ATTACHMENT B

Questions for EPA Regarding EO IRIS Assessment

Introduction

The major scientific issue regarding the EPA IRIS (2016) ethylene oxide (EO) risk assessment is whether EPA's or TCEQ's (2020) model is the most appropriate statistical computer model to apply to the NIOSH human data set. TCEQ's (2020) model is superior to EPA's model in satisfying key EPA IRIS (2016, p. 116) objectives for model selection (Table 1).

Table 1. Comparison of TCEQ's and EPA's Model in Fulfilling Key EPA Objectives for Model Selection

Key EPA IRIS (2016, p. 116) Objectives for Model Selection	EPA IRIS	TCEQ
Use the individual-level continuous exposure data	ü	ü
Prioritize models that are more tuned to local behavior in the low exposure data over more global models.		ü
Consider the principle of parsimony		ü
Weigh models on both biological plausibility and statistical considerations		ü

The TCEQ model uses individual-level continuous exposure data and is a more parsimonious (simpler) statistical model with only one parameter. It is a nearly linear model, the shape of which is supported by mode of action data and the biological and epidemiological evidence. The model was validated by proving the TCEQ model accurately predicts the total number of cases across all exposures (globally) as well as at lower exposures (locally). In contrast, the EPA IRIS model over predicts the number of cases locally and globally. EPA's unconventional 2-piece linear spline dose-response model is a complex model with the following 3 modeled parameters: (1) an initial steep slope that ends in (2) an abrupt dose-response bend point (i.e., "knot") followed by (3) a shallower slope. The EPA IRIS model has a comparable statistical p-value to that of the simpler TCEQ model but is less consistent with the biological and epidemiological evidence for EO.

The EPA IRIS (2016) and the follow-up EPA (2019) memo presented a multitude of curve-fitting models but failed to integrate any consideration of the epidemiological and biological evidence. The EPA SAB (2015) review of the draft EO assessment emphasized that "any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data". ACC (2020, 2024) provided detailed evidence for why the TCEQ model has greater biological plausibility and greater consistency with the epidemiological evidence. This was done by integrating several lines of evidence from the animal mode of action, toxicokinetic (TK) and cancer bioassay data and the original peer-reviewed conclusions of the NIOSH human study publication.

In contrast, the only instances in which EPA claims they considered biological plausibility is when EPA rejects models with steeper slopes that approach infinity or are based on too few

cases. Yet, EPA provides no biological evidence for why the EPA model has greater biologically plausibility than other models, including TCEQ's model. EPA (2016, 2019) ignores its own 2005 Guidelines for Carcinogen Risk Assessment which state:

> "Another problem occurs when a multitude of alternatives are presented without sufficient context to make a reasoned judgment about the alternatives. This form of model uncertainty reflects primarily the availability of different computer models and not biological information about the agent being assessed or about carcinogenesis in general. . . In situations where there are alternative models with significant biological support, the decisionmaker can be informed by the presentation of these alternatives along with their strengths and uncertainties.

EPA relies on statistical and visual fit comparisons to support EPA's model selection. EPA's (2024) Response To Comments (RTC) on the HON includes new evidence of EPA's arbitrary application of statistics and flawed visual comparison. EPA (2024) incorrectly states that the knot parameter was pre-determined visually based on comparisons with the categorical (grouped) estimates, and so does not need to be accounted for statistically. This is a misrepresentation of EPA IRIS (2016) statistically driven search for the knot for both lymphoid mortality and breast cancer incidence. The EPA (2024) also presents new analysis that is essentially the visual comparison that EPA IRIS (2016) Figure 4-7 clearly indicates should not be done[1].

These and other contradictions indicate the EPA IRIS (2016) assessment should be revisited because it is flawed scientifically and does not fulfill key EPA (2016) objectives. We raise several scientific questions which to date the Agency has either not addressed or are raised by EPA's Response to Comments on the HON (EPA 2024). We believe that an unbiased appraisal of the issues raised by these question leads to the inexorable conclusion that the IRIS **value** is not scientifically sound. Given the importance of the issue, it may well be that additional independent peer review of the responses may be appropriate.

