Public Comments Received on the 2019 Ethylene Oxide Draft Development Support Document

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Public Comments

January 31, 2020

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

September 26, 2019

Submitted via: tox@tceq.texas.gov

Dr. Michael Honeycutt, Director
Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality
12100 Park 35 Circle
Austin, TX 78753

Re: TCEQ Proposed Development Support Documents (DSDs) for Ethylene Oxide (EtO) Carcinogenic Dose-Response Assessment

Dear Dr. Honeycutt:

The Ethylene Oxide Panel (Panel) of the American Chemistry Council (ACC), submits its comments on the proposed TCEQ Development Support Document (DSD) for Ethylene Oxide (EtO) Carcinogenic Dose-Response Assessment (TCEQ, 2019[1]). The Panel supports the inhalation-based unit risk factor (URF) derived by TCEQ for EtO. TCEQ's approach to ground-truth the selection of the extrapolation model based on biological and epidemiological evidence is a critical missing step in EPA's IRIS EtO assessment (IRIS, 2016[2]). An overly conservative assessment can result in misplaced public concern, supply chain disruption of critical products, and the unnecessary use of resources.

The TCEQ proposed EtO DSD calculated a URF of 2.5E-6 per ppb (1.4E-6 per µg/m^3) and a 1/100,000 extra risk chronic health-based effects screening level for non-threshold dose response cancer effect of 4 ppb (7 µg/m^3) based on the NIOSH epidemiology study and an assumption of a 15-year exposure lag period. Although ACC has previously recommended a different approach based on the two strongest epidemiology studies and zero lag period[3,4], ACC finds the TCEQ proposal acceptable because it is much more scientifically sound, biologically plausible, and statistically correct compared to the IRIS (2016) EtO Assessment. The IRIS' URF of 9.1E-3 per ppb (5.0 E-3 per µg/m^3) results in a 1/100,000 excess risk concentration of 1 ppt

[1] https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/proposed/jun19/eo.pdf
[2] EPA/635/R-16/350Fa (December 2016)
[3] https://www.epa.gov/sites/production/files/2018-10/documents/iqa_petition_eo-_sept_2018_0.pdf
[4] Ethylene Oxide Panel Comments on EPA Proposed Amendments to "National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review" Docket ID No. EPA-HQ-OAR-2018-0417 (84 Fed. Reg. 1570; Feb. 4, 2019)

($0.0018 \mu g/m^3$), which is inconsistent with the epidemiological and biological evidence and unreasonably conservative. The major reason for the 4000-fold difference in the URFs derived by TCEQ and IRIS is the selection of different statistical models used for low dose extrapolation.

TCEQ used mode of action (MoA) information as the primary basis for informing the low dose extrapolation, and systematically considered endogenous levels, key epidemiological data and model prediction to check and ground-truth the selection of the final model. Although IRIS (2016) also considered the MoA, toxicology and epidemiology studies for cancer classification, IRIS (2016) did not fully utilize these studies in the final selection of the extrapolation model. Instead, IRIS relied primarily on incorrect statistical analysis and flawed visual representation of the exposure-response data. TCEQ's approach to ground-truth the selection of the extrapolation model based on biological, epidemiological and statistical model prediction evidence is the critical missing step in the IRIS assessment that TCEQ completes in the proposed DSD.

ACC has five key recommendations for strengthening TCEQ's use of mode of action and epidemiological weight of evidence to ground-truth the final selection of the URFs. These recommendations will be discussed in greater detail below:

1. While TCEQ's reality check of the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels is appropriate based on endogenously generated EtO relative to those contributed by exogenous EtO exposures, it can be strengthened by brief discussion of endogenously produced EtO DNA adducts.

2. TCEQ's arguments to support the selection of lymphoid cancer as the "critical cancer endpoint", while valid, would be enhanced by including a weight of evidence evaluation of the breast cancer findings from the six relevant epidemiology studies.

3. TCEQ should consider simplifying and clarifying a few sections and tables to better support TCEQ's principled approach of using MoA, biological plausibility and epidemiological weight of evidence to inform selection of the final model and the point-of-departure (PoD). The following are a couple of examples:

    - ACC[5] previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with the IRIS (2016) approach. Several tables can be simplified to only show the zero and 15-year lag data.
    - TCEQ should clarify that the 1/100,000 extra risk level was estimated directly from the Cox proportional hazard model. This excess risk level is at the low end of the observable range of responses consistent with EPA (2005) guidance for selecting a PoD for cancer risk assessment.

4. ACC agrees with TCEQ's emphasis on the biological mode of action and the epidemiology weight of evidence as the primary basis for selecting the type of model for low-dose extrapolation. TCEQ also provides additional statistical evidence that the final adopted TCEQ model accurately predicts the observed number of lymphoid cancer deaths in the NIOSH cohort compared to EPA's supra-linear spline model. Further clarifications and comparisons could be added to help the reader more fully appreciate these model-prediction results:

    - TCEQ should clarify in Section 3.4.1.2.2..3 that regardless of whether the maximum likelihood estimate (MLE) or the 95% upper confidence limit (UCL) model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI).
    - In contrast, both the MLE and the UCL for TCEQ's Cox proportional hazard log-linear model accurately predict the observed mortalities.
    - Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional "apples-to-apples" comparison based on similar IRIS assumptions for both model estimates.

5. TCEQ should clarify that contrary to EPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data (IRIS Appendix D-4, D-29), whereas, TCEQ's model estimates are based on the full NIOSH data set.

In summary, TCEQ appropriately relies on the biological MoA as the primary basis for selecting the model for low-dose extrapolation to build a strong case for why TCEQ should not adopt the EtO IRIS Assessment's inhalation of 1 in 100,000 excess risk-based air concentration of 1 ppt. TCEQ's conservative and scientifically supportable approach to an exposure response analysis should be used. This alternative approach makes use of the full data set and yields a more realistic risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000.

If you have any questions or would like to discuss these comments further, please contact me at [redacted]

Sincerely,

William Gulledge

William P. Gulledge
Senior Director
Chemical Products & Technology Division

DETAILED COMMENTS

Key Comment #1: While TCEQ's reality check of the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels is appropriate based on endogenously generated EtO relative to those contributed by exogenous EtO exposures, it can be strengthened by a discussion of endogenously produced EtO DNA adducts.

ACC agrees with the TCEQ draft DSD conclusion that the overall integrated cancer MoA assessment indicates that reliance on the EPA-hypothesized EtO supra-linear dose-response model of epidemiology data to estimate human cancer risks in the low-dose region (< 1 ppb) is not biologically plausible. This is apparent when consideration is given to doses of endogenously generated EtO exposures, and the inter-human variability of such, relative to those contributed by exogenous EtO exposures at the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels. However, the formation of pro-mutagenic DNA adducts in cancer critical genes is hypothesized as the molecular initiating event[6] for the mutagenic MoA proposed by IRIS for EtO carcinogenesis. Thus, the TCEQ conclusions would be further strengthened by consideration that DNA adduct data from animal and cell-based studies are also consistent with the conclusion that EtO tumorigenicity operates by a low-dose linear and not supra-linear dose-response.

TCEQ clearly articulates toxicological MoA principles, including formation of DNA adducts, that can be used to inform selection of the most biologically plausible dose response for modeling EtO human cancer risks. TCEQ effectively emphasizes this point when stating:

> "Consideration of a direct acting DNA-reactive chemical in conjunction with normal detoxification processes and baseline levels of DNA repair enzymes that have evolved to efficiently detoxify and/or repair significant levels of endogenous EtO and associated adducts (in the endogenous range) suggests a no more than linear low-dose response component near the endogenous range where the body can no longer effectively detoxify EtO and/or repair the resulting damage."

[6]Moore MM, Schoeny RS, Becker RA, White K, Pottenger LH. 2018. Development of an adverse outcome pathway for chemically induced hepatocellular carcinoma: Case study of afb1, a human carcinogen with a mutagenic mode of action. Crit Rev Toxicol 48:312-337

This TCEQ conclusion is also consistent with the EPA IRIS statement that "it is highly plausible that the dose-response relationship over the endogenous range is sublinear".

TCEQ can further amplify this conclusion by referencing the study of Marsden et al. (2009) which provides a highly sensitive analysis of the dose-response related formation of N7-HEG DNA adducts in rats following intraperitoneal (i.p.) injections. While the kinetics of i.p. exposures may be different from inhalation exposures, it could be argued that the i.p. dosing represents a reasonable parallel to endogenously generated EtO at low doses. Furthermore, although N7-HEG is a non-mutagenic adduct, it is present at much higher levels than other potentially mutagenic DNA adducts and, in general, would be representative of a worse case for possible increase in pro-mutagenic DNA adducts.

The dose-response data from Marsden et al. (2009) provide two important MoA considerations that support at most a linear dose-response (i.e. do not support a supra-linear dose-response). First, the exquisitely sensitive methodology for assessment of DNA adducts over a 1000-fold range of EtO doses demonstrates that exogenous EtO adduct formation is conservatively represented by a low dose linear, and not supra-linear, dose response for this key MoA molecular initiating event (EPA IRIS, 2016; Moore et al, 2018; OECD, 2018). Second, and consistent with and paralleling the TCEQ analysis of the dose-response implications of endogenous EtO production evidenced by hemoglobin adduct exposure biomarkers in humans, the rat DNA data similarly show that DNA adducts resulting from low-dose exogenous EtO are a small and non-significant contributor to the overall adduct burden inclusive of endogenously-present EtO adducts. Even the inter-individual variability of endogenous DNA adducts was substantially greater than the DNA adducts contributed by low dose exogenous EtO.

Thus, these data collected from the molecular target of EtO are consistent with the conclusion of Swenberg et al. (2011)[7] that:

[7] Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, Starr T. 2011. Endogenous versus exogenous DNA adducts: Their role in carcinogenesis, epidemiology, and risk assessment. Tox Sci 120: S130-S145

> "The endogenous EtO adducts outnumber the exogenous adducts by such a vast margin that the exogenous adducts are not likely to be causal for EtO-induced mutations or cancer. When looked at from the perspective of the total number of endogenous DNA adducts in a cell, it is clearly implausible."

The *in vivo* rat DNA adduct findings of Marsden et al. (2009)[8] are also consistent with the *in vitro* DNA adduct data of Tompkins et al. (2009)[9]. After a wide range of *in vitro* EtO exposures to a bacterial plasmid, increased pro-mutagenic DNA adducts and associated increased *supF* mutation frequency in human Ad293 cells were observed only after high-, but not low-concentration EtO exposures.

Taken together, these data further support and inform the overall TCEQ conclusion that the low-dose carcinogenicity of EtO conservatively operates by a low-dose linear and not supra-linear dose response.

Key Comment # 2: TCEQ's arguments to support the selection of lymphoid cancer as the "critical cancer endpoint", while valid, would be enhanced by including a weight of evidence evaluation of the breast cancer findings from the six relevant epidemiology studies.

For purposes of hazard assessment and consideration of breast cancer as a possible health endpoint, it is useful to examine all relevant EtO studies of female breast cancer, even those inadequate for cumulative dose-response analyses (Table 1). There is no pattern of breast cancer increase across these six studies and the overall number of observed breast cancers do not exceed expectation. TCEQ could consider including such a table in the DSD to support focus on the lymphoid cancer as the critical cancer endpoint.

[8] Marsden DA, Jones DJL, Britton RG, Ognibene T, Ubick E, Johnson GE, Farmer PB, Brown K. 2009. Dose-response relationships for N7-(2-hydroxyethyl)guanine induced by low-dose [14C]ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer Res 69(7):3052–3059.

[9] Tompkins EM, McLuckie KIE, Jones, DJL, Farmer PB, Brown K. 2009. Mutagenicity of DNA adducts derived from ethylene oxide exposure in the pSP189 shuttle vector replicated in human Ad293 cells. Mut Res 678: 129-137

Table 1. Ethylene Oxide Epidemiology Studies of Female Breast Cancer

Study	Observed	Expected	Obs./Exp. (95% CI)
Coggon et al. 2004	11	13.1	0.84 (0.42, 1.51)
Steenland et al. 2004	102	103.0	0.99 (0.81, 1.20)
Steenland et al. 2003	319	367.0	0.87* (0.77, 0.97)
Mikoczy et al. 2011	41	50.9	0.81 (0.58, 1.09)
Norman et al. 1995	12	7.0	1.72 (0.93, 2.93)
Hogstedt et al. 1986	0	---	---
Summary (incident cases only)	372	424.9	0.88* (0.79, 0.97)
Summary (mortality cases only)	113	116.1	0.97 (0.80, 1.17)

The more recent study by Mikoczy et al. (2011)[10] has been incorrectly cited by IRIS (2016) as supportive of an association with breast cancer, despite an overall deficit of breast cancer, with or without consideration of a latency period. However, the two higher cumulative exposure groups had statistically significant elevated rates of breast cancer in an *internal* Poisson analysis, due to a substantial and statistically significant deficit of breast cancer in the low-dose reference group[11]. Selection of a referent group that has an unusual deficit of the disease of interest creates an artifact of an excess, as illustrated in the Mikoczy et al. (2011) study (Marsh et al. 2019[12]).

The most informative study reported overall results very close to expectation (mortality) or a significant deficit (incidence) due to case under-ascertainment (Steenland et al. 2004[13],

[10] Mikoczy Z, Tinnerberg H, Bjork J, Albin M. Cancer incidence and mortality in Swedish sterilant workers exposed to EO: updated cohort study findings 1972-2006. Int J Environ Res Public Health 2011;8(6):2009-19.
[11] Table 5 of Mikoczy et al. (2011) reports an external standardized incidence ratio (SIR) of 0.52 for breast cancer indicating a statistically significant 48% deficit in breast cancer incidence in the baseline category
[12] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM. Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 2019 doi: 10.1007/s00420-019-01438-z. [Epub ahead of print]
[13] Steenland K, Stayner L, Deddens J. Mortality analyses in a cohort of 18 235 EO exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 2004;61(1):2-7

2003[14], respectively). The only statistically significant positive mortality trends were detected using a model with log cumulative exposure as the exposure metric and a 20-year lag (Steenland et al. 2004). With respect to breast cancer incidence modeled using a 15-year lag period in relation to log cumulative exposure, Steenland et al. (2003) noted that "The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure," which they viewed as a factor that tended "to weaken the case for a causal relationship." The inappropriateness of using a log cumulative exposure metric that forces supra-linearity has been described by Valdez-Flores et al. (2010)[15].

The breast cancer findings were weakened not only due to inconsistencies in the exposure-response, but also due to an incomplete cancer ascertainment and the subsequent potential for selection bias. Selection bias (referred to as "possible biases due to patterns of non-response" (Steenland et al. 2003)) remains a concern, however, with duration reported as a stronger risk factor than cumulative exposure in both analyses. Those who work longer and stay in the area longer are more likely to get picked up in the state tumor registries and be found for interview, therefore with the potential to impact the results of both analyses. Shorter duration workers with lower cumulative exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. Their diagnoses may get missed, creating a possible biased positive exposure-response. Steenland et al. (2003) recognized this limitation and admitted he was unable to fully address it.

The above arguments support TCEQ's decision to exclude breast cancer as "a critical cancer endpoint" in the estimation of a URF. Furthermore, these arguments also demonstrate that EPA's reliance on this study as the primary justification for a supra-linear slope is not

[14] Steenland K, Whelan E, Deddens J, Stayner L, Ward E. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 2003;14(6):531-9.
[15] Valdez-Flores C, Sielken RL, Jr., Teta MJ. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to EO. Regul Toxicol Pharmacol 2010;56(3):312-20.

scientifically sound. The following are a few additional specific comments regarding breast cancer incidence:

2.1 **p. 60-** last paragraph regarding Table 10. TCEQ states that "NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, Table 10 results will not be utilized." Perhaps these two sentences can be switched in order to improve clarity:

> Regarding Table 10, the log-linear model did not fit the breast cancer mortality data statistically better than the null model (zero slope). However, it does fit the breast cancer incidence data better than the null model . . . Therefore, the TCEQ will not utilize Table 10 results, but rather consider log-linear (standard Cox regression) 15-year exposure-lagged model results for breast cancer incidence (subcohort with interviews) from USEPA (2016). Unfortunately, the NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, the TCEQ will use Table 11 adapted from Table 4-12 of USEPA.

2.2 **p. 64-** first sentence in italics explains the rationale for ignoring breast cancer incidence excess risk. This section should incorporate consideration of the weight of evidence for breast cancer incidence described under Key Comment #2 above. The epidemiology data does not support a potency for breast cancer that is stronger than for lymphoid cancer.

2.3 **p. 84 and 90-** the statement is made in reference to Swaen et al. (2009)[16] and Mikoczy et al. (2011)[17] that "Healthy Worker Effect (HWE)" likely influenced results". HWE is a well-known form of bias in occupational cohort studies in which increased risks may be missed when comparisons are made to an external, general population, considered to be less healthy than the worker population. However, the epidemiologic literature has shown that HWE is predominately related to shorter follow up and non-cancer causes (Monson 1986[18]; Fox and Collier 1976[19]). Swaen (2009) had a very long follow up (36.5 yr. average) and deficits in major non-cancer

[16] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. Mortality study update of EO workers in chemical manufacturing: a 15 year update. J Occup Environ Med 2009;51(6):714-23.
[17] Mikoczy Z, Tinnerberg H, Bjork J, Albin M. Cancer incidence and mortality in Swedish sterilant workers exposed to EO: updated cohort study findings 1972-2006. Int J Environ Res Public Health 2011;8(6):2009-19.
[18] Monson RR. Observations on the healthy worker effect. J Occup Med. 1986 Jun;28(6):425-33. https://www.ncbi.nlm.nih.gov/pubmed/3723215
[19] Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. Br J Prev Soc Med 1976; 30:225-30

causes only among those hired after 1956. There is no indication that cancer increases have been missed due to HWE. Similarly, for Mikoczy et al. (2011), mortality was no longer decreased with a 15 yr. "induction latency" period. A study to test HWE in Sweden as it relates to breast cancer has been published showing no HWE (Gridley et al. 1999[20]). To avoid misleading the reader, we recommend deleting these statements in the report or specifying that they relate to non-cancer causes.

