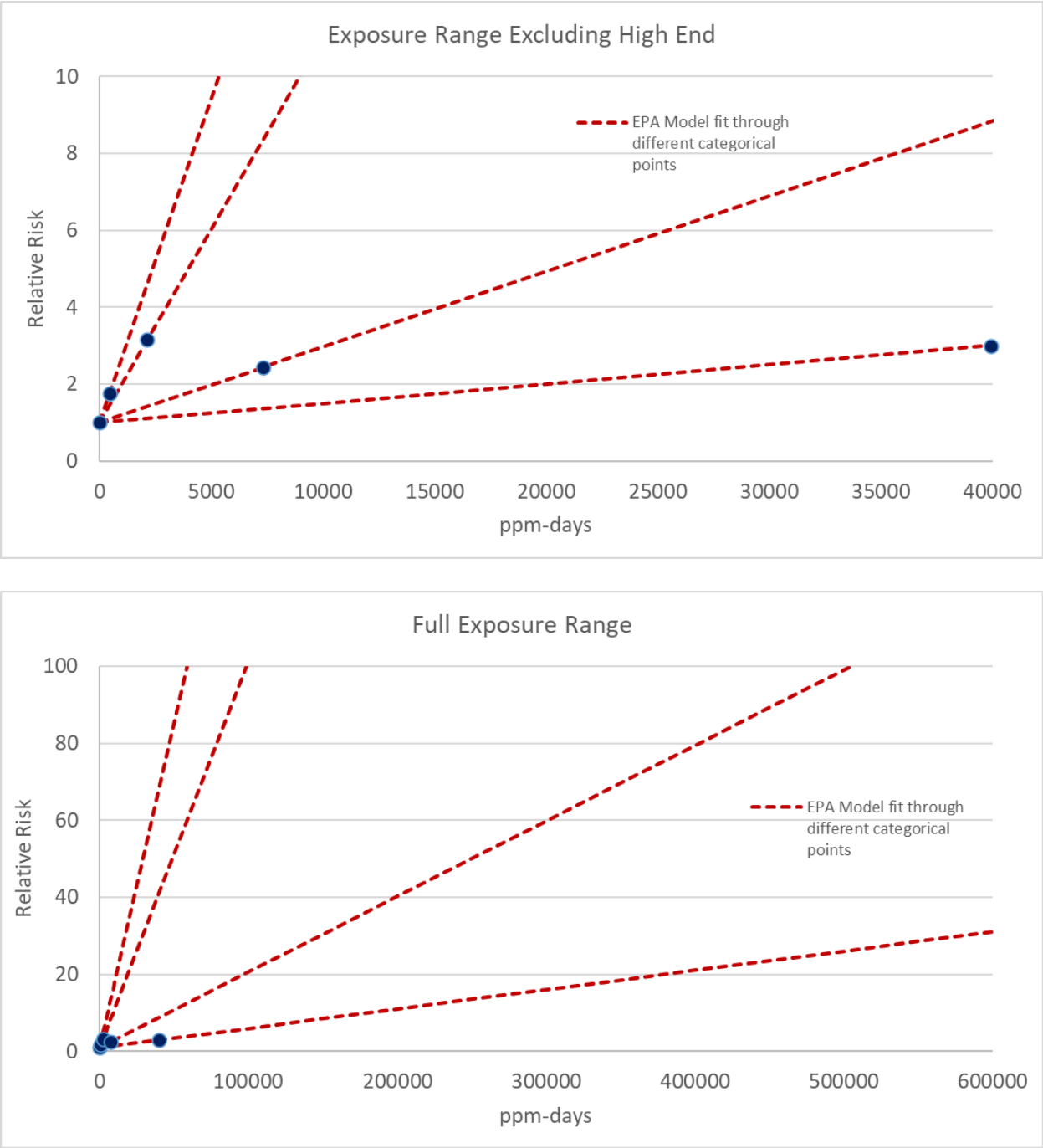

Figure 1. EPA model fit through different categorical points for the exposure range excluding the high end, and for the full exposure range.

The criticism that TCEQ's model "explodes" upwards resulting in unrealistic estimates of the RRs at the highest cumulative exposures to EtO is unfounded. TCEQ evaluated the estimated RRs for the standard Cox proportional hazards model used by TCEQ and EPA's two-piece spline model. The RRs estimated by EPA are larger than the RRs estimated by TCEQ's model for the entire range of exposures in the NIOSH study. These results hold even at the highest cumulative exposure to EtO in the NIOSH study (642,925 ppm-days). EPA's model predicts a RR of 8.6 versus 6.1 predicted by TCEQ's model at the highest exposure. TCEQ Figure 14 shows that the TCEQ model and the EPA model conform approximately equally to categorical RRs defined to include exactly one lymphoid cancer death in each category for the full range of exposures of lymphoid cancer decedents.