[1] EPA IRIS Figure 4-3 state that "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."

Before listing these questions, we first summarize the following areas of agreement with EPA.

1. ACC agrees that the NIOSH study is the most appropriate epidemiological study to use for quantitative risk assessment.
2. ACC agrees with EPA IRIS (2016) that direct-acting mutagenicity is the putative mode of action for EO, and that a default linear no-threshold approach to extrapolating increased cancer risk at very low exposure/risk levels is consistent with established EPA policy.
3. ACC agrees that lymphoid and breast cancers have been associated with EO in the NIOSH study by Steenland et al. (2003, 2004). However, breast cancer mortality and not incidence should be used for quantitative risk assessment because of the substantial number of missing cases for breast cancer incidence reported by Steenland et al, (2003) and subsequent risk deficits in the lower exposures.
4. ACC agrees that correct statistics should play an important role in model selection but disagrees with the EPA (IRIS) rationale for ignoring the knot as 1 of 3 key statistical parameters. EPA's (2024) new rationale is that this parameter was selected visually by comparing it with the categorical estimates. This rationale is contradicted by the EPA IRIS (2016, Appendix D) explanation that a local and overall maximum likelihood value was selected for lymphoid and breast cancer, respectively. When all parameters are considered, the simpler TCEQ CPH model has a comparable p-value but is more parsimonious.
5. ACC agrees that categorical analysis of data is a useful epidemiological tool but disagrees with EPA's reliance on incorrect visual-fit comparisons of continuous models to these categorical grouped estimates.
6. ACC agrees with the important EPA IRIS (2016) warning noted in all Figures of rate ratios (RR) that visual comparisons of different models along the y-axis is inappropriate. However, the EPA (2024) new tabular comparison supporting the EPA model ignores this warning.
7. ACC agrees EO is naturally produced in the body and is pervasive in the environment but disagrees with EPA (2024) that these data are unreliable as reality checks for the risk assessment and risk management decisions.

We urge EPA to address the following scientific questions so that EPA-based actions impacting EO production and use are based on correct statistics, rigorous model validation, and science-based integration of the biological and epidemiological evidence.

Scientific Questions that EPA's Response to Comments has not Adequately Addressed:

EPA's Errors in Statistical and Visual Fit

(1) Statistical fit: ACC (2020, 2024) and TCEQ (2020) provided evidence that the p-values for EPA's model are incorrect and leads to a substantive change in the summary tables that EPA SAB (2015) reviewed (Table 1). EPA claims their statistics are correct for calculating the

Table 1. Original and Corrected p-values for IRIS 2-slope linear spline and IRIS standard CPH model

	EPA IRIS (original) 2-slope linear spline	EPA IRIS (corrected) 2-slope linear spline	EPA IRIS Standard CPH Model
Lymphoid Mortality	**P= 0.07**	**P=0.14** corrected from 0.07	**P=0.22**
Breast Cancer Incidence	**P= 0.01**	**P=0.04** corrected from 0.01	**P=0.02**

Source: Corrected and IRIS reported p-values are based on IRIS (2016; Tables 4-2, 4-4, 4-6, 4-12, 4-13, Appendix D) and TCEQ (2020).

p-value for the 2-slope linear spline model because the knot of 1600 ppm-days connecting the two linear models was selected based on "better visual fit to the lower dose data on lymphoid cancer" rather than the maximum likelihood knot of 100 ppm-days. However, EPA clearly estimated the knot position based on a systematic optimization approach to find the most optimal global or local maximum likelihood knot location for breast cancer incidence and lymphoid mortality, respectively. The strategy to pick the best model for regulatory decision making should be subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding additional model parameters vs. the more parsimonious model (NRC, 2007, pp. 174)

In light of the EPA IRIS (D29-D30; D40-42) use of statistical methods to select the knot for breast cancer incidence and lymphoid mortality, what is the basis for EPA's claim that it is not a parameter? What reference does EPA rely upon to support its approach?