Key Comment #3: TCEQ should consider simplifying and clarifying a few sections and tables to better support TCEQ's principled approach of using MoA, biological plausibility and epidemiological weight of evidence to inform selection of the final model and the point-of departure (PoD).

3.1 Table 6 (p. 56) includes some cancer endpoints that are not relevant based on the epidemiological weight of evidence. This table should only include lymphohematopoietic and breast cancers, which are the only cancers that IRIS (2016, p. 3-13) associated with EtO exposures.

3.2 Table 7-10, 12-14 (pp. 57-62) can be simplified to just show the zero and 15-year lag. TCEQ should indicate in the text and footnote of these tables that a large number of lag periods were tested and none were statistically different from zero lag. ACC previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with IRIS (2016) approach. However, it should be noted that in some cases the 95% UCL URFs for zero lag were slightly higher (more conservative) than for the 15-year lag.

3.3 Section 3.4.1.5.2 Risk-Based Concentrations and URFs and Tables 12-14 should add explanations that the 1/100,000 extra risk level was estimated directly from the Cox

[20] Gridley G, Nyren O, Dosemeci M, Moradi T, Adami HO, Carroll L, Zahm SH. Is there a healthy worker effect for cancer incidence among water in Sweden? Amer J Indust Med 36:193-199

proportional hazard model, and that this is consistent with EPA (2005[21]) cancer guidelines on selection of the PoD at the low end of the observable range of responses. For example, with rodent models, a 10% (1 in 10) PoD is typically used as a 10% extra risk and is near the limit of detection for a typical assay. For epidemiologic data, a lower PoD can be used. When the standard Cox proportional hazard (log-linear) model is used for the NIOSH males-only 15-year lag data, all of the lymphoid mortalities with non-zero exposure occurred **below** the 1 in 100 PoD (Table 2). Therefore, 1 in 100 is not an appropriate PoD for "extrapolation" in the conventional sense.

Table 2. Number of male lymphoid cases out of approximately 18,000 workers with concentrations below the EC (1/100) and EC (1/100,000)

	Male Lymphoid EC 1/100		Male Lymphoid EC 1/100,000[2]	
	0-Lag	15-Lag	0-Lag	15-Lag
EC (1/100,000) Env. Conc (ppm)	3.52	5.80	5.83E-03	9.67E-03
Equivalent[1] Occupational Exposure 70 years (ppm-days)	326,105.9[2]	354,399.0[2]	453.4[2]	590.87[2]
Total Number of Deaths	27	27	27	27
Number with zero exposure	0	6	0	6
Number With Non-Zero Exposure below EC	27	21	1	1

[21] EPA (2005) Guidelines for Carcinogen Risk Assessment. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

Percentage of Deaths below EC	100%	100%	3.70%	25.93%

[1]Equivalent Occupational Exposure 70 years (ppm-days) = EC×(365/240)×(20/10)×365.25×(70-lag)

[2]The maximum occupational exposure concentration for lymphoid deaths was less than 326,106 ppm-days for the unlagged and 137,243 ppm-days for the 15-year lag exposure.

A typical POD extrapolates from the edge of the observed range through the unobserved range of the data. Thus, for the NIOSH male only data, it is appropriate to use the model to extrapolate to 1 in 100,000, which is below the 50th percentile of exposure where there is only one lymphoid mortality for subjects with non-zero exposure.

IRIS (2016) used a 1% (1 in 100) extra risk for the PoD but did not provide evidence that this level would establish a PoD near the edge of the observed data range. ACC does not have the NIOSH data to determine the validity of the 1% for the supra-linear spline model.

3.4 The Cox proportional hazard model selected by TCEQ has the form exp(β z) and is usually described as a sublinear model. However, this model becomes linear at extra risk levels of 1/100,000 and lower as concentration "z" approaches zero. Selection of this model is appropriate based on mode of action considerations which indicate that the exposure response is no more than linear.

Key Comment # 4: ACC agrees with TCEQ's emphasis on the biological mode of action and the epidemiology weight of evidence as the primary basis for selecting the type of model for low-dose extrapolation. TCEQ also provides additional statistical evidence that the final adopted TCEQ model accurately predicts the observed number of lymphoid cancer deaths in the NIOSH cohort compared to EPA's supra-linear spline model. Further clarifications and comparisons could be added to help the reader more fully appreciate these model-prediction results.

4.1 **P. 41-46, Section 3.4.1.2.2.3**: TCEQ used the final selected 95% upper confidence limit (UCL) model to predict lymphoid mortalities. TCEQ may want to further clarify that regardless of whether the maximum likelihood estimate (MLE) or the 95% upper confidence limit (UCL) model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI).

4.2 In contrast, the MLE and UCL models for TCEQ's Cox proportional log-linear model accurately predicts the number of mortalities. The section on model prediction analysis could also clarify that this comparison is based on the model fit prior to any additional adjustments based on age or other factors.

4.3 **Figures 8 to 12:** TCEQ might consider including IRIS's Cox proportional log-linear model in Figures 8 to 12 for comparison with IRIS's supra-linear two-piece spline slope. Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional comparison based on similar IRIS approach (i.e. using a random subset of the data). .

Key Comment # 5: TCEQ should clarify that contrary to EPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data (IRIS Appendix D-4, D-29), whereas, TCEQ's model estimates are based on the full NIOSH data set.

5.1 EPA SAB recommended that IRIS utilize the full NIOSH data set to estimate the cancer slope coefficients that would in turn be used to extrapolate risk instead of a small subset used by IRIS (IRIS Appendix H-10).

5.2 TCEQ's model estimates are based on the full NIOSH data set. However, the IRIS (2016) model use the subset of 100 controls. There is no strong biologic or statistical justification for selecting a subset of the data to estimate dose response curves. Thus, TCEQ's analysis is a more robust and complete analysis based on all the available data.

ADDITIONAL COMMENTS

- **3.6 p. 14 and p.27** authorship should be corrected in the section in italics regarding update of the UCC cohort. Dr. Valdez-Flores is not a co-author of the Bender et al. 2019 paper (submitted), but is an author of a risk assessment paper based, in part, on the Bender et al. 2019 paper.
- **3.9 p.25, para.2:** This text effectively describes how the implausibly high cancer risk associated with low dose EtO exposures as estimated by EPA also infers an implausibly high cancer risk associated with exogenous long term exposure to ambient levels of ethylene (due to its metabolism to EtO). However, the analysis should be expanded to clarify that, unlike EtO, the current risk assessments for ethylene are based on robust negative chronic rodent inhalation bioassays and genotoxicity assessments, and thus should not be targeted for cancer risk reevaluation based on extrapolation from the EPA EtO cancer risk assessment.
- **3.10.p. 31 Table 4** A footnote should be added next to Valdez-Flores et al. 2010 that only the first and fourth column are based on data from Valdez Flores et al. 2010.
- **p.31 Table 4** The breast cancer row incorrectly indicates the highest 5th quantile is elevated risk, but we believe this is incorrect because there was no statistical increase. Instead it should indicate Not Applicable.
- **p. 32 Table 5** Similar to Table 4, a footnote should be added to clarify that only columns 1 and 4 are from Steenland et al. (2004, 2003) and that other values were estimated by TCEQ.
- **p. 57-60** This series of tables was difficult to follow. We recommend separating the p-value vs. null and p-value vs. zero lag into separate columns by themselves.

COMMENTS OF SIERRA CLUB, TEXAS ENVIRONMENTAL JUSTICE ADVOCACY SERVICES, AIR ALLIANCE HOUSTON, COASTAL ALLIANCE TO PROTECT OUR ENVIRONMENT, ENVIRONMENT TEXAS, PUBLIC CITIZEN'S TEXAS OFFICE, TEXAS CAMPAIGN FOR THE ENVIRONMENT, EARTHJUSTICE, AND ENVIRONMENTAL INTEGRITY PROJECT

September 26, 2019

Texas Commission on Environmental Quality
Toxicology Division, MC 168
P.O. Box 13087
Austin, TX 78711-3087

BY EMAIL: tox@tceq.texas.gov

Re: **Comments opposing TCEQ's Proposed Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document, and seeking external scientific peer review and adequate time for public notice and comment.**

The above-listed environmental, health, and environmental justice organizations submit the following comments to raise serious concerns about public health. Members, constituents, and staff of the undersigned groups live and work—and their children play and attend school—near industrial facilities in Texas (and, in some instances, across the United States) that emit ethylene oxide. For the reasons provided herein, we urge the Texas Commission on Environmental Quality (TCEQ) to follow the best available science and not to weaken protections for the thousands of Texans exposed to the carcinogen ethylene oxide. We respectfully request that TCEQ not finalize the proposed Development Support Document (DSD),[1] and instead adopt the robust, final, peer-reviewed cancer risk factor that the Integrated Risk Information System (IRIS) of the U.S. Environmental Protection Agency (EPA) finalized in 2016.

INTRODUCTION

No one should have to get cancer just from breathing the air in Texas, or anywhere. TCEQ has a responsibility to protect Texas communities, including women and children, from developing cancer from air pollution. TCEQ must recognize the best available science which demonstrates the potent carcinogenicity

[1] TCEQ, Proposed Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document (June 28, 2019), https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/proposed/jun19/eo.pdf [hereinafter Proposed DSD].

of ethylene oxide, instead of rubber-stamping industry attempts to undermine public health protections.

Ethylene Oxide Threatens Public Health

Ethylene oxide is a flammable, colorless gas used to make industrial chemicals such as ethylene glycol or products like plastics, antifreeze, detergents, and adhesives, and for commercial sterilization or fumigation.[2] Chemical manufacturing plants and sterilizers emit ethylene oxide into communities' air regularly—and this pollution can spike dramatically when there is an upset or malfunction.[3]

Ethylene oxide is a well-known human carcinogen.[4] Breathing air contaminated with ethylene oxide increases risk of breast cancer and various lymphoid cancers. Ethylene oxide is especially dangerous because it is a mutagenic carcinogen, meaning it damages DNA.[5] Children are particularly vulnerable to mutagenic carcinogens and exposure during early life further increases the likelihood of developing cancer.[6] Even short-term exposure to ethylene oxide can

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[2] EPA, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide In Support of Summary Information on the Integrated Risk Information System at 1-1 (Dec. 2016), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf [hereinafter IRIS], and appendices available at https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730 [hereinafter IRIS appendices]; Proposed DSD at 1, 10; EPA, Risk Assessment Report for the Sterigenics Facility in Willowbrook, Illinois (Aug. 2019), https://www.epa.gov/sites/production/files/2019-08/documents/risk_assessment_for_sterigenics_willowbrook_il.pdf; EPA, *What is Ethylene Oxide?* (last updated Aug. 20, 2019), https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/background-information-ethylene-oxide#what.

[3] EIP, Gaming the System (Aug. 2004), https://www.environmentalintegrity.org/wp-content/uploads/2016/11/2004_GamingTheSystem.pdf; EIP, Breakdowns in Enforcement (July 7, 2017), https://www.environmentalintegrity.org/wp-content/uploads/2017/02/Breakdowns-in-Enforcement-Report.pdf; EIP, Accident Prone: Malfunctions and "Abnormal" Emission Events at Refineries, Chemical Plants, and Natural Gas Facilities in Texas, 2009-2011 (2012), https://www.environmentalintegrity.org/news_reports/documents/20120718AccidentProneFinal.pdf.

[4] ACC, Ethylene Oxide Panel Ethylene Oxide Safety Task Group, EO Product Stewardship Manual (3d Ed.) (May 2007), https://www.americanchemistry.com/EO-Product-Stewardship-Manual-3rd-edition/; IRIS at 1-1; Proposed DSD at 1, 11.

[5] IRIS at 1-1; Proposed DSD at 1, 11 (citing Int'l Agency for Research on Cancer, 2012: Group I "carcinogenic to humans"; World Health Organization, 2003: "highly likely to be carcinogenic to humans"); *see also* National Toxicology Program, Report on Carcinogens, Fourteenth Addition, Ethylene Oxide (2016), https://ntp.niehs.nih.gov/ntp/roc/content/profiles/ethyleneoxide.pdf; International Agency for Research on Cancer, IARC Monographs 100F Ethylene Oxide (2012), https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-28.pdf; Occupational Safety and Health Administration, OSHA Fact Sheet Ethylene Oxide (2002), https://www.osha.gov/OshDoc/data_General_Facts/ethylene-oxide-factsheet.pdf.

[6] IRIS at 3-71.

cause health impacts including irritation to the eyes, skin, nose, throat, and lungs, and damage the brain and neurological system.[7]

Due to the serious cancer risk from exposure to ethylene oxide, in 2016, EPA completed a robust, scientific, and peer-reviewed process[8] to protect public health and finalize a toxicity factor[9] for ethylene oxide of 0.005 per µg/m^3, or 0.0091 per ppb.[10] EPA demonstrated that breathing just 0.0002 of a microgram of ethylene oxide per cubic meter of air, or 0.0001 parts ethylene oxide per billion parts air over a lifetime increases cancer risk by 1-in-1 million.[11] EPA's cancer risk factor is "based on strong epidemiological evidence supplemented by other lines of evidence" on lymphoid and breast cancers, and accounts for the increased risk to children through applying age-adjustment factors.[12] EPA has "relatively high" confidence in its factor as an estimate of the upper bound on risk from lifetime exposure, with "particularly high" confidence for its breast cancer component.[13]

Texas Communities Need Protection from Ethylene Oxide

The most current National Air Toxics Assessment shows that there are over 100 census tracts in Texas facing upper-bound cancer risk *above the national average* of 30-in-1 million and 15 census tracts in at least three counties—Harris, Jefferson, and Webb—facing an extreme, unacceptable increased cancer risk above *100-in-1 million*, due to ethylene oxide emissions.[14] There are at least 27 existing facilities in Texas that emit more than 48.4 tons of ethylene oxide every year, with

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[7] EPA, *What is Ethylene Oxide*?, https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/background-information-ethylene-oxide#what (last updated Aug. 20, 2019); ACC, Ethylene Oxide Panel Ethylene Oxide Safety Task Group, EO Product Stewardship Manual (3d Ed.) (May 2007), https://www.americanchemistry.com/EO-Product-Stewardship-Manual-3rd-edition/; *see also* Ethylene Oxide and Derivatives Producers Ass'n, Guidelines for the distribution of Ethylene Oxide (Fourth Revision) (2013), https://www.petrochemistry.eu/wp-content/uploads/2018/01/Guidelines_EO_2013_UK_v6-final.pdf.

[8] EPA, Basic Information about the Integrated Risk Information System, https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process (last visited Sep. 23, 2019).

[9] Also known as an inhalation unit risk estimate and defined as "the upper-bound excess risk estimated to result from continuous lifetime exposure to an agent at a concentration of 1 µg/m3 in air (i.e., risk estimate per µg/m3)." TCEQ, Guidelines to Develop Toxicity Factors, 5 (revised Sept. 2015), https://www.tceq.texas.gov/assets/public/comm_exec/pubs/rg/rg-442.pdf [hereinafter TCEQ Guidelines or RG-442] (attached).

[10] IRIS at 1-4.

[11] *Id.*

[12] *Id.* at 1-4, 4-92.

[13] *Id.*

[14] EPA, 2014 National Air Toxics Assessment (NATA), https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results (from link entitled "2014 NATA emissions by facility (ZIP)", https://www.epa.gov/sites/production/files/2018-08/emissions_facilitytotal_2014nata.zip, filtered to show emissions of ethylene oxide from facilities in Texas) [hereinafter NATA data].

the majority—more than 34 tons—emitted by chemical manufacturing facilities.[15] At least another nine chemical or petrochemical manufacturing facilities are planned, likely increasing emissions of ethylene oxide and other carcinogens—unless TCEQ requires effective emissions controls.[16]

These facilities are disproportionately located near, and thus disproportionally affect, communities of color and low-income communities.[17] For example, 11 of the existing 27 facilities described above are located in Harris County, primarily in the East Houston and Houston Ship Channel communities, including Pasadena (6), La Porte (1), Channelview (1), Houston (2) and Crosby (1).[18]

As EPA recognized in issuing the Texas Environmental Justice Collaborative Action Plan in 2016, there are significant environmental justice concerns for these communities, and EPA specifically identified Pasadena and nearby communities in the Houston Ship Channel.[19] These communities are predominantly Latinx and include a significant portion of lower income people. For example, Pasadena is 67.7% Latinx, compared to 38.9% state-wide, and 19.3% of people live below the poverty level.[20] The health effects of long-term daily exposures to air pollution often go unaddressed in these communities due to many residents' limited financial resources and limited access to health care.[21] And, these communities often lack ambient air monitoring to even track their exposure to chemicals like ethylene oxide.

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[15] *Id.*; 2014 NEI Data – Search Results (Texas; Ethylene Oxide) https://iaspub.epa.gov/enviro/nei.html?pType=Facility&pYear=2014&pState=48&pPollutant=75218.
[16] Industrial Info Resources, USA & Canada Chemical Industry Outlook at 16 (Sept. 12, 2018) (showing nine chemical industry "Mega projects" planned in Texas in 2019); *see also* N. Powell, *New Texas petrochemical projects add millions of tons of greenhouse gas pollution, report finds*, Hous. Chron. (Sep. 27, 2018) (updated Oct. 5, 2018), https://www.houstonchronicle.com/news/houston-texas/houston/article/New-Texas-petrochemical-projects-add-millions-of-13264492.php (stating Texas approved 43 petrochemical projects since 2012).
[17] *See, e.g.*, EPA Region 6, Texas Environmental Justice Collaborative Action Plan at 4 (Aug. 3, 2016), https://www.epa.gov/sites/production/files/2016-12/documents/texas_ej_plan_8-3-16_final.pdf.
[18] *See* NATA data, above.
[19] EPA Region 6, Texas Environmental Justice Collaborative Action Plan at 4 (Aug. 3, 2016), https://www.epa.gov/sites/production/files/2016-12/documents/texas_ej_plan_8-3-16_final.pdf.
[20] US Census Bureau, FactFinder, https://factfinder.census.gov/faces/nav/jsf/pages/community_facts.xhtml (search for city or state);; Pew Research, Demographic and Economic Profiles of Hispanics by State and County, 2014, https://www.pewresearch.org/hispanic/states/state/tx.
[21] UCS & t.e.j.a.s., Double Jeopardy in Houston (Oct. 2016), https://www.ucsusa.org/sites/default/files/attach/2016/10/ucs-double-jeopardy-in-houston-full-report-2016.pdf.