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Appendix

Detailed calculations of the expected number of cause specific deaths when the end of follow up is 12/31/1998 and the model assumes cumulative exposure lagged 15 years.
Equivalent to TCEQ Sections A.3.5.1 and A.3.5.2

A3.5.1 Expected Number of Cause-Specific Deaths in a Study Group – Follow up through 12/31/1998

The calculations for the contribution of the hypothetical worker to the *Expected* number of lymphoid cancer deaths in the study group are in Table A.1 below (patterned based on Table 32 in the TCEQ DSD, but with end of follow up = 12/31/1998). 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 (TCEQ 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 that for 1960. (Note that the age group in TCEQ Tables 33 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 (TCEQ Tables 34 to 38). Thus, the observation intervals in Table 32 (end of follow up = 12/31/1998) are split by calendar year with occasional intervals defined to accommodate observation intervals corresponding to different age groups. In order to help the reader to follow the calculations, the applicable hazard rates are boldfaced in TCEQ Tables 34 to 38.

The last column in Table A.1 is the hazard rate per 100,000 person-days 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 A.1). The sum of all values on the last column (68437.55) 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 0.001866 (=68137.55/(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 A.1 (end of follow up = 12/31/1998) the *CumulativeProbability* is equal to 0.001864.

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 A.1 (Based on Table 32 of TCEQ DSD, but with end of follow up = 12/31/1998): 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
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

[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 cancer deaths per 100,000 per year" is the hazard rate for lymphoid cancer 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– Follow up through 12/31/1998 and Cumulative Exposure Lagged 15 Years

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 A.2 (patterned based on Table 32 in the TCEQ DSD, but with end of follow up = 12/31/1998 and cumulative exposure lagged 15 years). 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 the worker was exposed to a concentration of 20 ppm from 1/1/1965 through 12/31/1968. From 1/1/1969 through the end of follow-up on 12/31/1998 the worker was not exposed to EtO at his workplace.

Cumulative exposures (ppm-days) lagged 15 years are calculated as follows. For the first 15 years of employment, the cumulative lagged exposure is zero ppm-days. Thus, from start of employment on 6/22/1964 to 6/22/1979 the cumulative exposure lagged 15 years is equal to zero. For the observation period 6/22/1979 to 9/11/1979 (81 days), the worker accumulated exposure lagged 15 years is 1215 ppm-days (=81×15). Because the worker was unexposed from 9/12/1964 to 12/31/1964, his cumulative exposure to EtO lagged 15 years remained at 1215 ppm-days from 9/12/1979 through 12/31/1979. 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 (=365×20) during the interval, to end with 8515 ppm-days (=1215+7300) on 12/31/1980 after accounting for a 15-year lag. During 1966 (1/1/1966 through 12/31/1966) the worker accumulated another 7300 ppm-days to end with 15815 ppm-days (=8515+7300) of 15-year lagged exposure on 12/31/1981. Similarly, in 1967 the worker accumulated another 7300 ppm-days to end the year of 1981 with 23115 ppm-days (=15815+7300) of lagged exposure. 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 with 24595 ppm-days (=23115+1480) of 15-year lagged exposure on 3/14/1983. 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 of 1983 with 30435 (=24595+5840) ppm-days lagged 15 years. Because the worker was not occupationally exposed to EtO starting on 1/1/1969 his cumulative EtO exposure lagged 15 years remained at 30345 ppm-days after 12/31/1983.

The reference population lymphoid cancer mortality rates are taken from TCEQ 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 (TCEQ 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 TCEQ 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 A.2 are split by calendar year with occasional intervals defined to accommodate observation intervals corresponding to different age groups. In order to help the reader to follow the calculations, the applicable hazard rates are boldfaced in TCEQ Tables 34 to 38.

The penultimate column in Table A.2 is the rate ratio function that multiplies the reference population lymphoid cancer 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 A.2 the *RR(d)* is calculated at the midpoint of the cumulative exposure in the interval (the cumulative exposure lagged 15 years of exposure history is zero). Thus, for the first interval in the table after 15 years (6/22/1979 to 9/11/1979) the cumulative exposure lagged 15 years is 1215 and the midpoint is 607.5 ppm-days (=(1215+0)/2) resulting in a *RR(d)* for this interval of 1.00288370 ($=e^{4.74\times10^{-6}\times607.5}$). For the second interval (9/12/1979 to 12/31/1979), 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 (1/1/1980 to 12/31/1985) 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 A.2.

The last column in Table A.2 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 (76822.08009) 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 0.002103274 (=76822.08009/(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 A.2 the *CumulativeProbability** is equal to 0.002101.