(2) Visual Fit: The EPA (2024) RTC Table 1 is a new table EPA uses to claim that TCEQ's model has poor visual fit because it underestimates the NIOSH categorical estimates. The internal rate ratio (or relative rate, RR) values were derived using the model parameters and the average concentrations for each exposure quartile. In other words, EPA is making comparisons along the y-axis of EPA IRIS Figure 4-3 in direct contradiction to a note in Figure 4-3 specifically stating such comparisons are invalid[1]. Also, the 4 categorical estimates are grouped estimates that are not the individual estimates that were modeled. **Does EPA agree that EPA (2024) Table 1 compares the rate ratios (relative rate) that reflect those on Figure 4-3, and that this analysis is the same as comparing the models along the y-axis? If not, why not? How does EPA explain this approach in light of EPA**

(IRIS) Figure 4-3 footnote warning against such comparisons? What references or citations does EPA have to refute or fail to adhere to the EPA (IRIS) 2016 Figure 4-3 footnote warning?

(3) EPA (2024) incorrectly states that all models are compared with a baseline hazard rate of the unexposed control group. While this is correct for the categorical results, *this is not the way that continuous models of the individual results estimate the implicit baseline hazard rate*! Rather, SAS program generates baseline hazard rates. The resulting y-intercept is the result of the model, which is influenced by both exposed and unexposed workers, but is not a comparison with the same unexposed group as the categorical analysis as stated by EPA (2024). This is an important point because EPA (2024) appears to use this incorrect explanation as the basis to support comparisons of relative rates contrary to the EPA IRIS (2016) warning that this should not be done. **What specific modeling file or other information supports EPA's contention that the continuous models are based solely on a comparison against an unexposed group?**

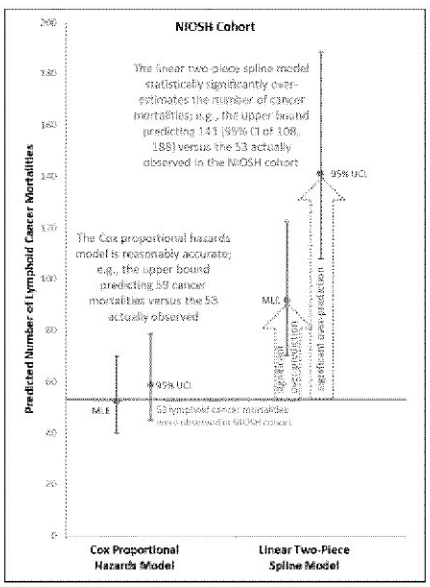
(4) EPA's RTC (2022, 2024) repeatedly claims that EPA's selected continuous model has a better fit based on the shape of the first 2 of 4 categorical (grouped) estimates of the individual data. Yet, SAB (2015) advised EPA to not select the linear regression of categorical estimates unless individual exposure model results are biologically implausible. In fact, EPA SAB advised that if EPA had to rely on the categorical model they should consider using more groupings. In other words, EPA use of EPA's categorical estimates as the gold standard as a basis for selecting a model is incorrect and contradicts advice received from SAB. Valdez-Flores and Sielken (2013) and TCEQ (2020) illustrate how the shape of the exposure-response changes depending on the number of categories selected. While categorical analysis is a well-accepted tool for evaluating epidemiological data, it is inappropriate to use these categorical estimates as the gold standard for selecting continuous models of individual data. **How does EPA reconcile using an individual exposure model while relying ultimately on visual comparisons with the categorical estimates, which SAB advised against using?**