TCEQ Should Not Finalize a Factor That Ignores Substantial Cancer Risk

Since EPA finalized the IRIS factor for ethylene oxide in 2016, TCEQ has made every effort to ignore or discredit it. TCEQ appears to favor industry in pushing weaker and weaker factors that fail to protect Texas communities—especially those already overburdened by toxic air pollution, and particularly women and children.

First, in March 2017, TCEQ adopted a risk factor of 0.000076 per $\mu g/m^3$—65 times weaker than the 2016 IRIS factor.[22] In a three-page document announcing the 2017 factor (that only became available after a Public Information Request to TCEQ by Sierra Club),[23] TCEQ considered and rejected two studies—just as EPA had done: Valdez-Flores et al. (2010) and Kirman et al. (2004). TCEQ rejected Valdez-Flores et al. (2010) because it failed to capture cancer risk for all but the highest exposure groups, and rejected Kirman et al. (2004) for various reasons, including its failure to consider breast cancer.[24] The value selected in 2017 by TCEQ was actually part of EPA's IRIS assessment but based just on rodent data (as opposed to the final 2016 IRIS risk factor which was based on the entire systematic review, including human data). TCEQ selected the 2017 factor due to the "high quality" of the rodent study, without providing a reasoned basis then for rejecting the remaining conclusions of EPA's determination or the final 2016 IRIS factor.[25]

Subsequently, in August 2017, without reference to TCEQ's March 2017 factor or conclusions, without any explanation, and without any apparent reason, TCEQ began to create a new factor that was even weaker.[26] TCEQ publicized a request for information on its website, and the American Chemistry Council (ACC) submitted comments urging TCEQ to develop a weaker factor, like that of Valdez-Flores et al. (2010).[27]

TCEQ was close to releasing its proposed assessment in June 2018[28] when it met with the ACC. As part of an hour-long presentation to TCEQ, the ACC again recommended TCEQ (1) "[u]se the estimate from Valdez-Flores et al. (2010) instead of from the U.S. EPA IRIS (2016)"[29]—calling the Valdez-Flores factor a "reasonable

[22] EPA's factor based on "female mouse tumors." IRIS at 4-98, Table 4-27.
[23] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached); Public Information Request to TCEQ (Aug. 12, 2019) (attached).
[24] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached).
[25] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached).
[26] Proposed DSD at i.
[27] See American Chemistry Letter to TCEQ, Submission of Toxicology Information for Ethylene Oxide (Nov. 2017) (attached).
[28] TCEQ, June 18, 2018 update (attached).
[29] Exponent, American Chemistry Council Ethylene Oxide Panel, Recommendation for Inhalation Cancer Risk 1 (attached); *see also* Exponent, Powerpoint of Jane Teta at 46 (June 26, 2018) (attached).

alternative;"[30] (2) incorporate a data update identified as Bender et al.;[31] (3) ignore breast cancer,[32] and (4) ignore what was described as endogenous exposure to ethylene oxide.

In August 2018, EPA released the National Air Toxics Assessment showing extreme cancer risk hot spots in communities around the country, including in Texas.[33] TCEQ took no action to protect public health from this extreme risk. Instead, TCEQ alerted EPA that it was creating a "reasonable alternative"—a weaker factor—for ethylene oxide.[34] Shortly after, in May 2019, the National Environmental Justice Advisory Council to the EPA recommended *strengthening* regulatory protections from ethylene oxide due to the health impacts and disproportionate exposure and impact to communities of color and low-income communities.[35] Again, TCEQ continued to question the IRIS value and work towards creating a weaker factor.

Indeed, despite TCEQ's own March 2017 conclusions, despite the extreme cancer risk demonstrated by EPA, and despite the urging of the National Environmental Justice Advisory Council to *strengthen* protections, on June 28, 2019, TCEQ proposed a risk factor for ethylene oxide of 0.0000014 per µg/m^3—more than 50x weaker than its March 2017 value and *3,500x weaker* than the IRIS factor:

Cancer Risk Factor for Ethylene Oxide Exposure		**Difference from EPA IRIS (2016)**
EPA IRIS (2016):	0.005 per µg/m^3	---
TCEQ (March 6, 2017):	0.000076 per µg/m^3	65x weaker
TCEQ (June 28, 2019):	0.0000014 per µg/m^3	***3,500x weaker***

TCEQ's resulting effects screening level is 4,000 times weaker than EPA's value at the same excess risk level.[36]

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[30] Exponent, Powerpoint of Jane Teta at 46 (June 26, 2018) (attached).
[31] Exponent, Powerpoint of Jane Teta at slide 27-28 (June 26, 2018) (attached).
[32] Exponent, Powerpoint of Jane Teta at slide 2 (June 26, 2018) (attached) (describing breast as inappropriate target organ).
[33] *See* NATA data, above.
[34] TCEQ comment to EPA on Stationary Combustion Turbines Proposed Rule at 2 (Apr. 26, 2019), https://www.regulations.gov/document?D=EPA-HQ-OAR-2018-0417-0142 (stating the TCEQ is in the process of deriving a URF for ethylene oxide. . . ." and describing a "draft" of this document); TCEQ comment to EPA on Hydrochloric Acid Production Proposed Rule (May 30, 2019), https://www.regulations.gov/document?D=EPA-HQ-OAR-2017-0688-0089.
[35] National Environmental Justice Advisory Council letter (May 3, 2019), https://comingcleaninc.org/assets/media/documents/NEJAC-Letter-Ethylene%20Oxide-May-3-2019-Final.pdf (attached).
[36] Proposed DSD at 93.

Just as instructed by the ACC, and despite TCEQ's own March 2017 conclusions, TCEQ (1) selected Valdez-Flores et al. (2010) as its key study;[37] (2) incorporated the unpublished, not peer-reviewed update, Bender et al., with the help of Dr. Valdez-Flores, an ethylene oxide and sterilant trade group consultant;[38] (3) ignored breast cancer, even though TCEQ admits that breast cancer incidence data supports a much stronger toxicity factor,[39] because the "results [were] not consistent with TCEQ conclusions;"[40] and (4) ignored what it described as endogenous exposure. Neither TCEQ's proposed DSD, Dr. Valdez-Flores's analyses, nor the underlying study Bender et al. have undergone any independent peer review.[41] And, the study measuring endogenous exposure suggests normal, endogenous levels of ethylene oxide more than 65 times higher than the equivalent exogenous exposure of living directly next to a sterilizer facility, like Willowbrook or Burr Ridge.[42]

TCEQ Must Abandon the Proposed DSD and Adopt the IRIS Factor

The results of TCEQ's assessment appear predetermined. Industry wanted a weaker factor, and TCEQ is giving it to them. Far from rational and reasoned decision-making, TCEQ's attack on IRIS was and is merely a means to that end. For example, TCEQ had apparently chosen its factor *before* it decided how far off to allege the IRIS factor was, at one point claiming the IRIS factor overestimated 1,179 deaths, later revised to just 141.[43]

In addition, the public comment period for this action has been insufficient. TCEQ Guidelines require a 90-day public comment period for proposed DSDs, while data-rich or controversial chemicals deserve more than 90 days. Despite TCEQ Toxicology Division Director Michael Honeycutt recognizing that this factor would be "controversial,"[44] TCEQ originally only provided a 45-day public comment period. While we appreciate the extension of the comment period after Sierra Club and

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[37] Proposed DSD at 90.
[38] See the conflict of interest statement accompanying Valdez-Flores & Sielken, *Misinterpretation of categorical rate ratios and inappropriate exposure-response model fitting can lead to biased estimates of risk: Ethylene oxide case study*, 67(2) Regulatory Toxicology & Phamacology 206 (Nov. 2013), available https://www.sciencedirect.com/science/article/pii/S027323001300113X.
[39] Proposed DSD at 65 (supporting a factor of 1.36E-4 per ppb, while IRIS value is 9.1E-3 per ppb and proposed TCEQ value is 2.5E-6 per ppb).
[40] Proposed DSD at 65.
[41] Proposed DSD at 14 ("unpublished").
[42] Figure from PIR request release (citing Kirman and Hays, 2017 for "General Population Endogenous-Equivalent Exposure") (attached).
[43] Email from Michael Honeycutt to Erin Chancellor (June 18, 2019, 12:50PM) (attached).
[44] Email from Michael Honeycutt to Stephanie Perdue (June 18, 1:19PM) (attached). TCEQ guidelines require 90-days, and "[f]or data-rich or controversial substances, additional time may be allowed so interested parties will have adequate time to submit comments on the Proposed DSD." TCEQ Guidelines at 24.

other Texas groups[45] called attention to TCEQ's requirements, TCEQ still has refused to release the studies and calculations it relies on in its proposed DSD, such as Bender et al.[46] Commenters and the public still have not been provided a reasonable opportunity to evaluate the basis for TCEQ's proposed DSD.[47]

TCEQ cannot finalize its proposed cancer risk factor as is. TCEQ must (1) use a supralinear modeling approach, as EPA IRIS did, and stop ignoring risk at what TCEQ calls the endogenous exposure level. Further, TCEQ must (2) consider increased risk to children; (3) consider increased risk to women; (4) consider cancer incidence, not only mortality; (5) consider lifetime risk until the age of 85, not only 70; and (6) rely on scientifically sound, independent, peer-reviewed and published authority.

The EPA IRIS cancer risk factor for ethylene oxide represents the best available science, is peer reviewed, and accounts for increased risks to women and children. TCEQ's proposed value is not peer reviewed, ignores breast cancer risk and ignores increased risk to children. It also treats ethylene oxide that people breathe as equivalent to endogenous exposure that TCEQ argues can be ignored. But, as science shows, and EPA originally found, there is no safe level of exposure to a carcinogen. Cancer risk adds up, and EPA's IRIS value appropriately quantifies that excess cancer risk instead of treating it as zero or *de minimis* as TCEQ seeks to do with its sublinear analytical approach. TCEQ must adopt the 2016 IRIS factor to protect public health.

ANALYSIS

I. TCEQ may not finalize the proposed DSD because it has not satisfied the rulemaking requirements of Texas law.

A rule is (1) an agency statement of general applicability that either (a) implements, interprets, or prescribes law or policy, or (b) describes the procedure or practice requirements of a state agency; and (2) affects private rights or

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[45] Including Community In-Power and Development Association, Environmental Integrity Project, Air Alliance Houston, Environment Texas, and Texas Campaign for the Environment. Letter from Texas groups to TCEQ Toxicology Division (July 12, 2019), https://www.sierraclub.org/sites/www.sierraclub.org/files/sce-authors/u2034/CHP-TX-1900-TCEQToxicologydivEtOrequest.pdf (attached).

[46] Public Information Request (PIR) from Sierra Club to TCEQ (July 1, 2019) (attached); Letter from TCEQ Regarding PIR (July 17, 2019) (withholding documents) (attached); Letter from Sierra Club to Texas Attorney General (Aug. 27, 2019) (attached).

[47] Commenters reserve our right to submit additional relevant comments within a reasonable amount of time after withheld public information is made available.

procedures.[48] Agency statements that affect the interests of the public at large are rules that cannot be given the effect of law without public input.[49]

An agency must follow the rule-making procedures of the Texas Administrative Procedure Act, including providing public notice, a reasonable opportunity for and full consideration of comments, and a reasoned justification for the rule.[50] To satisfy the reasoned justification requirement, an agency's order adopting a rule must explain how and why the agency reached the conclusion it did;[51] an agency must demonstrate in a relatively clear and logical fashion that the rule is a reasonable means to a legitimate objective.[52] The essential legislative objective of the reasoned justification requirement is (1) to explain the rational factual, policy, and legal bases for the rule;[53] and (2) to ensure the agency fully considers submitted comments.[54]

A rule's reasoned justification is reviewed using an "arbitrary and capricious" standard, with no presumption that facts exist to support the rule.[55] An agency must demonstrate that it considered all the factors relevant to the legitimate objectives of the agency's rulemaking authority and engaged in reasoned decision-making.[56] An agency acts arbitrarily if it omits consideration of a factor the legislature intended the agency to consider; considers an irrelevant factor; or reaches a completely unreasonable result.[57]

A. TCEQ's proposed DSD is part of an unlawful rulemaking.

TCEQ's proposed DSD must follow the rulemaking requirements, but fails to do so.[58] The proposed DSD "implements" TCEQ "policy" guidance[59] to "prescribe"

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[48] Tex. Gov't Code § 2001.003(6); The Office of the Attorney General of Texas, Administrative Law Handbook 52 (2018), https://www.texasattorneygeneral.gov/sites/default/files/files/divisions/general-oag/AdministrativeLawHandbook.pdf.
[49] *El Paso Hosp. Dist. v. Tex. Health & Human Servs. Comm'n*, 247 S.W.3d 709, 714 (Tex. 2008).
[50] Tex. Gov't Code § 2001.023, .029, .033; *Reliant Energy, Inc. v Public Utility Comm'n of Texas*, 62 S.W.3d 833, 839 (Tex. Ct. App. 2001).
[51] *Reliant Energy*, 62 S.W.3d at 840; *see also National Ass'n of Indep. Insurers v. Texas Dep't of Ins.*, 925 S.W.2d 667, 669 (Tex. 1996).
[52] *TXU Generation Co LP v. Pub. Util. Comm'n of Texas*, 165 S.W.3d 821, 847 (Tex. Ct. App. 2005).
[53] *Reliant Energy*, 62 S.W.3d at 841 (citing *Railroad Comm'n v. ARCO Oil & Gas Co.*, 876 S.W.2d 473, 491 (Tex. App. 1994) (writ denied)).
[54] *Reliant Energy*, 62 S.W.3d at 841 (citing *ARCO*, 876 S.W.2d at 491).
[55] *Reliant Energy*, 62 S.W.3d at 841; *see also* ARCO, 876 S.W.2d at 490-491.
[56] *Reliant Energy*, 62 S.W.3d at 841; *see also ARCO,* 876 S.W.2d at 491.
[57] *Reliant Energy*, 62 S.W.3d at 841; *Statewide Convoy Transps. Inc. v. Railroad Comm'n*, 753 S.W.2d 800, 84 (Tex. Ct. App. 1988); *see also Bullock v. Hewlett-Packard Co.*, 628 S.W.2d 754, 756 (Tex. 1982) (stating a rule is arbitrary and capricious when it lacks a legitimate reason to support it).
[58] *See* Tex. Gov't Code 2001.003(6); *see also* 30 Tex. Admin. Code § 20.3 (subjecting the commission to APA rulemaking requirements).
[59] TCEQ Guidelines.

toxicity and screening values for ethylene oxide. These values will be incorporated into TCEQ's permitting, enforcement, and remediation processes, affecting the interests and rights of both permittees and the public. The public has a right to clean air,[60] and weaker values threaten this right. Further, TCEQ's proposed DSD is a rulemaking because it diverges from the procedure and practice requirements of TCEQ guidance,[61] thus "describ[ing]" amended "procedure or practice" of TCEQ.[62] TCEQ has not and cannot meet the rulemaking requirements of the Texas Administrative Procedure Act, including the reasoned justification requirement.

B. TCEQ's proposed DSD is a major environmental rule, requiring an in-depth regulatory analysis and impacts.

Additionally, rules with "the specific intent . . . to protect the environment or reduce risks to human health from environmental exposure and that may adversely affect in a material way," among others, "the public health and safety of the state" are major environmental rules. [63] Major environmental rules that are not adopted under a specific state law "shall" undergo an in-depth regulatory analysis and impact analysis.[64] The proposed DSD is a major environmental rule because toxicity factors are meant to measure and "reduce risks to human health;" the proposed DSD "may adversely affect . . . the public health;"[65] and the proposed DSD is not adopted under a specific state law. TCEQ must conduct the required in-depth regulatory and impact analyses.

C. TCEQ has not satisfied the Texas rulemaking requirements, including providing "all interested persons" a "reasonable opportunity" to participate.

TCEQ "shall follow [Texas] APA rulemaking requirements,"[66] and "when an agency promulgates a rule without complying with the proper rule-making procedures, the rule is invalid."[67] The Texas Administrative Procedure Act requires that proposed rules be published in the Texas Register,[68] and be reviewed by the legislature.[69] Major environmental rules must undergo in-depth regulatory and

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[60] 30 Tex. Admin. Code § 382.001; *see* F/R Cattle Co., Inc. v. State, 866 S.W.2d 200 (Spector, J., dissenting).
[61] TCEQ Guidelines.
[62] For example, the Texas Supreme Court invalidated an agency's calculations because they diverged from the agency's published rules, thereby describing amended procedures. *El Paso Hosp. Dist. v. Tex. Health & Human Servs. Comm'n*, 247 S.W.3d at 714.
[63] Tex. Gov't Code § 2001.0225(g)(3).
[64] Tex. Gov't Code § 2001.0225.
[65] *Id.* at § 2001.0225(g)(3).
[66] 30 Tex. Admin. Code § 20.3
[67] *El Paso Hosp. Dist. v Tex. Health & Human Services Comm'n*, 247 S.W.3d 709 (Tex. Sup. Ct. 2008); *see also* Tex. Gov't Code §§ 2001.035(a), 2001.038.
[68] Tex. Gov't Code § 2001.023.
[69] *Id.* at § 2001.032.

impact analyses.[70] Further, the agency must "give all interested persons a reasonable opportunity to submit data, views, or arguments, orally or in writing."[71]

TCEQ has fundamentally failed to meet the requirements of the Texas Administrative Procedure Act and its own regulations. TCEQ has deprived the public of the requisite "reasonable opportunity" to review and comment by (1) failing to provide notice to all interested persons, and (2) withholding the studies and other information on which TCEQ directly relies.