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 A.2 (Based on Table 32 of TCEQ DSD, but with end of follow up = 12/31/1998 and cumulative exposure lagged 15 years): 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	0	1960	20-24	1.226908823	1.00000000	99.37961
9/12/1964	12/31/1964	21.50	21.80	111	0	1960	20-24	1.226908823	1.00000000	136.18688
1/1/1965	12/31/1965	21.80	22.80	365	0	1960	20-24	1.226908823	1.00000000	447.82172
1/1/1966	12/31/1966	22.80	23.80	365	0	1960	20-24	1.226908823	1.00000000	447.82172
1/1/1967	12/31/1967	23.80	24.80	365	0	1960	20-24	1.226908823	1.00000000	447.82172
1/1/1968	3/15/1968	24.80	25.00	74	0	1968	20-24	1.853888452	1.00000000	137.18775
3/16/1968	12/31/1968	25.01	25.80	292	0	1968	25-34	1.948937829	1.00000000	569.08985
1/1/1969	12/31/1969	25.80	26.80	365	0	1969	25-34	1.826095184	1.00000000	666.52474
1/1/1970	12/31/1970	26.80	27.80	365	0	1970	25-34	1.642712607	1.00000000	599.59010
1/1/1971	12/31/1971	27.80	28.80	365	0	1971	25-34	1.866738121	1.00000000	681.35941
1/1/1972	12/31/1972	28.80	29.80	366	0	1972	25-34	1.436085831	1.00000000	525.60741
1/1/1973	12/31/1973	29.80	30.80	365	0	1973	25-34	1.559640328	1.00000000	569.26872
1/1/1974	12/31/1974	30.80	31.80	365	0	1974	25-34	1.639344262	1.00000000	598.36066
1/1/1975	12/31/1975	31.80	32.80	365	0	1975	25-34	1.467136150	1.00000000	535.50469
1/1/1976	12/31/1976	32.80	33.80	366	0	1976	25-34	1.432199802	1.00000000	524.18513
1/1/1977	12/31/1977	33.80	34.80	365	0	1977	25-34	1.456079472	1.00000000	531.46901
1/1/1978	3/15/1978	34.80	35.00	74	0	1978	25-34	1.578877537	1.00000000	116.83694
3/16/1978	12/31/1978	35.01	35.80	291	0	1978	35-44	3.414494959	1.00000000	993.61803
1/1/1979	6/22/1979	35.80	36.27	173	0	1979	35-44	3.156437471	1.00000000	546.06368
6/23/1979	9/11/1979	36.27	36.49	81	1215	1979	35-44	3.156437471	1.00288370	256.40871
9/12/1979	12/31/1979	36.50	36.80	111	1215	1979	35-44	3.156437471	1.00577572	352.38817
1/1/1980	12/31/1980	36.80	37.80	366	8515	1980	35-44	3.505925696	1.02332804	1313.10262
1/1/1981	12/31/1981	37.80	38.80	365	15815	1981	35-44	3.005275142	1.05935698	1162.03561
1/1/1982	12/31/1982	38.80	39.80	365	23115	1982	35-44	3.607423846	1.09665441	1443.97550
1/1/1983	3/14/1983	39.80	40.00	73	24595	1983	35-44	3.210907205	1.11971333	262.45658
3/15/1983	12/31/1983	40.00	40.80	292	30435	1983	35-44	3.210907205	1.13930804	1068.19802

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		
1/1/1984	12/31/1984	40.80	41.80	366	30435	1984	35-44	3.607591475	1.15518661	1525.28354
1/1/1985	12/31/1985	41.80	42.80	365	30435	1985	35-44	3.900017727	1.15518661	1644.41562
1/1/1986	12/31/1986	42.80	43.80	365	30435	1986	35-44	3.907493293	1.15518661	1647.56764
1/1/1987	12/31/1987	43.80	44.80	365	30435	1987	35-44	3.733309396	1.15518661	1574.12420
1/1/1988	3/14/1988	44.80	45.00	74	30435	1988	35-44	3.744331675	1.15518661	320.07973
3/15/1988	12/31/1988	45.00	45.80	292	30435	1988	45-54	10.121231500	1.15518661	3414.03805
1/1/1989	12/31/1989	45.80	46.80	365	30435	1989	45-54	10.454357070	1.15518661	4408.00766
1/1/1990	12/31/1990	46.80	47.80	365	30435	1990	45-54	11.342008040	1.15518661	4782.27958
1/1/1991	12/31/1991	47.80	48.80	365	30435	1991	45-54	11.299132130	1.15518661	4764.20125
1/1/1992	3/15/1992	48.80	49.00	75	30435	1992	45-54	10.765886720	1.15518661	932.74562
3/16/1992	12/31/1992	49.00	49.80	291	30435	1992	45-54	10.765886720	1.15518661	3619.05299
1/1/1993	12/31/1993	49.80	50.80	365	30435	1993	45-54	10.498471340	1.15518661	4426.60814
1/1/1994	12/31/1994	50.80	51.80	365	30435	1994	45-54	11.240727670	1.15518661	4739.57541
1/1/1995	12/31/1995	51.80	52.80	365	30435	1995	45-54	10.956518360	1.15518661	4619.74051
1/1/1996	12/31/1996	52.80	53.80	366	30435	1996	45-54	10.384872210	1.15518661	4390.70632
1/1/1997	12/31/1997	53.80	54.80	365	30435	1997	45-54	10.941259100	1.15518661	4613.30655
1/1/1998	3/15/1998	54.80	55.00	74	30435	1998	45-54	10.085567830	1.15518661	862.15276
3/16/1998	12/31/1998	55.01	55.80	291	30435	1998	55-64	28.278055700	1.15518661	9505.93153

[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 cancer deaths per 100,000 per year" is the hazard rate for lymphoid cancer 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.