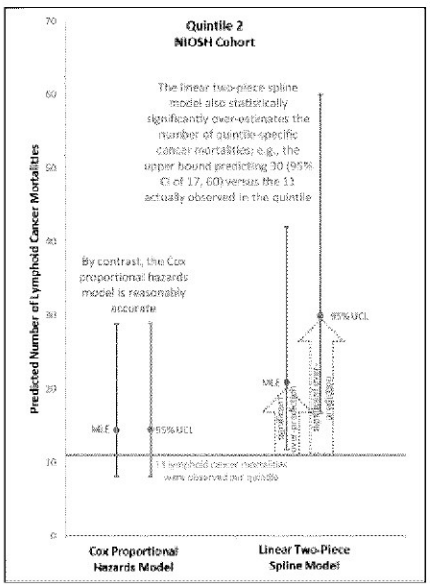
(5) EPA (2022) introduced a new visual evaluation of the lymphoid categorical data as proof that TCEQ's standard CPH approach is a flawed approach and that TCEQ's model explodes upwards at the highest cumulative exposures. The EPA (2022, 2024) RTC failed to address the misstatements and errors in their analysis that were raised by ACC (2020, 2024). For perspective, in TCEQ's and EPA's model equations, the rate ratios are higher for EPA than for TCEQ at 40,000 ppm-days and 64,000 ppm-days. If TCEQ's model is exploding upwards, then this is even more dramatic for EPA's model. **Does EPA agree that applying the CPH model to each categorical estimate using one categorical modeled estimate at a time is incorrect and irrelevant to TCEQ's analysis? If not, why not and what literature supports EPA's approach? Does EPA agree that applying the same approach to the linear spline model focusing on the initial linear CPH model below the knot would result in similar overprediction of the categorical estimates at later exposures? Does EPA agree that this approach is diametrically opposite from SAB's strong recommendation to NOT model the categorical data? If not, why not?**

Validation of Model Fit

(6) TCEQ (2020) includes an objective model validation procedure (Figure 1). Model validation is an objective ground-truthing procedure to statistically determine whether model predictions are consistent with the observed data used to estimate the model parameters. TCEQ's analysis applied EPA's and TCEQ's model to general population background hazard rates of lymphoid cancers to show that the TCEQ model estimates agree with the actual number of lymphoid cancers observed in the NIOSH study with and without a healthy worker effect (HWE) assumption of 16-17% and whether based on the maximum likelihood estimate (MLE) or the associated 95% upper confidence limit (UCL). In contrast, EPA's model statistically significantly over-predicts the number of lymphoid cancers. This applies to the cohort as a whole and to the cumulative exposure groups, including the lowest exposure Quintile 2. ACC's (2023) comments explained that the prediction of Quintile 2 best reflects "local" fit below the knot. **Assuming that a HWE of 16-17% (or less) is accurate, (1) does EPA agree that in TCEQ's model validation procedure, TCEQ correctly applied the central estimate? (2) Does EPA agree that the results of TCEQ's and ACC (2023) comments indicate that the CPH model not only has better local fit below the knot, but also overall? If not, why not?**

Figure 1. TCEQ's (2020) Model Validation Procedure shows TCEQ's model (blue error bars) better predicts the actual number of cases in the NIOSH cohort (green line) and Quintile 2





(7) EPA dismissed TCEQ's model validation alleging that a healthy worker effect (HWE) of 28% is needed. EPA (2022, p. 90) points to a non-statistically significant SMR of 0.72 for "all haematopoietic" cancers in Steenland et al. (2004) Table 3 in support of a large HWE (i.e., 28%). The "all haematopoietic" classification encompasses many more cancers than just the lymphoid cancers. When one considers NHL which is a major contributor to lymphoid cancers, there is no deficit. Thus, EPA cherry picks a value to support their incorrect conclusion that there is a large HWE and ignores the NIOSH study authors

conclusion there is likely no HWE (Steenland et al. 2004). Steenland's conclusion is consistent with basic understanding in epidemiology that indicates that a HWE is not expected with longer term follow up studies, especially for cancer (IARC, 1999). The TCEQ's model better predicts the actual cases even with a reasonable HWE assumption of 16-17%, despite the strong evidence that there is no HWE. **Does EPA agree that the category "all hematopoietic cancers" include cancers that are not lymphoid cancers? Does EPA agree that NHL is a major contributor to lymphoid, and there is no deficit for NHL? What studies or references contradict the Steenland (et al. 2004) and IARC (1999) conclusions that the huge HWE claimed by EPA (2024) is not expected?**