First, rules are required to be published in the Texas Register. Online-only requests for information and online-only notice of rulemakings are insufficient to alert interested parties, particularly those living near facilities that emit ethylene oxide. Second, TCEQ relies on unpublished studies and calculations yet has refused to release them to the public on request.[72] TCEQ has deprived the public of a "reasonable opportunity" to participate; the public cannot reasonably present their views or arguments on studies they have not seen.[73] TCEQ's proposed DSD is invalid.

Further, TCEQ guidelines require at least a 90-day public review and comment period and, "[f]or data-rich or controversial substances, additional time may be allowed so interested parties will have adequate time to submit comments on the Proposed DSD." Evidencing TCEQ's disregard for public comment, TCEQ provided, at first, only a 45-day comment period, despite the Director of the Toxicology Division, Dr. Michael Honeycutt's recognition that the document would be "controversial."[74] And, despite repeated requests, TCEQ continues to withhold the very studies and calculations it relies on from public disclosure.

At this point, due to the importance of this issue, the complexity of the proposed DSD and the many data-points it cites and on which it relies which it has not released for public review, Commenters still have not had an adequate opportunity to evaluate the proposed DSD. This is an instance where TCEQ must provide more than 90 days—at least another 45 days *after* public release, on TCEQ's website, of all documents on which TCEQ relies—to ensure a meaningful opportunity for public participation.

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[70] *Id.* at § 2001.0225.
[71] *Id.* at § 2001.029.
[72] Public Information Request from Sierra Club to TCEQ (July 1, 2019) (attached); Letter from Sierra Club to Texas Attorney General (Aug. 27, 2019) (attached).
[73] Public Information Request from Sierra Club to TCEQ (July 1, 2019) (attached); Letter from Sierra Club to Texas Attorney General (Aug. 27, 2019) (attached).
[74] Email from Michael Honeycutt to Stephanie Perdue (June 18, 2019, 1:19 PM) (attached).

II. TCEQ guidelines and regulations require TCEQ to adopt the IRIS cancer risk factor for ethylene oxide.

TCEQ guidelines and regulations direct use of the IRIS factor[75] and TCEQ has given no valid basis for rejecting the 2016 IRIS factor. If published toxicity factors are developed with procedures similar to TCEQ's procedures—such as IRIS factors, "TCEQ considers adoption of the published toxicity factor," "with preference given to values that have undergone an external peer review and public involvement process."[76] The IRIS factor has undergone extensive, external peer review and public involvement, while TCEQ's proposed factor has neither undergone external peer review nor reasonably involved the public.

"IRIS assessments undergo an external peer review,"[77] and substantial public involvement including: public nominations of substances for assessment or reassessment, multiple public availability and comment opportunities, including listening sessions and opportunity to comment and present at open, independent expert peer review meetings. On the other hand, "DSDs are not routinely submitted for external scientific peer review,"[78] and are only announced for public review online.[79] As such, "EPA's IRIS is often the preferred database from which to obtain existing inhalation and oral toxicity factors,"[80] and this preference is explicitly repeated in Texas regulation.[81]

TCEQ's present rejection of EPA IRIS is particularly irrational and arbitrary given that it previously adopted an IRIS calculation based on what TCEQ admitted was a "high quality" study of mouse tumors.[82] Yet, TCEQ's new factor is more than 50 times weaker, and TCEQ has provided no explanation, or even referred to its March 2017 factor.

Further, and importantly, as part of the scientific IRIS process, EPA considered, rejected, and provided a thorough, scientific explanation, supported by evidence in the record, for why it was *not* taking the very type of approach TCEQ now proposes to use. Unlike TCEQ's proposed DSD, EPA relied on the best available, published, peer-reviewed science; considered all relevant inhalation exposures; recognized and evaluated the breast cancer risk and the increased vulnerability and risk from childhood and early-life exposure; applied a model that fit the best available data; followed well-established scientific principles and

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[75] TCEQ Guidelines at 13; 30 Tex. Admin. Code § 350.73, 334.203.
[76] TCEQ Guidelines at 110.
[77] *Id.* at 135.
[78] *Id.* at 24.
[79] *Id.*
[80] TCEQ Guidelines at 135.
[81] *See, e.g.*, 30 Tex. Admin. Code § 350.73, 334.203.
[82] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached).

guidelines; and allowed for meaningful public review and multiple rounds of independent, scientific peer review that approved EPA's methodology and conclusions.[83]

TCEQ guidelines follow IRIS in determining factors protective of public health, and give preference to factors that are peer-reviewed and meaningfully involve the public. TCEQ must adopt the IRIS factor which was developed with the "well-established" procedures identified and allegedly used by TCEQ, and was peer-reviewed and reasonably involved the public. TCEQ cannot arbitrarily diverge from its own guidelines and must abandon its proposed cancer risk factor.

III. TCEQ cannot finalize the proposed cancer risk factor because TCEQ has not provided any valid reason to develop its own cancer risk factor.

The IRIS factor for ethylene oxide represents the best available science and TCEQ has no valid reason to develop its own toxicity factor. TCEQ selects chemicals for toxicity factor development if (1) they have been detected in air monitoring, (2) permits are frequently issued for them, (3) the public has expressed concerns about them,[84] or (4) the existing factor is outdated.[85] Ethylene oxide has been detected in air monitoring, included in issued permits, and has concerned the public long before TCEQ decided to create its factor. And, the existing IRIS factor, finalized in December of 2016, is not outdated.

TCEQ's new, second factor is doubly strange and arbitrary considering it is more than 50 times weaker than TCEQ's first selected cancer risk factor—a factor TCEQ itself found was based on a "high quality" study.[86] And, TCEQ has provided no explanation for why it has abandoned the value it selected in March 2017 (which was also too weak—though stronger than the newly proposed DSD cancer risk factor). TCEQ has no valid reason to try to develop a different toxicity factor for ethylene oxide in light of the robust, scientific, peer-reviewed 2016 IRIS factor.

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[83] *See* IRIS; EPA IRIS Assessment History for Ethylene Oxide, https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025#tab-3 (last visited Sept. 23, 2019); Letter from Scientists J. Sass *et al.* to EPA on IRIS Factor (Apr. 26, 2019); Union of Concerned Scientists' Comment Letter to EPA on IRIS Factor (2019) (attached); Nat'l Ass'n of Clean Air Agencies' Comment Letter to EPA on IRIS Factor (2019) (attached); Comments of Environmental and community groups to EPA regarding Proposed National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review (Apr. 26, 2019) (attached).

[84] TCEQ, *About the Chemicals Under Consideration for Toxicity Factor Development*, https://www.tceq.texas.gov/toxicology/esl/develop (last visited Sept. 22, 2019).

[85] TCEQ Guidelines at 24.

[86] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached).

IV. TCEQ cannot finalize the proposed cancer risk factor because this factor would not properly protect public health as required by the Texas Clean Air Act and Texas Risk Remediation Program, particularly the health of women, children, and communities already overburdened by toxic air pollution.

The Texas Clean Air Act (TCAA) and Texas Risk Reduction Program (TRRP) charge TCEQ with "controlling or abating air pollution and emissions of air contaminants, consistent with the protection of public health,"[87] and cancer risk factors "must be protective of human health and the environment."[88] Cancer risk factors represent the upper-bound excess risk estimated to result from continuous lifetime exposure to one microgram of a chemical per cubic meter of air.[89] TCEQ uses these factors to determine (1) health-protective soil and groundwater cleanup levels under the TRRP,[90] and (2) to calculate air permitting effects screening levels under the TCAA[91]—TCEQ assumes that exposure to emissions under an effects screening level is safe.

However, TCEQ's proposed toxicity factor and resulting effects screening level fail to protect public health, as required by both the TCAA and the TRRP. First, TCEQ's claimed "reality check" on EPA's IRIS factor is flawed—EPA's IRIS factor represents the best available science and accurately reflects risk. Further, TCEQ must (1) use a supralinear modeling approach; (2) consider increased risk to children; (3) consider increased risk to women; (4) consider cancer incidence, not only mortality; (5) consider lifetime risk until the age of 85, not only 70; and (6) rely on scientifically sound, independent, peer-reviewed and published authority.

A. EPA's IRIS factor represents the best available science and reflects real-world risk to public health from ethylene oxide.

TCEQ claims that it has performed a "reality check" of the exposure-response model selected by EPA and found that the observed cancer deaths would be higher if EPA's value were accurate. Its argument has no rational basis in the record and does not provide a reasoned ground to refuse to apply the IRIS value. TCEQ's calculation relied on a flawed approach in that it uses baseline cancer rates attributable to the general population as opposed to EPA's approach, which estimates risk relative to the internal referent worker population.[92]

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[87] 30 Tex. Admin. Code § 382.002.
[88] *Id.* at § 350.73; *see also* Tex. Admin. Code § 382.002-.003.
[89] TCEQ Guidelines at 5.
[90] *Id.* at 10.
[91] *Id.* at 10-13.
[92] Proposed DSD at 98.

EPA appropriately recognized the need to compare cancer rates relative to workers with zero exposure as the internal referent population as opposed to TCEQ's method, which applies to an external population.[93] This method was both used by EPA and recommended by the Science Advisory Board (SAB) Panel in 2015. In defending its use of the internal referent population, EPA states that "[i]nternal analyses are generally preferred over external analyses because the referents are from the same cohort as the exposed subjects, potentially reducing confounding as well as the healthy worker effect, which can mask an increase in risk…"[94] In its 2015 review of EPA's ethylene oxide assessment, the SAB provided the following recommendation with respect to the use of external standards:

> The SAB recommends down-weighting all epidemiological results that are based on external standards (e.g., standardized mortality ratio, standardized incidence ratio). The presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases.[95]

Unlike the SAB recommendation, TCEQ bases its cancer rate estimates on the general population, which has higher baseline cancer risks compared to workers.

B. TCEQ must use a supralinear modeling approach; its discussion of "endogenous exposure" does not justify using, in effect, a threshold approach.

EPA properly applied a supralinear model to assess cancer risk from ethylene oxide.[96] TCEQ proposes, however, that the carcinogenicity of ethylene oxide "is no more than linear, and arguably sublinear."[97] However, instead of using at least a linear approach in the interest of public health, TCEQ selected a sublinear model, like Valdez-Flores et al. (2010), for the high exposure data, despite the supralinear dose-response behavior of ethylene oxide as explained by IRIS. TCEQ then extended that sublinear model far into the range of low-dose exposures, without scientific

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[93] IRIS appendices at H-2 (attached).
[94] *Id.* at J-711; *see, e.g.*, Arrighi, H & Hertz, Picciotto, I, *The evolving concept of the healthy worker survivor effect*, 5(2) Epidemiology 189 (Mar. 1994), https://insights.ovid.com/crossref?an=00001648-199403000-00009.
[95] SAB, Review of the EPA's *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014)* at 18-19 (EPA-SAB-15-012) (Aug.7, 2015), https://yosemite.epa.gov/sab/sabproduct.nsf/fedrgstr_activites/BD2B2DB4F84146A585257E9A0070E655/$File/EPA-SAB-15-012+unsigned.pdf.
[95] *Id.* at 1, 12.
[96] IRIS at 1-4, 3-7 to 3-8, 4-10.
[97] Proposed DSD at 20.

evidence to support this. The TCAA and TRRP require factors that protect public health—not "arguably" protect public health.[98]

Scientists assess dose-response, epidemiological, and other available data, often from workers or other people with high exposure to a chemical, and extrapolate to the lower doses to derive cancer risk factors. In modeling risk, dose-response models for carcinogens use an increasing line of increased risk based on increments (or doses) of increased exposure (often described as "linear" as shorthand, with variations based on fit to the best available evidence). These models recognize "that any dose, no matter how small, increases the probability of causing an effect," of causing cancer.[99] Sublinearity, which TCEQ is attempting to use, reflects a slowly increasing risk at low doses with the slope increasing at higher doses, or a concave curvature. Supralinearity, which EPA determined is appropriate here based on the evidence, reflects a sharper increase in risk at low doses with the slope decreasing at higher doses, or a convex curvature.[100] Because the dose-response relationship may not be easily studied for the lower doses of interest, typical risk assessment practice is to model the high exposure data and then extrapolate down to lower doses from a given point on the model at the low end of the observable range of the available data.[101] While supralinear, linear, and sublinear extrapolations recognize increased risk with increased exposure, threshold extrapolations (often used for non-carcinogenic exposure) assume that exposure below a certain limit, or threshold, is safe.[102] It is well-established that threshold models are unjustifiable for carcinogens, especially mutagenic carcinogens such as ethylene oxide.[103]

Yet, TCEQ's consideration of what it calls "endogenous exposure" levels of ethylene oxide creates in effect a threshold of *exogenous* exposure through inhalation of ethylene oxide. TCEQ disregards inhaled pollution and cancer risk resulting from that exposure at levels below that threshold. Specifically, TCEQ claims that ethylene oxide's effects "would be buffered by cellular repair mechanisms," "at doses near the endogenous range."[104] Instead of recognizing that "any dose, no matter how small, increases the probability of causing an effect," TCEQ decides some risk is "not biologically meaningful," or "biologically

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[98] *Id.* at 20.
[99] TCEQ Guidelines at 3.
[100] *Id.* at 19, Fig. 1.
[101] EPA, Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F (Mar. 2005), https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf), https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf; Proposed DSD at 78 ("extrapolate from the adjusted POD to lower exposure based on MOA analysis").
[102] TCEQ Guidelines at 3.
[103] *Id.* at 3-4; *NRDC v. EPA*, 824 F.2d 1146, 1147 (D.C. Circ. 1987) (en banc) ("Current scientific knowledge does not permit a finding that there is a completely safe level of human exposure to carcinogenic agents.").
[104] Proposed DSD at 4.

significant."[105] It is settled science, however, and recognized by both Congress and the courts that carcinogens have no safe threshold.[106] TCEQ's proposed DSD would treat harmful ethylene oxide exposure as "insignificant" for people breathing this pollution.

TCEQ cannot justify its use of a sublinear model based on Valdez-Flores et al. (2010). Both IRIS and even TCEQ itself—in March 2017—took issue with Valdez-Flores et al. (2010). IRIS detailed a number of concerns with Valdez-Flores et al. (2010) and explained that its sublinear modeling approach was a "poor fit" to the data;[107] EPA did not consider it a strong study.[108] TCEQ also similarly rejected the values derived by Valdez-Flores et al. (2010) in March 2017.[109] TCEQ has provided no reason or explanation for why it now uses the sublinear model of Valdez-Flores et al. (2010) or selects it as its key study.

Further, TCEQ's use of "endogenous exposure" to ignore serious cancer risk is problematic for at least three reasons: (1) TCEQ improperly considers what it calls "cellular repair mechanisms" as able to undo cancer risk, without adequate evidence or explanation, (2) TCEQ ignores the already high background rates of lymphatic and breast cancer likely attributable in part to exposure to ethylene oxide, and (3) the studies on which TCEQ rely appear to vastly overestimate any "endogenous levels" of ethylene oxide and fail to fit the available data.

First, TCEQ has not cited and cannot point to any evidence demonstrating that the human body can negate cancer risk from inhaling any threshold level of ethylene oxide through a process of "cellular repair." While the body has DNA repair mechanisms to address DNA adducts formed by naturally occurring endogenous ethylene oxide levels, this response mechanism is imperfect and does not account for or protect against inherent variability and increased susceptibility for vulnerable populations.[110] Even if there were any such evidence that "cellular repair" could negate cancer risk in a healthy individual in a community, TCEQ has provided no evidence that a child, a fetus in utero, or another vulnerable member of the population, could rely on "cellular repair" to avoid developing cancer altogether.

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[105] *Id.* at 6, 24.
[106] S. Rep. No. 101-228 at 171, 1990 U.S.C.C.A.N. at 3560 (amending the provision, 42 U.S.C. § 7412, that requires regulation of ethylene oxide as a hazardous air pollutant); S. Rep. No. 101-228, at 175, 1990 U.S.C.C.A.N. at 3560; *NRDC v. EPA*, 824 F.2d 1146, 1147 (D.C. Circuit 1987) (en banc) ("Current scientific knowledge does not permit a finding that there is a completely safe level of human exposure to carcinogenic agents.").
[107] IRIS at 4-19.
[108] IRIS appendices at Sec. A.2.20.
[109] TCEQ, Ethylene Oxide (Mar. 6, 2017) (attached).
[110] IRIS at 3-66, 3-72.

Second, in assuming endogenous levels are safe, TCEQ fails to consider that inhaling ethylene oxide results in exposure above and beyond any background endogenous exposure. The endogenous levels and background ambient concentrations of ethylene oxide that TCEQ ignores likely contribute to the high background rates for both lymphatic and breast cancer incidence in the general population.[111] The chart TCEQ provides demonstrates that TCEQ treats risk at lower doses, in the range of what it considers endogenous exposures, as essentially zero.[112] TCEQ's approach is scientifically unjustifiable.

Third, the study TCEQ relies on, Kirman and Hays (2017) suggests normal endogenous levels of ethylene oxide more than 65x higher than equivalent exposure from living directly next to a sterilizer, like in Willowbrook or Burr Ridge.[113]

For these reasons, TCEQ's approach is scientifically unjustifiable. As EPA found, ethylene oxide is a "DNA-reactive, mutagenic, multi-site carcinogen in humans and laboratory animal species," such that "low-dose extrapolation is strongly supported," and "[t]he inclusion of a nonlinear approach is not warranted."[114] TCEQ's attempt to use endogenous levels to ignore communities' inhalation of carcinogenic industrial toxic air pollution below any threshold is unjustifiable and unsupported. TCEQ has not justified and cannot justify treating any amount of inhalation of ethylene oxide as if it is safe or can be ignored and assumed not to cause cancer. A supralinear modeling approach, like that of EPA IRIS, is supported by the best available science.

C. TCEQ must consider increased risk to and vulnerability of children and properly use age-dependent adjustment factors.

TCEQ acknowledges that children are more susceptible to the mutagenic effects of ethylene oxide,[115] and claims to "include adjustments for [EPA (2005b) age-dependent adjustment factors (ADAFs)] using the approach described in Sielken and Valdez-Flores (2009)."[116] However, EPA found this study "misinterpreted the application of the [ADAFs] such that, even though they purported to apply the factors, this application had no impact on the risk estimate."[117] Toxicity factors must protect not only adults but also children. TCEQ's proposed factor is invalid because it fails to consider increased risk to from childhood exposures, and TCEQ must adopt the 2016 IRIS value.

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[111] *Id. at* 4-95.
[112] Proposed DSD at 19, Fig. 1.
[113] Figure from PIR request release (citing Kirman and Hays, 2017 for "General Population Endogenous-Equivalent Exposure") (attached).
[114] *See* IRIS appendices at H-13.
[115] Proposed DSD at 69.
[116] *Id.* at 61, 69.
[117] IRIS appendices at A-34 to A-35.

Further, prenatal exposure to carcinogens increases susceptibility to those carcinogens throughout life. EPA has recognized this fact, but has not yet developed adjustment factors to account for this risk.[118] The National Academy of Sciences has identified the lack of accounting for "*in utero* periods" of exposure as a major omission in EPA's 2005 cancer guidelines.[119] TCEQ should apply a factor that is *more protective* than the 2016 IRIS value to account for the additional cancer risk a person faces over their lifetime due to cross-placental carcinogenic exposure during early fetal development.

In 2009, California's Office of Environmental Health Hazard Assessment (OEHHA) published a review of the scientific literature surrounding prenatal susceptibility,[120] and developed procedures for exposure assessment during fetal development.[121] OEHHA specifically discusses the use of a 10X adjustment factor for cancer risk to account for prenatal (third trimester) to age 2 exposures.

EPA staff in the Office of Children's Health Protection published a recent peer-reviewed analysis of the dataset used by OEHHA that validates the use of a 10X factor for prenatal exposure, demonstrating that TCEQ's proposal (which does not account at all for transplacental or *in utero* exposure) underestimates harm and risk to public health.[122]

TCEQ's proposed DSD is insufficient to prevent harm at the critical stage of embryonic development, and fails to protect public health. Exposure to toxic agents in the intrauterine stage of life has one of the most important impacts on lifelong

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[118] EPA, Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001B at 4-5 (Mar. 2005), https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf; EPA, Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, EPA/630/R-03/003F at 14 & Table 1a, (Mar. 2005) (discussing research on human and animal cancer risks from prenatal exposure).

[119] National Academy of Sciences, National Research Council, Science and Decisions: Advancing Risk Assessment at 112-13, 196, (2009) https://doi.org/10.17226/12209 ("NAS 2009") (noting that it is a "missing" default that EPA recognizes in utero carcinogenic activity, but fails to take account of it or calculate any risk for it as "EPA treats the prenatal period as devoid of sensitivity to carcinogenicity").

[120] *See* CalEPA, Technical Support Document for Cancer Potency Factors appx. J, *In Utero* and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures (May 2009), https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf.

[121] *See* CalEPA, Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis at 1-6 to 1-7 (Aug. 27, 2012), https://oehha.ca.gov/air/crnr/notice-adoption-technical-support-document-exposure-assessment-and-stochastic-analysis-aug.

[122] Dzubow, R. et al., *Comparison of carcinogenic potency across life stages: implications for the assessment of transplacental cancer risk*, 82(13) Journal of Toxicology and Environmental Health 769 (Aug. 11, 2019), DOI: 10.1080/15287394.2019.1650860.

health, and can be irreversible. TCEQ should use the approach described by OEHHA to properly account for the effects of in utero exposure.

D. TCEQ must consider breast cancer risk.

TCEQ admits that breast cancer incidence data supports a much stronger toxicity factor.[123] However, TCEQ discounts this as "not consistent with TCEQ conclusions" and "endogenous [ethylene oxide] levels,"[124] and thus ignores it,[125] notwithstanding data showing relatively high background levels of breast cancer incidence in the U.S. population.[126] TCEQ's proposed factor is invalid and unlawful because it fails to consider risks to women. The EPA IRIS value fully considered breast cancer and must be adopted to protect women.

To appropriately model breast cancer incidence, IRIS used a two-piece linear spline model. Such a model is particularly useful in exposure-response relationships in which the relative risk increases initially with increasing exposure but then tends to increase less or plateau at high exposures—supralinearity[127]—this is most certainly the case when modeling the unit risk estimate for breast cancer incidence. In its 2015 review, the SAB endorsed IRIS's modeling approach.

Health effects and risks are more certain when present in both animal and human data. Evidence of breast cancers from exposure to ethylene oxide are present in both mice,[128] and human data.[129] However, TCEQ decided there was "no statistically increased cancer incidence" for breast cancer[130] and eliminated breast cancer as a health endpoint of concern. TCEQ cannot arbitrarily ignore breast cancer risk.

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[123] Proposed DSD at 65 (supporting a factor of 1.36E-4 per ppb, while IRIS value is 9.1E-3 per ppb and TCEQ value is 2.5E-6 per ppb).
[124] Proposed DSD at 65.
[125] *Id.* at 65.
[126] IRIS at 4-95 ("DNA damage from low exogenous [ethylene oxide] exposures may appear "negligible" (Marsden et al., 2009) compared to those from endogenous [ethylene oxide] exposure, low levels of exogenous [ethylene oxide] may nonetheless be responsible for additional risk (above background risk) above *de minimis* risk levels, which are generally 10-6 to 10-4 for cancer. This is not inconsistent with the much higher levels of background cancer risk, to which endogenous [ethylene oxide] may contribute, for the two cancer types observed in the human studies… lymphoid cancers have a background lifetime incidence risk on the order of 3%, while the background lifetime incidence risk for breast cancer is on the order of 15%.").
[127] IRIS appendices at D-2.
[128] Houle, CD., et al., *Frequent P53 and H-Ras Mutations in Benzene- and Ethylene Oxide-Induced Mammary Gland Carcinomas from B6C3F1 Mice*, 34(6) Toxicologic Pathology 752 (Oct. 1, 2006), doi:10.1080/01926230600935912 (animal evidence of mammary gland carcinomas in female mice was observed in a standard rodent bioassay).
[129] *See* IRIS appendices at A-54 (discussing breast cancer mortality vs incidence).
[130] Proposed DSD at 89-90.

E. TCEQ must consider cancer incidence, not only cancer mortality.

TCEQ underestimates cancer risk by analyzing cancer mortality and arbitrarily ignoring cancer incidence.[131] TCEQ specifically chooses lymphoid cancer mortality as its critical cancer endpoint.[132] However, lymphoid cancers have substantial survival rates.[133] Focusing on cancer mortality, especially lymphoid cancer mortality, and not incidence underestimates the excess cancer risk of ethylene oxide exposure. *Survival* is not a reason to discount cancer. Toxicity factors must not only protect the public from *dying* from cancer, but from developing cancer at all. Further, looking at mortality ignores that there is disproportionate mortality for particular demographic groups, such as people with limited financial resources and access to health care. IRIS appropriately analyzed incidence, not mortality, and TCEQ must adopt the IRIS value.

F. TCEQ must consider a sufficient lifetime period of exposure of 85 years instead of 70 years.

TCEQ's use of a 70-year cutoff underestimates risk by ignoring cancer incidence or mortality after age 70 attributable to exposure to ethylene oxide.[134] EPA computed risk up to 85 years, including an average lifespan of about 75 years, in part to appropriately address early-life exposure.[135] TCEQ should include exposure and potential harm at ages up to 85 years in its life-table analysis rather than arbitrarily stopping at 70 years, without any reasoned explanation based on the best available science.

G. TCEQ must consider the disproportionate exposure of people of color and communities with multiple sources of ethylene oxide.

TCEQ does not acknowledge or address the disproportionate exposure or risk that Texas communities with environmental justice concerns face from ethylene oxide. TCEQ has a responsibility to consider and address environmental justice, for similar reasons stated in the 1994 Executive Order on Environmental Justice.[136] There is strong scientific evidence that socioeconomically vulnerable groups, such as people of color and low-income people, have increased susceptibility and thus

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[131] *Id.* at 65-66.
[132] *Id.* at 66.
[133] IRIS at 1-2 to 1-3.
[134] Proposed DSD at 91.
[135] IRIS at 4-9.
[136] Executive Order 12898, Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations (Feb. 11, 1994), https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf.

increased risk from environmental exposure to pollutants.[137] Yet TCEQ's proposed DSD completely ignores this increased risk and vulnerability. TCEQ includes no adjustment factors to account for the higher vulnerability that Texans exposed to ethylene oxide face—particularly if they are already in a community with unacceptably high cancer risk, or where there are multiple sources of carcinogenic pollution, such as the Houston Ship Channel communities.[138] Furthermore, TCEQ's decision not to include breast cancer incidence or mortality as a critical health endpoint in its derivation of its toxicity factor completely ignores the fact that Black women face a greater mortality rate from breast cancer—39% higher in 2015, according to the American Cancer Society than White women.[139]

Evidence of increased vulnerability and harm due to socioeconomic disparities and multiple source exposure only further demonstrates that TCEQ cannot rationally justify applying a toxicity factor that is weaker than the IRIS value. If anything, TCEQ should apply a factor that is *more protective* than the 2016 IRIS value to assure that overburdened communities like neighborhoods in the Houston Ship Channel, Port Arthur, and Corpus Christi, do not face as much additional ethylene oxide exposure as a community where there was no existing excess cancer risk or pollution already.

Further, TCEQ must follow all applicable civil rights law in this proceeding and all other actions. TCEQ has previously faced a serious complaint (No. 01R-00-R6) that it did not follow applicable requirements of Title VI of the Civil Rights Act, 42 U.S.C. § 2000d et seq., including public participation and calculations, in regard to an air permit modification, and EPA accepted that complaint for investigation. Recently, TCEQ entered into an agreement to attempt to avoid liability for civil rights violations and discrimination, and that agreement is attached.[140] Notably, under that agreement (see Section III), EPA is now requiring, and TCEQ has agreed, to hold at least two accessible community meetings to discuss opportunities for public involvement, with advance notice, accessibility, consideration of multilingual information and interpretation services for that process. TCEQ must ensure at least that it grants a public hearing and supports a similar level of public

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[137] *See, e.g.,* NAS 2009, at 135-39, 145-51 (explaining that "[h]ow the population responds to chemical insults depends on individual responses, which vary among individuals"; and "[i]f the sensitive people constitute a distinct group either because of their numbers or because of identifiable characteristics—such as ethnicity, genetic polymorphism, functional or health status, or disease—they should be considered for separate treatment in the overall risk assessment"); *id.* at 112 (noting that it is important to address variability due to factors "such as age, ethnic group, socioeconomic status, or other attributes," and explaining that "there is a need for a nonzero default to address the variation in the population expected in the absence of chemical-specific data").

[138] NATA data, above.

[139] *See* American Cancer Society, Breast Cancer Facts & Figures 2017-2018, at 9 & Fig. 6b (2017), https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf.

[140] Informal Resolution Agreement between the TCEQ and US EPA at 2 (May 2017) (attached).

participation in this proceeding because TCEQ is proposing to use the ethylene oxide cancer risk factor for permitting proceedings. Failure to provide a meaningful opportunity for public participation here would contravene Title VI.

H. TCEQ must rely on scientifically sound, independent, peer-reviewed and published studies which the public can reasonably evaluate.

TCEQ relied heavily on a dataset—the UCC cohort—that EPA found "crude[]" and "not of sufficient quality . . . for the derivation of unit risk estimates."[141] TCEQ further relied on analysis by Dr. Valdez-Flores of an "unpublished update" of the UCC cohort that "has become available" to him.[142] Dr. Valdez-Flores is a former consultant for ethylene oxide chemical and sterilant trade groups, and his research has been funded by the Ethylene Oxide Sterilant Association and the American Chemistry Council.[143] And, though the UCC study update has been submitted for publication, TCEQ has thus far declined to share this study with the public.

Science must be conducted objectively, present results fairly and accurately, and avoid conflicts of interest.[144] However, TCEQ relies on a number of studies—published in response to the finalized 2016 IRIS review—each of which are funded by industry including, for example, the American Chemistry Council.[145] These studies do not meet principles of scientific integrity or reasoned decision-making.

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[141] IRIS appendices at K-6.

[142] Proposed DSD at 91, 14, 27. Even as TCEQ tries to rely on an unpublished study, TCEQ discounts breast cancer incidence data because underlying information used by researchers is "not publicly available." Proposed DSD at 51, 60-61. By contrast with the unpublished, not peer-reviewed study on which TCEQ is attempting to rely here, EPA considered and used the breast cancer data through reliance on a published, peer-reviewed study that considered those data. *See, e.g.*, IRIS Summary at 2; IRIS at 4-104 (citing Steenland 2003).

[143] See the conflict of interest statement accompanying Valdez-Flores & Sielken, *Misinterpretation of categorical rate ratios and inappropriate exposure-response model fitting can lead to biased estimates of risk: Ethylene oxide case study*, 67(2) Regulatory Toxicology & Phamacology 206 (Nov. 2013), available https://www.sciencedirect.com/science/article/pii/S027323001300113X.

[144] EPA, Policy on EPA Scientific Integrity, https://www.epa.gov/osa/policy-epa-scientific-integrity (last visited Sept. 23, 2019).

[145] See the conflict of interest statement accompanying Valdez-Flores & Sielken, *Misinterpretation of categorical rate ratios and inappropriate exposure-response model fitting can lead to biased estimates of risk: Ethylene oxide case study*, 67(2) Regulatory Toxicology & Phamacology 206 (Nov. 2013), available https://www.sciencedirect.com/science/article/pii/S027323001300113X; and the conflict of interest statement accompanying Kirman & Hays, *Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide,* 91 Regulatory Toxicology & Pharmacology 165 (Dec. 2017), available at https://www.sciencedirect.com/science/article/abs/pii/S0273230017303471?via%3Dihub.

By contrast, IRIS follows the EPA's Office of the Science Advisor's[146] Principles of Scientific Integrity. These principles "ensure scientific integrity throughout the EPA and promote scientific and ethical standards" throughout agency actions.[147] Regarding conflicts of interest, "the Principles of Scientific Integrity sets forth the Agency's commitment to conducting science objectively, presenting results fairly and accurately, and avoiding conflicts of interest." EPA's IRIS value follows these principles but thus far TCEQ's proposal does not.

V. TCEQ's proposed DSD must be independently, externally peer-reviewed.

TCEQ guidelines generally avoid peer review for its DSDs due to the cost.[148] However, TCEQ guidelines allow for external scientific review with "sufficient public interest [] and if resources are available."[149] TCEQ must engage in an external, *independent* scientific peer review if it proceeds with the proposed DSD. Review by industry affiliates will not suffice.[150]

Resource constraints are not a reason to avoid independent, external peer review. TCEQ has already disregarded any concerns about "time and resource constraints" by deciding to develop its own factor, and spend as-of-yet undisclosed taxpayer funds to contract and pay for another analysis of data.[151] The most efficient and least expensive and resource-intensive approach would simply be to adopt the EPA IRIS peer-reviewed value.

EPA went through nearly a decade of thorough external, independent scientific peer review before finalizing the 2016 cancer risk value, and TCEQ's proposed toxicity factor *is three orders of magnitude weaker* than EPA's factor. EPA's evaluation process benefited both from internal agency review as well as review by other federal agencies, included two extensive external peer review processes (in 2006 and 2014) conducted by its independent Science Advisory Board (SAB). EPA further hosted public meetings where input could be incorporated into the process, and it even convened an additional panel of experts under SAB during its second round of review. On that basis alone, TCEQ must subject its value to independent, external peer review that is equivalent to, and equally robust as, the IRIS review process. It can have no rational basis to reject or ignore the EPA peer-

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[146] The Office of the Science Advisor "…provides leadership on science and technology issues and policy to facilitate the integration of the highest quality science into the Agency's policies and decisions." EPA, *About OSA*, https://www.epa.gov/osa (last visited Sep. 23, 2019).
[147] EPA, *Policy on EPA Scientific Integrity*, https://www.epa.gov/osa/policy-epa-scientific-integrity (last visited Sept. 23, 2019).
[148] TCEQ Guidance at 24.
[149] *Id.* at 24.
[150] EPA, Policy on EPA Scientific Integrity, www.epa.gov/osa/policy-epa-scientific-integrity (last visited Sept. 23, 2019).
[151] TCEQ Guidance at 24.

reviewed value when TCEQ has not even subjected its own alternative to similar peer review.

TCEQ should simply adopt the EPA IRIS factor. However, if TCEQ chooses to pursue their own factor, Commenters request that: (1) the proposed DSD receive an independent, external peer review, and (2) TCEQ resubmit the proposed DSD for public notice and comment after making the necessary changes based on that independent, external peer review.

CONCLUSION

At every step, TCEQ has sided with industry and against its own guidelines and the public. First, TCEQ failed to adopt the EPA 2016 IRIS value, which represents the best available science, is peer-reviewed and reasonably involved the public. Next, TCEQ endeavored to develop its own toxicity factor, following industry requests and contrary to its own earlier conclusions—identifying Valdez-Flores et al. (2010) as the key study and ignoring breast cancer. And TCEQ's factor is *three orders of magnitude less protective,* as urged by industry. Despite recognizing this factor as "controversial," TCEQ initially failed to give the public the minimum required 90-day public comment and review period, and provided online-only notice. And even with the comment period extension, TCEQ continues to withhold from the public the very studies and calculations it relies on and directly cites, further depriving the public of a reasonable opportunity for participation. Finally, TCEQ has failed to subject its factor to independent, scientific peer review.

These many problematic decisions result in a factor that ignores cancer incidence, ignores breast cancer risk, and ignores increased risk from childhood exposures. Conveniently for industry members who wish to ignore the effects of their pollution and try to avoid common-sense pollution control measures, the extreme cancer risk Texas communities are experiencing would appear to be removed if TCEQ's proposed factor were applied, even though the best available scientific evidence demonstrates that Texans would continue to suffer from ethylene oxide pollution.