(8) EPA frequently points out differences in the details of the analysis to cast doubt on TCEQ's analysis. However, in many cases TCEQ's analysis is the preferred approach. For example, the EPA RTC (2024, p. 103) also noted that the fact that TCEQ chose to compute standardized mortality ratios (SMRs) for different exposure intervals than NIOSH does present some limitations. EPA states that the change in the category assumption introduces a complication in comparing the TCEQ SMR computations with NIOSH's findings for risks of lymphoid tumors by exposure category. In this case, EPA's RTC (2024) fails to acknowledge that TCEQ split the quantiles optimally by having the same number of responses in each quantile to minimize the variance. This is standard epidemiology procedure for any categorical analysis. In contrast, Steenland et al. (2004) first analyzed all haematopoietic (LH) cancers by evenly dividing LH into different categories of exposure, but this is a category broader than the cancer of concern. When evaluating lymphoid cancers, Steenland et al. (2004) and EPA IRIS (2016) failed to recalibrate how to develop true exposure quartiles for lymphoid, but instead applied the same exposure categories that had been developed for LH. In addition, it can be shown that even if EPA's intervals are used the results reported by TCEQ still hold true. **Does EPA agree that TCEQ's methods are valid and consistent with statistical principles regarding methods for defining exposure quantiles? What basis does EPA have for not making the more correct adjustment that TCEQ did?**

Biological Plausibility and Consistency with the Epidemiological Data

(9) The EPA IRIS (2016) states that an important objective for model selection is biological plausibility, but it never integrated different lines of biological evidence to evaluate EPA's or TCEQ's model selection. The EPA (2024) RTC dismissed the use of biological mode of action evidence provided by ACC (2020) by presenting many different patterns from many different studies without considering which of these studies is most relevant and informative or consideration of the statistical analysis of these studies. The ACC (2023) comments explain why the specific studies ACC evaluated are the most relevant and informative because they represent targets for EtO-induced tumors (lymphoid and breast) that had a range of exposure levels, not just high exposures. In all cases, there is no evidence for a steep initial slope at the low end. As a reactive chemical capable of alkylating DNA, but whose toxicity is modulated by DNA repair and epoxide clearance mechanisms (GSH transferases, epoxide hydrolase) common to rodents and humans, there is no mechanistic rationale to provide biological plausibility to a supralinear exposure response in the low-exposure region, as projected by IRIS as increasing cancer risks. Instead, the PBPK modeling indicates EO

blood concentrations in rats, mice and humans are equivalent and have an identical linear relationship with EO exposures up to 200 ppm, (Fennell and Brown 2001), with a steeper slope at higher exposures consistent with metabolic saturation, which is common. This pattern is opposite to the uncommon one of EPA IRIS. **Does EPA agree that for a direct acting alkylating agent with identical parent EO PBPK-model supported TK patterns in animals and humans are predictive of the shape of the EO dose-response human patterns? If not, what evidence does EPA have to depart from EPA's default assumption that animals are predictive of humans? In view of the lack of statistical difference between EPA's and TCEQ's model, does EPA agree that integration of biological and toxicokinetic evidence from animal data is relevant to dose-response modeling selection in humans? Does EPA agree that the toxicokinetic and most relevant biological data does not indicate a steep dose response at lower exposures? If not, why not?**