TCEQ should put protection of Texans' health above the desires of the chemical industry. For all of the above reasons, TCEQ's proposed factor is unlawful and invalid, and TCEQ must adopt EPA's 2016 IRIS value, which represents the best available science, is peer-reviewed, and reasonably involved the public.

We ask TCEQ to abandon the proposed DSD and simply adopt and apply the EPA's 2016 IRIS value, to protect public health, particularly the health of Texas children. Thank you for your time and consideration of these comments.

Sincerely,

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Texas Environmental Justice Advocacy Services (t.e.j.a.s.)
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Coastal Alliance to Protect our Environment (CAPE)
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LIST OF APPENDIX DOCUMENTS ATTACHED

1. EPA, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide In Support of Summary Information on the Integrated Risk Information System (Dec. 2016) (EPA IRIS 2016), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf.
2. EPA IRIS 2016 Executive Summary (Dec. 2016), http://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1025_summary.pdf.
3. EPA IRIS 2016 Appendices (Dec. 2016).
4. Informal Resolution Agreement between the TCEQ and US EPA (May 2017).
5. EPA, What is Ethylene Oxide? https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/background-information-ethylene-oxide#what (last updated Aug. 20, 2019).
6. TCEQ, Guidelines to Develop Toxicity Factors (revised Sept. 2015), https://www.tceq.texas.gov/assets/public/comm_exec/pubs/rg/rg-442.pdf.
7. TCEQ, Ethylene Oxide (Mar. 6, 2017).
8. American Chemistry Letter to TCEQ, Submission of Toxicology Information for Ethylene Oxide (Nov. 2017).
9. TCEQ, June 18, 2018 update.
10. Exponent, American Chemistry Council Ethylene Oxide Panel, Recommendation for Inhalation Cancer Risk.
11. Exponent, Powerpoint of Jane Teta (June 26, 2018).
12. National Environmental Justice Advisory Council letter (May 3, 2019), https://comingcleaninc.org/assets/media/documents/NEJAC-Letter-Ethylene%20Oxide-May-3-2019-Final.pdf.
13. Figure from TCEQ PIR request release (citing Kirman and Hays, 2017 for "General Population Endogenous-Equivalent Exposure").
14. Email from Michael Honeycutt to Erin Chancellor (June 18, 2019, 12:50PM).
15. Email from Michael Honeycutt to Stephanie Perdue (June 18, 2019, 1:19PM).
16. Public Information Request (PIR) from Sierra Club to TCEQ (July 1, 2019).
17. Letter from TCEQ Regarding PIR (July 17, 2019).
18. Letter from Sierra Club to Texas Attorney General (Aug. 27, 2019).
19. Union of Concerned Scientists' Comment Letter to EPA on IRIS Factor (2019).
20. Nat'l Ass'n of Clean Air Agencies' Comment Letter to EPA on IRIS Factor (2019).
21. Comments of Environmental and community groups to EPA regarding Proposed National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review (Apr. 26, 2019).
22. Sierra Club's Lone Star Chapter, Community In-Power and Development Association, Environmental Integrity Project, Air Alliance Houston, Environment Texas, and Texas Campaign for the Environment. Letter from Texas groups to TCEQ Toxicology Division (July 12, 2019), https://www.sierraclub.org/sites/www.sierraclub.org/files/sce-authors/u2034/CHP-TX-1900-TCEQToxicologydivEtOrequest.pdf.

Sept. 25, 2019

In the draft Cancer Dose-Response Assessment (6/28/2019) for ethylene oxide, the Texas Commission on Environmental Quality proposes alternative evaluations to the EPA IRIS (2016) ethylene oxide (ETO) quantitative cancer risk assessment. As there are not new basic data about cancer risks from ethylene oxide, the Texas assessment relies on the same science base as did EPA. Texas has chosen different interpretations and models for the data resulting in a cancer risk estimate more than 1000 times lower than the IRIS recommended cancer unit risk. There are a sequence of choices in the Texas assessment that deserve comment, and in my view, are wrong choices, which do not protect public health. I have noted below some of the major ones. More detailed comments are available upon request.

I should note that I, along Dr. Stayner and other NIOSH colleagues, conducted the original epidemiologic studies providing the key data supporting the association of ETO with lymphoid and breast cancer, and that I have conducted several risk assessments for ETO and cancer, some in support of the EPA's risk assessment.

(1) A choice not to include risks to women from breast cancer in the quantitative assessment is an error. NIOSH conducted a breast cancer incidence study which clearly showed a significant positive exposure response for ETO, using an appropriate lag. Several smaller studies have supported this finding. Incidence is preferable to mortality for many outcomes, including breast cancer and hematopoetic cancer. TCEQ is choosing to simply ignore the breast cancer findings. I note that breast cancer incidence data also support a supra-linear exposure-response model, and that the incidence data are supported by breast cancer mortality findings.

(2) A choice to use the linear model among a variety of models for lymphoid cancer mortality that were previously examined by EPA, even though this model did not fit as well as the other models which show that the exposure-response is supra-linear, is a major error (eg, the two piece spline and the log cumulative dose model, both of which showed good fit to the data, $p<0.05$, unlike the linear model, see Appendix D in the EPA's risk assessment). The linear model results in much lower estimates of risk in the low dose region, which is the region of interest.

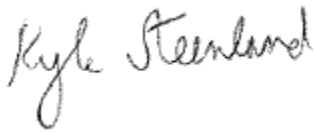
(3) The TCEQ interpretation of data on protein adduct levels associated with ETO exposure is misleading. We don't know if endogenous (internal) levels of ETO contribute to background levels of cancer, but we do know that increasing them with exogenous (external) exposures leads to increased cancer. That is what is important. Furthermore, the animal (positive rat and mice studies) and mechanistic data (mutagenicity, effect on chromosomal aberrations) all support the positive human data. That combined evidence is what IARC has determined that ETO is a definite human carcinogen.

(4) Extrapolating curve-fit model down to environmental dose. The Texas draft in contrast to the IRIS ETO assessment relies on direct extrapolation of the selected models from high to down to low (i.e., environmental) dose. This approach contrasts with the emphasis in EPA's Cancer Guidelines on limiting use of curve fit dose response models to the observable range – to support estimation point

of departure (BMDL) that can then be used for straight line extrapolation to low dose when appropriate (as for a direct acting mutagenic carcinogen like ETO). Choice of the better fitting model (the supra-linear model), then extrapolating down from a point of departure, is the best approach to ETO risk assessment.

(5) The draft's approach to comparing of observed and expected rates in the NIOSH cohort is incorrect. The use of national tumor rates to predict cancers in the NIOSH worker cohort is inappropriate because it ignores the healthy worker effect, whereby working populations have lower mortality rates than the national population. The use of internal comparisons, as used by NIOSH investigators and EPA risk assessors, avoids this issue, and is standard in occupational risk assessment. The models used by EPA predict quite well the observed occurrence of cancer in the cohort.

(6) The use of the UCC cohort as equivalent in importance to the NIOSH cohort is inappropriate. The UCC cohort was much smaller (2000 vs 18,000) and had far less developed exposure estimates, making conclusions about exposure-response in that cohort less valuable. This is why the EPA and its Scientific Advisory Board (SAB) recommended reliance on the NIOSH cohort.



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September 26, 2019

Comments on Texas Commission on Environmental Quality (TCEQ) proposed Development Support Document (DSD),"Ethylene Oxide Carcinogenic Dose-Response Assessment" (28 June 2019)

Submitted by email to tox@tceq.texas.gov

These comments are submitted on behalf of the undersigned scientists. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support unless indicated otherwise.

We appreciate the opportunity to provide written comments on TCEQ's Development Support Document (DSD) for ethylene oxide.[1] Ethylene oxide is classified as "carcinogenic to humans" by the International Agency for Research on Cancer [2] and the US Environmental Protection Agency (EPA),[3]and "known to be a human carcinogen" by the National Toxicology Program.[4] Ethylene oxide has a mutagenic mode of action (MOA) and there is no 'safe' level of exposure to this chemical.

In 2016, after public comments, peer review and extensive input from its independent Science Advisory Board (SAB), EPA's Integrated Risk Information System (IRIS) program finalized a unit risk estimate of 5.0 x 10^{-3} (per ug/ m^3) for ethylene oxide based on lymphoid and breast cancers which also accounted for increased risks from early life exposures (see Table). [5] The EPA value was derived following a robust scientific review, and using established methodology and current principles for risk assessment as encompassed in EPA's Guidelines for Carcinogen Risk Assessment and other Agency guidance documents. As such, the EPA value reflects the best available science necessary to ensure the protection of the public's health from cancer risks. We recommend that TCEQ adopt the EPA value for ethylene oxide.

Our analysis found that TCEQ's DSD has such serious scientific problems that the conclusions should not be used. As a consequence of these critical problems, TCEQ greatly underestimates the cancer risks posed by ethylene oxide and its cancer unit risk estimates are orders of magnitude below those of EPA, and therefore less health protective (see Table). Of particular note is the completely inadequate treatment of vulnerable populations including women and children, as the DSD ignores risks from breast cancer and fails to account for increased lifetime cancer risks caused by early-life exposures. We are concerned that the DSD unit risk estimate is about 3500 times less protective than the EPA value, does

[1] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Available: https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/proposed/jun19/eo.pdf

[2] IARC. (2018) Ethylene Oxide. Available: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-28.pdf

[3] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730

[4] NTP/NIEHS. (2016) Report on Carcinogens, Fourteenth Edition: Ethylene Oxide. Available: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/ethyleneoxide.pdf

[5] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730

not accurately reflect the science on ethylene oxide cancer risks, and would leave the public, especially women, at unacceptable risk of developing and dying from cancers caused by ethylene oxide.

Table. Comparison of TCEQ and EPA unit risk estimates for ethylene oxide. TCEQ's estimates for total cancer are orders of magnitude below EPA's.

	Cancer unit risk estimate (per ug/ m^3), including age-dependent adjustment factors	**Source**
Highest **~3500x difference** Lowest	5.0×10^{-3}	EPA IRIS (2016)[6] Total cancer
	4.3×10^{-3}	EPA IRIS (2016)[7] Lymphoid cancers
	7.6×10^{-5}	TCEQ (2017)[8] Total cancer
	1.4×10^{-6}	TCEQ (2019)[9] Total cancer (includes lymphoid only)

TCEQ's conclusions on ethylene oxide cancer risks are not scientifically supported because:

1. **The DSD's final risk estimate does not include breast cancer risks.**
2. **The DSD discounts the role of expert peer review.**
3. **The DSD incorrectly interprets EPA's statements regarding the plausible sublinearity of dose-response relationships for endogenous doses of ethylene oxide as also applying to exogenous exposures.**
4. **The DSD ignores background rates of cancer and incorrectly assumes that given endogenous EtO production, low exogenous exposures would not produce biologically meaningful internal doses.**
5. **The DSD incorrectly uses EPA's unit risk estimate which is applicable to exogenous exposures only to estimate the cancer risks of endogenous ethylene oxide levels.**
6. **The DSD makes flawed claims about EPA's use of a two-piece spline model for lymphoid cancer and misstates the exposure range over which the model is applied for derivation of the unit risk estimate.**
7. **The DSD criticism of how EPA addressed the knot in the two-piece spline models are contrary to SAB recommendations to the EPA.**
8. **The DSD inappropriately uses a Cox proportional hazards (PH) model for the NIOSH cohort, despite its lack of fit to the data.**
9. **The DSD is incorrect in its claim that EPA should have considered environmental exposures to ethylene.**
10. **The DSD ignores issues with the Swaen et al. (2009) analysis that decreased the ability of that analysis to detect associations for lymphoid cancer.**
11. **The DSD's approach to deriving a quantitative cancer risk estimate for ethylene oxide exposure has a number of scientific problems that lead to underestimating risk.**

[6] Total cancer based on human data for breast and lymphoid cancers from EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

[7] Lymphoid cancers based on human data from EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

[8] Total cancer, which TCEQ took from EPA IRIS (2016) based on rodent data. See Appendix A.

[9] Total cancer, only includes lymphoid cancers based on human data from TCEQ (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment.

12. **The DSD does not appropriately account for the science showing increased cancer risks from early life exposures to carcinogens with a mutagenic mode of action.**
13. **The DSD uses a scientifically inappropriate comparison explicitly rejected by the SAB to "predict" the numbers of cases in the NIOSH cohort.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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DETAILED COMMENTS

1. **The DSD's final risk estimate does not include breast cancer risks.**

EPA's conclusion of a potential breast cancer hazard from exposure to ethylene oxide (EtO) was supported by the SAB.[10] TCEQ seems to acknowledge a potential breast cancer hazard and considers EPA's quantitative risk estimates for breast cancer, but then rejects EPA's estimates and includes no alternative estimates for breast cancer.

The SAB explicitly endorsed EPA's use of a two-piece spline model for modeling the breast cancer incidence data,[11] and EPA's unit risk estimates for breast cancer incidence are based on this model. TCEQ's rationales for rejecting EPA's approach are flawed because TCEQ conflates endogenous (background) exposures with low exogenous exposures, assuming that small increases in exposure above background would not be biologically meaningful, despite the fact that breast cancer has relatively high background rates. There is uncertainty about the risks at low levels of exposure, and this is why EPA applies a linear extrapolation from models derived in the observable range of the data. Use of linear low-exposure extrapolation was supported by the established mutagenic mode of action (MOA) and the SAB. These issues are discussed in more detail below (see comments #3, 4, 6, 11e).

Having rejected EPA's human-based breast cancer risk estimates in the proposed DSD, TCEQ could have considered the rodent-based estimates presented by EPA, rather than completely discounting breast cancer risk. Indeed, in March 2017 TCEQ did exactly that, adopting a value of $7.6x10^{-5}$ per $\mu g/m^3$, the EPA IRIS value for total cancer risk based on rodent data (see Table and Appendix A). Yet, TCEQ's 2019 total risk estimates are for lymphoid cancers only, and the DSD does not provide a valid scientific rationale for not including breast cancer risks in the final unit risk estimate. Because the DSD fails to include breast cancer, TCEQ's final risk estimate is a major underestimation of the actual cancer risks posed by ethylene oxide.

2. The DSD discounts the role of expert peer review.

EPA's EtO carcinogenicity assessment was the subject of extensive review. In addition to review by other offices in EPA and other agencies in the federal government, the assessment twice underwent external peer review by EPA's independent SAB, which included discussions at open public meetings in 2006 and 2014; the SAB also considered public comments made at the meetings. In addition to addressing the SAB's comments, EPA considered public comments made at the 2006 and 2014 SAB meetings as well as at a public meeting in 2013. For the 2014 review by the SAB, the Board set up a

[10] SAB (Science Advisory Board). (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012). Available: https://yosemite.epa.gov/sab/sabproduct.nsf/fedrgstr_activites/BD2B2DB4F84146A585257E9A0070E655/$File/EPA-SAB-15-012+unsigned.pdf

[11] Id. Pp. 1, 12

panel of 14 experts from a range of relevant disciplines. After the review, the panel's report was reviewed and endorsed by the larger SAB.

As described in the comments below, the SAB explicitly endorsed EPA's approaches and rejected the model ultimately chosen by TCEQ, where the Commission's conclusions and approaches differed from those of EPA (e.g., discounting the breast cancer models, rejecting two-piece spline models, not using linear low-exposure extrapolation). The DSD does not present new data or evidence that was not considered by the SAB, nor does it provide an appropriate scientific explanation for the significant departures from EPA's methodology. In contrast to the Agency, academic and public expert input and extensive peer review of the EPA assessment, the DSD has not been peer reviewed or subject to any external comments.

3. The DSD incorrectly interprets EPA's statements regarding the plausible sublinearity of dose-response relationships for endogenous doses of EtO as also applying to exogenous exposures.

The DSD states EPA determined "that the low-dose region of the EtO dose-response curve is highly plausibly sublinear…"[12] but this interpretation of the EPA assessment is incorrect. EPA made no such determination about low-dose exogenous exposures.

Rather, EPA made general statements[13] in the context of conceptual models presented by Starr and Swenberg[14] and Crump et al.[15] In this context, EPA was referring to a range of hypothetical *endogenous* doses from no (zero) endogenous exposure to the point of no (zero) exogenous exposure. The rationale for postulating that the dose-response relationships for relevant cancers across that hypothetical range of doses are likely to be sublinear is based on the conceptual model presented in detail by Crump et al. (2014). In brief, the reasoning is that the body has defense mechanisms (e.g., DNA repair mechanisms) to deal with endogenous exposures. However, these defenses are imperfect and limited, which may account for some level of background cancer risk even without exogenous exposures; and as endogenous doses increase across this hypothetical range, the body's available defenses get diminished, such that the slope of the dose-response curve may be essentially linear at the point of zero exogenous exposure (see Figure 1 in Crump et al. (2014)). The postulated sublinearity is not meant to apply to the range of exogenous exposures.

EPA's unit risk estimates are explicitly for extra risk *above background*, i.e., *above* the risk from endogenous doses (unit risk estimates are derived from exposure-response modeling of exogenous exposures; endogenous doses are common to both exposed and unexposed subjects, independent of

[12] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 1

[13] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. pg. 4-95.

[14] Starr TB, Swenberg JA. (2013) A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. Regul. Toxicol. Pharmacol. 65 (3), 311–315.

[15] Crump KS, Bussard DA, Chen C, Jinot J, Subramanium R. (2014) The ''bottom-up'' approach does not necessarily bound low-dose risk Regul Toxicol Pharmacol 70:735-736.

exogenous exposure, and thus are part of background risk). Variability in levels of background doses of endogenous EtO are accounted for in the modeling of the exogenous exposures, along with other sources of variability. While sublinearity across endogenous doses is plausible, one cannot infer anything from that about the exposure-response relationship at low exogenous exposures. Thus, the DSD's application of the hypothetical sublinear dose-response relationship for endogenous exposures to exogenous exposures, especially in light of background cancer rates (see comment #4), is not scientifically supported.

4. The DSD ignores background rates of cancer and incorrectly suggests that given endogenous EtO production, low exogenous exposures would not produce biologically meaningful internal doses.