(10) ACC (2020, 2023) provided comments that data from the ethylene cancer bioassay can be considered with that of the rat EO carcinogenicity study (IRIS, 2016 Table 3-5) to inform the shape of the EO rat carcinogenicity exposure response at lower exposures. Ethylene was not carcinogenic at any of the exposure levels of 300, 1000 and 3000 ppm using 120 rats/sex/dose group (Hamm et al. 1984). Filser and Klein (2018) used PBPK modeling to estimate that 3000 and 1000 ppm ethylene exposures were equivalent to 5.52 and 5.26 ppm EO, respectively in rats. Thus, these data provide additional biological evidence that the exposure response at lower exposures is not steep. As discussed above, there is no TK difference between rats and humans at blood concentrations up to 200 ppm EO exposures, and the direct alkylating MOA processes are likely to be very similar. **Does EPA agree that in rats there is no evidence of a steep exposure response at lower EO equivalent exposures? Does EPA agree that the TK process between rats and humans are similar?**

Breast Cancer Incidence vs Mortality for Quantitative Risk Assessment

(11) ACC (2020, 2023) raised concerns that EPA is relying on an incomplete data set for breast cancer incidence and EPA's conclusions are based on a deficit of expected cancer cases in lowest exposure group, which resulted from the inability to find individuals in this lowest exposure group in a ratio comparable to the higher exposed group (that is there, was underascertainment in the lowest control group). EPA relies on a statement that the interviews were "complete" to argue that the data set was complete but just because all of the contacted individuals were interviewed is not the same as the database being complete and representative. **What analysis of the data has EPA done to show that the individuals that the study author was not able to find were randomly distributed through the data set, as opposed to being concentrated in the lowest exposed group? What analysis has EPA done to demonstrate that there is no under ascertainment of cases in the lowest exposed group? Does EPA agree that the breast cancer mortality study which is fully ascertained shows a dose-response pattern that is more consistent with the standard CPH model?**

Reality Check Considerations

(12) EPA has noted that ambient EO concentrations near facilities could be probative on the anticipated impacts of EO emissions on residents. However, EPA declined to account for background EO concentrations from sources unrelated to industrial emission due to alleged uncertainty with measurements distant from facilities which they associate with insensitive, unreliable historic test methods. In doing so, EPA infers without analysis that near-facility concentrations are substantially greater than ambient background concentrations and pose a health issue. This approach fails to acknowledge that everyone is exposed to exogenous background EO concentrations as well as endogenous background concentrations. Commenters have previously demonstrated that the measured concentrations close to and away from facilities are often not statistically different. Based on EPA guidance improving the EO test method, state agencies have continued to collect EO data with the new method that continue to show a general pattern of many near facility location concentrations as indistinguishable from ambient background concentrations. Distinguishing higher exogenous exposures is an important initial step is management of EO risk. However, as everyone also has a large endogenous background EO exposure, total background exposure needs to be considered in management of EO risk. **What is the basis for EPA's concern regarding the reliability of background EO concentrations in light of new data using EPA-refined methods? How does EPA plan to consider total background concentration exposure in managing EO risk?**

(13) EPA dismisses multiple lines of converging evidence that everyone in the U.S. is exposed to EO from their own metabolism at concentrations substantially greater than proposed reference dose (Kirman et al. 2021). These data provide important reality checks for selection of dose-response models to apply to the NIOSH data and have important implications for risk management decisions. There is little value in attempting to manage risks from exposures to EO that are orders of magnitude lower than endogenous equivalent values. EPA's primary response is that cancer risk values estimate extra risk so that endogenous levels are already included in the estimate. While EPA's potency estimate technically only applies to exposures above endogenous levels, this is true for both EPA's and TCEQ's potency estimates. Yet only EPA's potency estimate leads to risk specific concentrations that are a fraction of endogenous levels[2]. From a risk management perspective, there is little value in attempting to manage risks from exposures at levels that are orders of magnitude lower than endogenous equivalent levels[2]. **How does EPA reconcile a potency estimate that suggests that EO is a highly potent carcinogen at levels substantially below that which the body produces through natural processes? What scientific rationale does EPA have for ignoring endogenous EO levels as a reality check**

[2] Endogenous exposures to EO are equivalent to inhalation exposures that range from 1-5 ppb, with an equivalent endogenous mean of 2-3 ppb. As a reality check for the different modeling approaches applied by TCEQ and EPA this mean is compared with the 10^{-5} risk specific concentrations (RSC) resulting from each approach. TCEQ's RSC is approximately equivalent to the endogenous equivalent mean. EPA's RSC is a very small fraction (1/1000) of the endogenous mean in humans, a level that is not expected to be biologically meaningful.

for selection of dose-response models and as a consideration for risk management decisions?

(14) The EPA (2024) RTC states that estimates of EO exposures at ambient exposure levels or of endogenous levels are unreliable because the simple linear model extrapolates below the occupational exposure levels used to develop the model. ACC (2023) provided new evidence based on NHANES biomonitoring data in smokers and in non-smokers that EPA (2024) did not address. There are only three simple assumptions made by Kirman and Hayes (2017) and Kirman et al. (2021): (1) The high quality CDC NIOSH NHANES HEV data can be used to quantify *total* (exogenous and endogenous) exposures to EO; (2) EPA's air monitoring data can be used to quantify exogenous exposure to EO in air; (3) a continuously linear relationship between EO exposures and HEV measurements can be quantified. Yet, the EPA (2024) RTC dismisses the linear model as hypothetical and fails to address the new data and validation exercise provided by ACC (2023**). What is the scientific basis for USEPA's continued skepticism on linear toxicokinetics for EO over the entire low- to mid-exposure range of NIOSH-cohort occupational exposures, when in fact by its own 2005 Carcinogen Risk Assessment Guidelines low-dose linearity serves as the default assumption for toxicokinetics (i.e., below metabolic saturation, co-factor depletion), and also serves as the default assumption for toxicokinetics and toxicodynamic factors for low-dose risk from exposure to chemical carcinogens?**

(15) ACC's comments on the HON (ACC, 2023) provided further validation of the Kirman et al. (2021) linear correlation for low level EO exposures and hemoglobin adduct formation (HEV) based on several different lines of data evidence and PK and PBPK analysis. This correlation was used to provide evidence supporting the estimation of endogenous EO-equivalent levels. Part of the validation of the linear correlation followed EPA's (2022 p. 69) own recommendation for such a "forwards" validation using analytically quantified EtO concentrations in cigarette smoke. The EPA (2024) RTC did not address this new analysis and asserted incorrectly that no data on EO in cigarette smoke had been presented. In light of the strong evidence provided to EPA, the burden of proof is on EPA to reject the well supported evidence for use of a linear model. **What concrete evidence does EPA have to support EPA's current vague claim of "uncertainty" based on some as-yet-to-be-identified source of nonlinear toxicokinetics?**

(16) EPA dismissed the absence of an association between EO lymphoid related cancers with smokers as a reality check based on the potential for antagonistic effects by other chemicals without citing specific evidence. The EPA (2016) IRIS predicts that EO exposures associated with typical cigarette smoking patterns should exhibit a relatively high incidence of lymphoid cancer (10^{-2} to 10^{-1} cancer risk) when in fact this type of cancer is not generally associated with cigarette smoking. Similarly, an association in the Union Carbide study where workers are exposed to high concentrations of EO should also be seen. EPA's dismissal is inconsistent with EPA guidelines for assessing chemical mixtures (USEPA, 2000); "*For low exposure levels when no interactions information is available, default methods using an additivity assumption are given...Response addition is the default approach when the component chemicals are functionally independent...response addition has often been used for the risk assessment of mixtures of carcinogens (Gaylor et al., 1997; U.S. EPA, 1989a).*"

Accordingly, and unless directly supported by countervailing experimental evidence, response addition should serve as the default assumption for cancer risk from mixtures of EO and other chemicals until conclusive evidence is obtained to demonstrate otherwise. Both sets of data do not show an association between EO exposure and the relevant cancers (or at most a weak association). **There are only two potential explanations for the disparity between this data and EPA's model and they are mutually exclusive, either : (1) EPA's model is wrong; or (2) when individuals are exposed to other chemicals, as they are in environmental settings, EO induced cancers are somehow prevented or cured by a strong antagonistic effect attributed to chemical co-exposures. What data does EPA have to support a mechanism for cigarette smoke preventing or curing EO-induced lymphoid cancers?**