The DSD states that "ambient EtO concentrations significantly less than 1 ppb…would not be expected to produce biologically meaningful internal doses considering the range of normal endogenously-produced background EtO levels."[16] However, normal endogenous EtO exposures may contribute to background cancer risks for lymphoid cancers and for breast cancers in females, as these are relatively common cancer types in the general population. As cited on p. 4-95 of EPA's assessment,[17] lymphoid cancers have a background lifetime incidence risk on the order of 3%, while the background lifetime incidence risk for breast cancer in females is on the order of 15%.

Low exogenous EtO exposures would be additive to the endogenous exposure and to background cancer processes, consistent with general principles of quantitative risk assessment.[18, 19] As to the variability in background doses of endogenous EtO, this is accounted for in the modeling of the exogenous exposures, as discussed in comment #3 above. Thus, DSD ignoring low levels of exogenous exposure claiming they are not biologically meaningful is not scientifically justified and results in an underestimation of risk. For example, the DSD ignores levels of exogenous exposure that EPA determined to be associated with upper bound extra risks of 10^{-4} (0.01%).

[16] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 1

[17] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. pg. 4-95.

[18] Crump KS, Hoel DG, Langley H, Peto R. (1976) Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res. 36:2973–2979.

[19] Lutz WK, Gaylor DW, Conolly RB, Lutz RW. (2005) Nonlinearity and thresholds in dose-response relationships for carcinogenicity due to sampling variation, logarithmic dose scaling, or small differences in individual susceptibility. Toxicol Appl Pharmacol 207:S565-S569.

5. The DSD incorrectly attempts to estimate the cancer risks of endogenous EtO levels using EPA's unit risk estimate which is applicable to exogenous exposures only.

The DSD applies EPA's unit risk estimate to endogenous ethylene oxide exposures,[20] but as noted above (comments #3, 4), EPA's unit risk estimates are for exogenous exposures only (extra risk *above background*[21]) and cannot be used to infer anything about risks from endogenous exposure. The extent of cancer risks from endogenous levels of EtO is not something that can be estimated from current knowledge.

6. The DSD makes flawed claims about EPA's use of a two-piece spline model for lymphoid cancer and misstates the exposure range over which the model is applied for derivation of the unit risk estimate.

The DSD claims that the EPA model over-predicts the NIOSH cohort results.[22] However, TCEQ's approach to predicting cases is flawed (see comment #13 below for a discussion of problems in the TCEQ's approach). In fact, EPA's model provides a reasonably good representation of the NIOSH data, as demonstrated by the statistical and visual fits. As seen in Figure 4-3 of EPA's assessment,[23] the model actually underestimates the categorical relative risks (RRs) determined nonparametrically (i.e., without any assumptions about the exposure-response relationship across the exposure categories) for the exposure quartiles.

The DSD claims that EPA was wrong to use a supralinear model.[24] However, the underlying data exhibit a supralinear exposure-response relationship. This is demonstrated by the shape of the nonparametric categorical results, as well as by the fact that the best-fitting models are supralinear (e.g., the Cox regression model with log cumulative exposure; see Table 4-6 of EPA assessment[25]).

[20] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 24-25

[21] Technically, when estimating extra risk (above background) from exposure-response models of occupational cohorts, background risk can also include risk from background levels of ambient (exogenous) exposure. Generally, this contribution is negligible and can be ignored when applying unit risk estimates to calculate risks from environmental exposure levels. Moreover, as discussed above with respect to endogenous exposures, just because the risk from background levels of ambient exposure is included in the background in the extra risk calculations does not mean that background levels of ambient exposure are without risk. Given uncertainties regarding the risk from background levels of ambient exposure, it is public-health-protective to apply the unit risk estimate to all exogenous exposures, i.e., down to zero exogenous exposure, and it is a minimal additional extrapolation relative to the extrapolation from higher occupational exposures to background levels of exogenous exposure used in the derivation of the unit risk estimates.

[22] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 2; Appendix 3

[23] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

[24] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 3

[25] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

Furthermore, EPA's independent SAB endorsed the use of two-piece spline models for such data,[26] recognizing the utility of such models for reflecting local behavior in the data more readily than the single-parameter models. In fact, EPA used a two-piece linear spline model to account for high-exposure plateauing while specifically avoiding the excessive supralinear curvature in the lower-exposure range objected to by TCEQ and sources it cites regarding supralinear models.[27]

A mechanistic explanation for overall supralinear exposure-response relationships in the observable range of the EtO epidemiological data may not be known; however, such relationships are not uncommon with epidemiological data and there are other possible explanations.[28] Moreover, after modeling all of the data using the two-piece spline model, EPA estimated a point of departure (POD) at the low end of the observable range and used linear low-exposure extrapolation from the POD to derive the unit risk estimate, consistent with EPA's guidelines.[29] (See comment #11e below for more discussion of EPA's approach to deriving unit risk estimates.) The conclusion of a mutagenic MOA, which was a finding of both EPA and the TCEQ, provides support for linear *low-exposure extrapolation*. Contrary to intimations by TCEQ, the mutagenic MOA does not preclude high-exposure plateauing, such as exemplified by tumors in rats exposed to vinyl chloride.[30]

Similarly, the plausibility of sublinearity in the conceptual range of endogenous exposures from internal doses of zero up to the point of zero exogenous exposure does not rule out the models used by EPA for exogenous exposures, i.e., supralinearity in the observable range from higher exposures and linear extrapolation for lower exposures.

Thus, the DSD's rationales for rejecting the model used by EPA are not valid.

7. The DSD criticism of how EPA addressed the knot in the two-piece spline models are contrary to SAB recommendations to the EPA.

The DSD objected to the fact that EPA did not include the knot as a parameter in its estimations of the Akaike Information Criterion (AIC).[31] Inclusion of the knot as a parameter would have been one way to do the calculation; however, the SAB supported EPA's approach. Consistent with SAB recommendations, the EPA did not make its model selections based solely on the AICs. As

[26] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012) Pg. 12. Available: https://yosemite.epa.gov/sab/sabproduct.nsf/fedrgstr_activites/BD2B2DB4F84146A585257E9A0070E655/$File/EPA-SAB-15-012+unsigned.pdf

[27] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 19-20

[28] Stayner L, Steenland K, Dosemeci M, Hertz-Picciotto I. (2003) Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. Scand J Work Environ Health 2003;29(4):317–324.

[29] EPA. (2005) Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. Available: http://www2.epa.gov/osa/guidelines-carcinogen-risk-assessment

[30] EPA. (2000) Toxicological review of vinyl chloride [EPA Report]. (EPA/635/R-00/004). Washington, DC: U.S. Environmental Protection Agency.

[31] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 48-50, Appendix 5

recommended by the SAB, EPA also gave consideration to the ability of models to reflect local behavior, e.g., prioritizing two-piece spline models, and to parsimony.[32] The SAB singles out the knot as a parameter that could be fixed in the interest of parsimony, stating "To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data…. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." Moreover, the SAB fully understood how EPA determined the knot, having reviewed the Agency's approach as a charge question, finding it "scientifically appropriate and a practical solution that is transparently described."[33] Thus, the DSD objections that the knot was estimated before it was fixed are not persuasive.

8. The DSD inappropriately uses a Cox proportional hazards (PH) model for the NIOSH cohort, despite its lack of fit to the data.

As a central part of its analysis to calculate the cancer unit risk estimate, the DSD uses a model for the NIOSH cohort that they note does not provide a statistically significant fit to the data (though the DSD does not present a *p*-value). In addition, the approach that they used to demonstrate that their model provides good "predictions" of the number of cases in the NIOSH cohort is flawed (see comment #13 below).

Furthermore, the model used by TCEQ is inherently sublinear and cannot reflect the overall supralinear shape of the exposure-response relationship (See model "e^(β*exp)" in Fig 4-3 of EPA's assessment and the *p*-values in Table 4-6).[34] The Cox PH model for lymphoid cancers in males and females in the NIOSH cohort has a *p*-value 0.22, while the best-fitting supralinear model has a *p*-value of 0.02—a much lower and statistically significant value, indicating the supralinear model provides a better fit to the data. The Cox PH model was presented in EPA's assessment for comparison with other models, therefore the SAB was able to consider it as an option, and yet, the SAB did not promote it but instead endorsed two-piece spline models.

EPA and the SAB recognized the importance of local fit to the data, as well as overall fit. The two-piece spline model used by EPA, and endorsed by the SAB, can represent the increasing response at lower exposures (without excessive curvature at the lowest exposures) and the relative plateauing at higher exposures, as discussed above (comment #6). To estimate the risks of environmental exposure levels from higher exposure data, such as occupational data, capturing this local behavior at the lower exposure range of the data is especially important because it reflects the data range most relevant to the even lower exposures of interest.

[32] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012) Washington, DC: U.S. Environmental Protection Agency, Science Advisory Board. Pg. 12

[33] Id. pg. 13

[34] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

In contrast, the Cox PH model used by TCEQ cannot accommodate supralinear exposure-response data and, in particular, cannot reflect the exposure-response relationship in the lower exposure range of the data. Instead, in order to attempt to fit the high-exposure plateauing, such a model must inflate the internal baseline hazard rate and depress the low-exposure slope. This is illustrated in Figure 21 of the DSD, where the dotted blue line depicts the model used by TCEQ with an approximated baseline hazard rate shown relative to the nonparametric baseline hazard rate. It is apparent from this depiction that the baseline rate in the Cox PH model has been markedly overestimated relative to the nonparametric (categorical) baseline (RR = 1). The nonparametric baseline, however, is the best available estimate of the baseline hazard rate in the cohort because it is based on the 0 (lagged) cumulative exposure group without any assumptions about the shape of the exposure-response model for the exposed workers and, thus, without any influence of the higher-exposure data on the model fit to the lower-exposure data.

Despite these clear problems, TCEQ goes on to calculate the point of departure (POD) using the sublinear Cox PH model, and Table 30 on p. 93 of the DSD presents a confidence score of "high" for the POD. This score is totally unwarranted because the Cox PH model does not provide a statistically significant fit to the data and is inconsistent with the overall shape of the exposure-response data. Moreover, the "predictive" value of the model is based on a flawed approach, as discussed in comment #13 below. Finally, even if the model and predictions were valid, there are insufficient data in the range of the POD, which was calculated at a risk level of 1 in 100,000, to conclude that the model yields reliable estimates in that range, as discussed in comment #11.

For all of these reasons, the DSD's model selection and POD derivation, and the subsequent cancer unit risk estimates based on them, are not scientifically supported.

9. The DSD is incorrect in its claim that EPA should have considered environmental exposures to ethylene.

Environmental exposures to ethylene would be part of background risk and would not affect EPA's EtO unit risk estimate, which is for extra risk *above background*.

10. The DSD ignores issues with the Swaen et al. (2009) analysis that decreased the ability of that analysis to detect associations for lymphoid cancer.

The DSD cites the Swaen, et al. (2009) [35] study of the Union Carbide Corporation (UCC) as reporting that "no indications were found for excess cancer risks from EtO exposures, including lymphohematopoietic malignancies,"[36] however the Swaen analysis has important limitations:

a) The trend analyses were done using the sublinear Cox model, which would be limited in detecting supralinear trends (see comment #8).

[35] Swaen, GMH; Burns, C; Teta, JM; Bodner, K; Keenan, D; Bodnar, CM. (2009) Mortality study update of ethylene oxide workers in chemical manufacturing: A 15 year update. J Occup Environ Med 51: 714-723.
[36] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 14

b) The categorical analyses were based on standardized mortality ratios (SMRs), which are notoriously deficient for analyzing occupational epidemiology data because workers often have background disease mortality rates below those of the general population. This concept is called the "healthy worker effect" (HWE), although it can reflect differences between an occupational cohort and the general population beyond health. In fact, EPA's SAB specifically recommended that epidemiological results based on external standards, e.g.,SMRs, be down-weighted, stating "[t]he presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases."[37]
c) The long follow-up in the UCC cohort, well past the occurrence of non-negligible exposures,[38] was likely observing proportionately more background cases associated with increasing age of the cohort than cases associated with exposures in the distant past. In other words, most of the workers who would die of exposure-related lymphoid cancers would likely have already passed; thus, proportionately more of the new cases picked up in the extended follow-up would be background cases. This excessive follow-up, given the time that had lapsed since non-negligible exposures ceased, would make it more difficult to observe an exposure-related effect. (See also p. A-30 to A-31 of Appendix A of EPA (2016b) for more discussion.[39])

The DSD's interpretation of the Swaen study does not account for these critical limitations.

11. The DSD's approach to deriving a quantitative cancer risk estimate for ethylene oxide exposure has a number of scientific problems that lead to underestimating risk.

a) TCEQ's quantitative risk estimates are for lymphoid cancer only and do not include the risks for breast cancer in females (see also comment #1).
b) For lymphoid cancer, as discussed above (comment #8), the DSD selected a sublinear Cox PH model that does not fit the data.
c) In addition, the use of a 70-year cut-off in the lifetable analysis is not consistent with a default (average) lifetime of 70 years. EPA also uses a default average lifetime of 70 years but recognizes that 70 years should not be used as a cut-off in lifetable analyses, because in such analyses, actual demographic data about mortality rates at different ages are incorporated rather than using an average default lifetime. Truncating the analysis at 70 years actually corresponds to an average lifetime of less than 70 years because the hypothetical population tracked in the lifetable analysis is allowed to die at younger ages than the would-be average of 70 years but not allowed to live beyond 70 years. In contrast, truncating the lifetable analysis at 85 years corresponds to an average lifetime of about 75 years, which is close to the default average of 70 years.[40]

[37] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012). Pg. 18-19
[38] Exposures in this cohort beyond 1989 were considered negligible by Swaen et al. (2009).
[39] EPA. (2016) Evaluation of the inhalation carcinogenicity of ethylene oxide: Appendices [EPA Report]. (EPA/635/R-16/350Fb).
[40] Id. p. H-35 of Appendix H.

d) Another difference between the EPA and TCEQ approaches is that the EPA estimates are for cancer incidence, whereas the TCEQ estimates are for mortality. The SAB endorsed EPA's approach for calculating incidence estimates from mortality data.[41]
e) Moreover, in the DSD, the modeling for lymphoid cancer was apparently done all the way down to a risk level of 1 in 100,000 using the (non-fitting) sublinear model. In so doing, the TCEQ over relies on a sublinear model that doesn't describe the overall data well and certainly can't reliably estimate risks at corresponding low levels of exposure where there are few data. In other words, this approach assumes that the sublinear model is valid not only in the observable range of the data, contrary to findings that the underlying exposure-response data are more supralinear in shape, as discussed above (comment #8), but also in the lower exposure range, where the data are insufficient to estimate risks with any confidence. On p. 5 of the DSD, the TCEQ criticizes the EPA, stating "High-dose carcinogenicity data alone are incapable of informing truly low-dose risk"; however, it is the TCEQ, not the EPA, that models from the high-dose data down to a risk level of 1 in 100,000.

In contrast, EPA's approach does not presume to be able to estimate risks at such low levels. Instead, EPA's Guidelines on Carcinogen Risk Assessment advocate modeling the data and then selecting a POD near the low end of the observable range, i.e., the low end of the range in which increased risks might be reasonably detectable above background variability, and applying an extrapolation method from the POD.[42] In the absence of sufficient evidence that a nonlinear approach is warranted, the default approach is to use linear extrapolation. In the case of EtO, the use of linear extrapolation from the POD is supported by the finding of a mutagenic MOA, in accordance with EPA's guidance.[43] Linear extrapolation was also endorsed by the SAB.[44] Given the background rates of lymphoid cancer, EPA chose a POD of 1% extra risk,[45] or 1 in 100, which is far from the risk level of 1 in 100,000 used by TCEQ.

TCEQ's own protocol for developing toxicity factors provided in Section A1.1 of Appendix 1 of the DSD states that one "extrapolate[s] from the adjusted POD to lower exposures based on MOA analysis"; however, as discussed above, in this DSD, modeling was done all the way down to a risk level of 1 in 100,000 using a (non-fitting) sublinear model. The DSD's approach is inconsistent with the guidance of EPA and other agencies (including possibly TCEQ as well, according to their protocol), in which a POD is selected near the low end of the observable range and then the mutagenic MOA established for EtO would support linear low-dose extrapolation.

[41] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012) Washington, DC: U.S. Environmental Protection Agency, Science Advisory Board. Pg. 15.
[42] EPA. (2005) Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.
[43] Id.
[44] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012) Washington, DC: U.S. Environmental Protection Agency, Science Advisory Board.
[45] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. pg. 4-22

See also Section A.2.20 of Appendix A of EPA's assessment (2016b) for more discussion of the above issues related to the lymphoid cancer risk estimates.[46] The section critiques the approach used by Valdez-Flores et al. (2010), which was largely adopted in this DSD.

All of these scientific flaws contribute to the DSD's final unit risk estimate being a gross underestimate of the cancer risks demonstrated by the evidence.

12. The DSD does not appropriately account for the science showing increased cancer risks from early life exposures to carcinogens with a mutagenic mode of action.

The DSD states that the approach of Sielken and Valdez-Flores (2009) was used to apply the age-dependent adjustment factors (ADAFs) to the cancer risk estimates;[47] however, the ADAF calculations were not done correctly by Sielken and Valdez-Flores (2009). Early life exposures to chemicals with a mutagenic MOA such as EtO can increase lifetime cancer risk, and thus EPA guidance recommends the application of ADAFs in quantitative risk calculations to adjust for this potential increased susceptibility.[48] This means that exposure to a mutagenic carcinogen at a young age can increase a person's risk of developing cancer later in life. Thus, the ADAFs are designed to adjust *lifetime risk*, to reflect increased lifetime cancer risk from increased susceptibility to early-life exposures.[49] But Sielken and Valdez-Flores (2009) incorrectly multiply the ADAFs to the age-specific cancer mortality rates in the lifetable, which just applies the factors to risk for those younger age groups and ignores increased risks for older ages (discussed in more detail in EPA's assessment[50]). In addition, assuming increased early-life susceptibility and applying the ADAFs along with the Cox PH model in the lifetable analysis, as done by Sielken and Valdez-Flores (2009), is inconsistent with a major assumption of the Cox model, that RR is independent of age.