Exposure Issues with the NIOSH Study

(17) The exposure model used by the NIOSH study was developed by Hornung et al. (2004). In that paper, the authors make clear that they simply assumed, without supporting data, that practices that would reduce worker exposure after 1978-1980 had not changed during the 1950s all the way through 1978. This NIOSH exposure model led to a prediction that the 90th percentile exposures considered relevant for highly exposed sterilizer operators is lower in earlier years (1940-1970) compared to 1976-1978 (Figure 2). Public comments, including references to a supporting peer-reviewed scientific publication (Bogen et al. 2019) were submitted providing published literature as well as a summary of interviews describing changes that would have resulted in higher worker exposures in earlier periods for sterilizer operators (ACC, 2020, 2023). EPA claims that the summary of interviews is not sufficient to question the Hornung et al. (2004) estimates or to support the exposure modeling by Bogen et al. (2019) but fails to address the published literature and the absence of any attempt by NIOSH to verify exposures in the early 1940-1970 period with data. EPA's exclusive reliance on the NIOSH cohort to estimate EO cancer potency and risk should be re-examined by evaluating other lines of evidence from other epidemiology and animal studies. **Does EPA agree that in general, substantial underestimates of exposures can lead to overestimates of cancer potency? What data or reports in the record demonstrate that there were no changes to practices or storage conditions of EO-treated products that would have increased exposures prior to 1976-1978 (e.g., as considered by Bogen et al. 2019)? What evidence can EPA point to that shows Hornung et al. (1994) did not simply assume that there were no changes in sterilizer worker practices or equipment that would reduce worker exposure prior to 1978?**

Figure 3. NIOSH exposure model predictions of historical 90th percentile 8-h time-weighted occupational EO concentrations during 1936-1986 based on the Hornung et al. (1994) model (Figure 1 of Bogen et al. 2019).

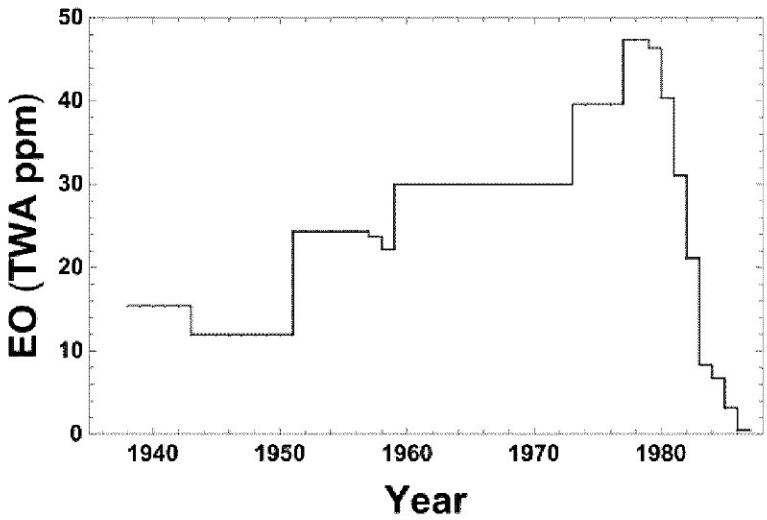


Figure 1. National Institute of Occupational Safety and Health (NIOSH) statistical regression (NSR) exposure model predictions of historical 90th percentile 8-h time-weighted average (TWA) occupational ethylene oxide (EO) concentration (C_{90}) during 1936–1986, specific to all facilities and job categories addressed by that model. Nearly all of the facilities sterilized medical/health products. The NSR model predicts that C_{90} = 47.4, 30.0, and 11.9 ppm in 1978, 1959, and 1949, respectively, and predicts TWA C_{90} values of 34.3, 27.5, and 15.9 ppm during the late, middle, and early periods defined for the present study, respectively.

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