In fact, because of the lagged exposures and low cancer mortality rates at young ages, applying the ADAFs just to young age groups had a negligible effect on the final risk estimates in Sielken and Valdez-Flores (2009). In contrast, the approach that correctly accounts for the science showing that early life exposures increase lifetime cancer risks (used by EPA) increased the lifetime risk estimates by about 22% (for both female breast cancer and lymphoid cancer combined).[51]

[46] EPA. (2016) Evaluation of the inhalation carcinogenicity of ethylene oxide: Appendices [EPA Report]. (EPA/635/R-16/350Fb).

[47] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Pg. 61

[48] EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens (pp. 1-125). (EPA/630/R-03/003F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf

[49] Id.

[50] EPA. (2016) Evaluation of the inhalation carcinogenicity of ethylene oxide: Appendices [EPA Report]. (EPA/635/R-16/350Fb). p. A-34 to A-35 of Appendix A

[51] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F. Section 4.4.

The DSD's confidence score for sensitive populations was "medium." However this score is not warranted because TCEQ discounts the breast cancer risk in females and misapplies the ADAFs for susceptibility from early-life exposures, both of which result in underestimations of the risks posed by ethylene oxide.

13. The DSD uses a scientifically inappropriate comparison explicitly rejected by the SAB to "predict" the numbers of cases in the NIOSH cohort.

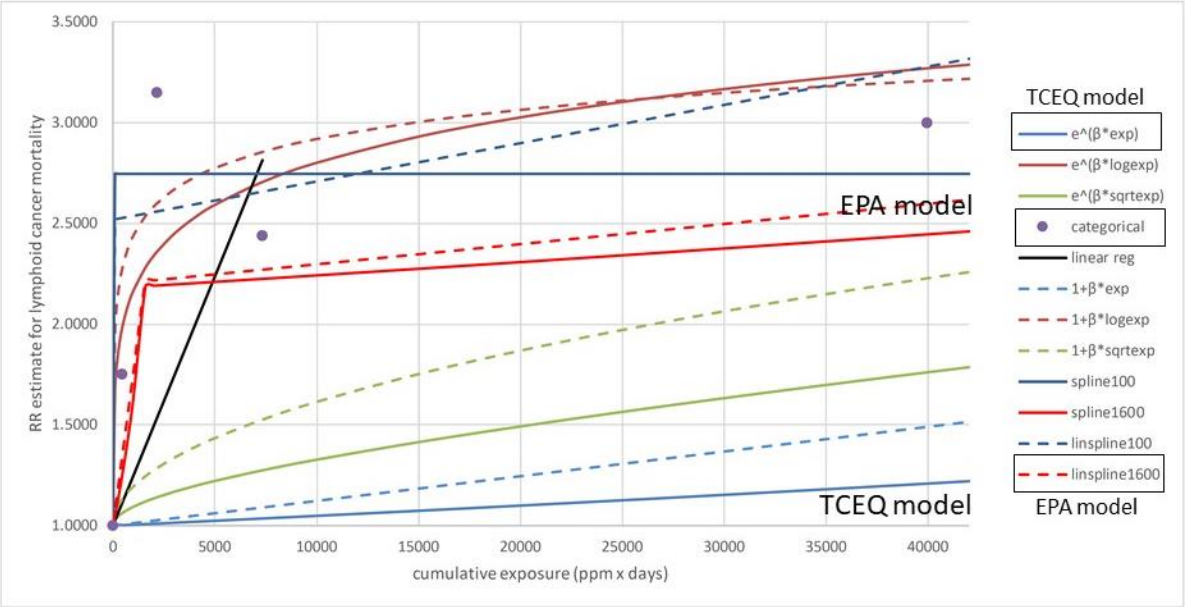
TCEQ's method for predicting the number of cases in the NIOSH cohort relies on a standardized mortality ratio (SMR) comparison.[52] As discussed in comment #10b, SMRs are notoriously deficient for analyzing occupational epidemiology data because workers often have background disease mortality rates below those of the general population. This concept is called the "healthy worker effect" (HWE), although it can reflect differences between an occupational cohort and the general population beyond health. In fact, EPA's SAB specifically recommended that epidemiological results based on external standards, e.g., SMRs, be down-weighted.[53] The SAB states "The presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases."

In the DSD, basing the "predictions" on an SMR comparison ignores the healthy worker effect apparent in the data and inflates the background risk expected in the cohort, equating it to the background risk in the general population. Therefore, all the relative risk (RR) models, which are based on an internal analysis estimating increases in risk relative to the actual (lower) background rates in the cohort, will overestimate cohort case numbers when the increases in risk are forced to be relative to the higher background rates of the general population. This will be true unless they're underestimating the risks to begin with, like the sublinear model selected by the TCEQ. The selected EPA models naturally "overpredict" case numbers under this flawed approach.

Instead, if one performs a more appropriate comparison based on the results of internal analyses (within the cohort), one can see that the sublinear model used by TCEQ is a poor predictor of the nonparametric categorical RR estimates for the exposure quartiles; see model "e^(β*exp)" in Fig 4-3 of EPA's assessment.

[52] TCEQ. (2019) Ethylene Oxide Carcinogenic Dose-Response Assessment. Appendix 3.

[53] SAB. (2015) Science Advisory Board Review of the EPAs evaluation of the inhalation carcinogenicity of ethylene oxide: Revised external review draft - August 2014 [EPA Report]. (EPA-SAB-15-012). Pg. 18-19



Reproduction of Figure 4-3 from EPA assessment, with black rectangles and text added to highlight TCEQ's model, the categorical RR estimates, and EPA's selected model.[54]

Comparing TCEQ's model, depicted by the solid blue curve near the bottom of the graph, to the nonparametric categorical RR estimates, depicted by the filled purple circles, shows that the model selected by the TCEQ substantially underestimates the nonparametric categorical RR estimates. In contrast, the EPA model depicted by the dashed red line (linspline1600) is a much better predictor of the nonparametric categorical RR estimates. As noted in comment #8, the nonparametric baseline estimate is the best available estimate of the baseline hazard rate in the cohort because it is based on unexposed referent group without any assumptions about the shape of the exposure-response model for the exposed workers and, thus, without any influence of the higher-exposure data on the model fit to the lower-exposure data. Similarly, the categorical RR estimates for the exposed groups are estimated with no assumptions about the shape of the exposure-response relationship across the groups.

In addition, proper comparisons of models against data should be based on maximum likelihood estimates (MLEs), as done in Figure 4-3 of EPA's assessment, not upper bounds as primarily reported by TCEQ.

Thus the DSD's reliance on this flawed calculation to support its rejection of EPA's model and its own use of a poorly fitting model is not supported by the evidence.

[54] EPA. (2016) Evaluation Of The Inhalation Carcinogenicity Of Ethylene Oxide (Final Report). EPA/635/R-16/350F.

Appendix A: TCEQ (March 2017) Ethylene Oxide Dose Response Assessment Review

Ethylene Oxide

CAS# 75-21-8

March 6, 2017

The Toxicology Division (TD) of the TCEQ has reviewed the 2016 dose-response assessment for the USEPA IRIS unit risk factor (URF of 3E-03 per µg/m^3) for ethylene oxide. Due to concerns about the assessment, the TD has adopted an alternative URF of 7.6E-05 per µg/m^3 (see below).

USEPA (2016) derived a URF for ethylene oxide (EtO) based on a large epidemiologic study conducted by the National Institute for Occupational Safety and Health (NIOSH). Overall, some human epidemiology studies support an association of cancer with inhalation exposure to EtO (although many of the associations are weak), whereas other do not. Animal studies do show a causal association for some of the cancer endpoints observed in the human studies.

The TCEQ has chosen not to adopt the USEPA URF for EtO due to several deficiencies in the USEPA assessment including:

1. The NIOSH key study used to derive the URF is unpublished and unavailable to the public.
2. Conclusions from the individual key studies used by NIOSH (Steenland et al. 2004 and Steenland et al. 2003) to derive the URF support, at best, positive exposure-response trends and weak causal associations between EtO and cancer.
3. There are several modeling issues in the NIOSH study, as discussed in Valdez-Flores and Sielken (2013) and Valdez-Flores et al. (2010), resulting in over-estimation of cancer risks. For example:
    a. USEPA calculated an excess cancer risk for 85 years, instead of the 70-year default commonly used by the TCEQ and others for cancer risk assessment (e.g., TCEQ 2015).
    b. Statistical procedures used to generate lower effective concentrations (LECs) are insensitive to the observed data. Furthermore, the observed shape of the dose-response relationship and the maximum likelihood estimate (MLE) of the environmental concentration (EC) is often preferable to an LEC for a risk estimate based on human data (e.g., by definition it is the best model fit, and uncertainty is reduced by the use of human data).

Alternative URFs are available and are presented in the USEPA IRIS assessment for EtO. URFs based on human epidemiology data and discussed in the USEPA IRIS assessment include:

1. Valdez-Flores et al. (2010) calculated several URFs based on multiple cancer endpoints, for both males and females, using two datasets: Steenland et al. (2004) and Union Carbide Corporation (UCC) mortality data of EtO chemical manufacturing workers. However, there was no evidence of a positive cumulative dose-response for any cancer endpoint, and only the highest exposure groups showed a statistically significant increase in cancer. Therefore, we did not adopt any of the URFs from this study.

2. Kirman et al. (2004) calculated a URF based on leukemia mortality data in combined earlier NIOSH and UCC cohorts (Stayner et al. 1993 and Teta et al. 1993, respectively). We chose not to adopt the URF from this study for several reasons: 1) it is based on older epidemiology studies that don't incorporate the most up-to-date information, 2) this study did not evaluate breast cancer, 3) the authors state that "the epidemiology data do not demonstrate a causal relationship between (EtO) exposure and leukemia" and 4) as discussed in detail in USEPA (2016), worker exposure data from the UCC cohort are unreliable for risk assessment purposes.

URFs derived based on studies conducted in both rats and mice are discussed in the USEPA IRIS assessment and include:

1. Kirman et al. (2004) calculated a URF based on four animal studies in mice and rats. URFs calculated from data for mononuclear cell leukemia tumors were not used due to uncertainties associated with relevance of this tumor type to humans. Lymphoma tumor data didn't show a positive dose-response in male or female mice so URFs calculated from these data were not used.
2. USEPA (2016) analysis of female tumor data from NTP (1987) yielded a URF of 7.6E-05 per µg/m^3. *The TCEQ chose to adopt this URF for EtO based on the high quality of the NTP (1987) study, positive dose-response relationships observed for multiple tumor types in female mice, and concordance with tumor types observed in human epidemiology studies.*

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References

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Stayner, L; Steenland, K; Greife, A; Hornung, R; Hayes, RB; Nowlin, S; Morawetz, J; Ringenburg, V; Elliot, L; Halperin, W. (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. Am J Epidemiol 138: 787-798.

Steenland, K; Whelan, E; Deddens, J; Stayner, L; Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 14: 531-539. http://dx.doi.org/10.1023/A:1024891529592

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

Teta, MJ; Benson, LO; Vitale, JN. (1993). Mortality study of ethylene oxide workers in chemical manufacturing: A 10 year update. Br J Ind Med 50: 704-709.

U.S. Environmental Protection Agency (USEPA). 2016. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide [CASRN 75-21-8] In Support of Summary Information on the Integrated Risk Information System (IRIS). (EPA-635/R-16/350Fa). National Center for Environmental Assessment Office of Research and Development: US Environmental Protection Agency Washington, DC. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1025_summary.pdf

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September 26, 2019

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Re: Proposed Development Support Document (DSD), Ethylene Oxide Carcinogenic Dose-Response Assessment, CAS Registry Number: 75-21-8

On behalf of the Union of Concerned Scientists (UCS), I submit this comment to the Texas Commission on Environmental Quality (TCEQ) on its proposed development support document (DSD) on dose-response assessment for ethylene oxide to urge the agency to reconsider its decision to replace EPA's risk value for ethylene oxide with a new value derived by the state that would significantly raise the acceptable threshold.

With more than half a million supporters, UCS is a science-based nonprofit working for a healthy environment and a safer world. Our organization combines independent scientific research and citizen action to support innovative, practical solutions and secure responsible changes in government policy, corporate practices, and consumer choices.

The TCEQ's proposed cancer risk value is not an appropriate replacement for the EPA IRIS risk value. The EPA IRIS assessment on the carcinogenicity of ethylene oxide issued in 2016 incorporated the best available science, public comment opportunities, interagency review, and scientific peer review by EPA's Scientific Advisory Board.[1] The proposed TCEQ risk value uses a sublinear dose response model to derive its toxicity factors that the EPA would deem inappropriate due to ethylene oxide's reactive, mutagenic, and multisite carcinogenicity.[2] Further, the TCEQ assessment relies on a key study that EPA chose not to include in its evaluation of the best available science because the data "were not of sufficient quality"[3] and other recent studies considered in the TCEQ's assessment would benefit from further conflicts of interest scrutiny as several are funded by the American Chemistry Council, which has a vested interest in ethylene oxide production and regulation.[4]

Choosing to abandon EPA's IRIS risk value for ethylene oxide, especially without an external review process, would mean a departure from the use of best available science. The EPA's IRIS program serves a critical scientific service to the public, providing assessments that inform the decisions that protect us from environmental contaminants. Its public searchable database contains EPA's scientific analysis of the potential human health effects of exposure to hundreds of chemicals, including highly hazardous chemicals such as vinyl chloride, butadiene, benzene, lead, mercury, asbestos, and ethylene oxide.[5] The IRIS program is housed in the National Center for Environmental Assessment within the Office of Research and Development and does important scientific work that is completely separate from the policymaking programs at EPA. Its placement is by design in order to ensure independent and objective assessments on

hazardous chemicals that pose serious risks to Americans. The output of this office is not just important for federal policymaking, but IRIS assessments and associated toxicity values are used by state environmental and public health agencies, as well as community groups, to assess local risks from facilities producing these chemicals across the country. The scientific work that comes out of this department should be incorporated into health-protective standards in the states, not ignored.

Data on ethylene oxide released by EPA's National Air Toxics Assessment (NATA) in 2018 revealed that the chemical is significantly contributing to higher cancer rates in areas surrounding chemical manufacturers and sterilizers using the chemical across the country.[6] About a quarter of the facilities contributing to these risks are located in Texas.[7] According to the NATA data, the probability of developing cancer from air pollutants was beyond the EPA's acceptable level of risk in over 100 communities, and 91 percent of the risk can be attributed to ethylene oxide, formaldehyde, or chloroprene.[8] Further, EPA issued its findings from air monitoring outside of the Sterigenics facility in Willowbrook, IL that was shut down by the state, comparing emissions before and after the shutdown. The monitors revealed levels 90 percent lower at the sites closest to Sterigenics, illustrating the direct relationship between the facility's operations and ethylene oxide levels.[9] A March report from the Illinois Department of Health found that cases of Hodgkin's lymphoma among women in the Willowbrook community were nearly 90 percent higher than in a nearby county.[10] This data is in agreement with the systematic review conducted by IRIS that evaluated the toxicological and epidemiological evidence available on the chemical and determined that it was carcinogenic to humans, and exposure was linked to an increased risk of cancer of leukemia, lymphoma and breast cancer in women.[11]

The TCEQ's move to ignore EPA's IRIS risk values is a departure from the best available science and will limit the ability of the agency to issue standards that best protect communities in Texas with the highest emissions and associated health risks. I urge TCEQ to abandon this ill-informed proposal.

Sincerely,

Genna Reed

Genna Reed, Lead Science and Policy Analyst
Center for Science and Democracy, Union of Concerned Scientists

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[1] Environmental Protection Agency (EPA). 2017. Ethylene Oxide CASRN 75-21-8, History, July 28. Online at *https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025#tab-3*, Accessed April 18, 2019.
[2] Haney, J.T. et al. 2019. Ethylene Oxide Carcinogenic Dose-Response Assessment, CAS Registry Number: 75-21-8. Texas Commission on Environmental Quality, June 28. Online at *https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/proposed/jun19/eo.pdf*, Accessed September 24, 2019; EPA. 2005. Guidelines for Carcinogen Risk Assessment. Online at *https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf*; EPA. 2014. Evaluation of the Inhalation

Carcinogenicity of Ethylene Oxide, Appendix C. Online at *http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=519748*, Accessed September 24, 2019.

[3] EPA. 2014. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Appendix K. Online at *http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=519748*, Accessed September 24, 2019; Valdez-Flores, C., Sielken Jr., R., and Teta, J. 2010. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data. *Regulatory Toxicology and Pharmacology*, 56:312-320.

[4] See Bogen, K. et al. 2019. Reevaluation of Historical Exposures to Ethylene Oxide Among U.S. Sterilization Workers in the National Institute of Occupational Safety and Health (NIOSH) Study Cohort. *International Journal of Environmental Research and Public Health*, 16(10); Kirman, C.R. and S.M. Hays. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91: 165-172.

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[6] EPA. 2018. 2014 National Air Toxics Assessment, September 18. Online at *https://www.epa.gov/national-air-toxics-assessment/2014-national-air-toxics-assessment*. Accessed September 5, 2019.

[7] Trevizo, P. 2019. Texas regulators may raise the acceptable level of a toxic chemical. Activists and East Harris County residents are worried. *Houston Chronicle*, September 2. Online at *https://www.houstonchronicle.com/news/houston-texas/houston/article/Texas-regulators-may-raise-the-acceptable-level-14403150.php*, Accessed September 24, 2019.

[8] *Ibid*.; Lerner, S. 2019. A Tale of Two Cities: The EPA's Bungled Response to an Air Pollution Crisis Exposes a Toxic Racial Divide. *The Intercept*, February 24. Online at *https://theintercept.com/2019/02/24/epa-response-air-pollution-crisis-toxic-racial-divide/*, Accessed September 5, 2019.

[9] EPA. 2019. EPA in Illinois: Outdoor Air Monitoring in the Willowbrook Community, March 28. Online at *https://www.epa.gov/il/outdoor-air-monitoring-willowbrook-community*, Accessed September 25, 2019; Hawthorne, M. 2019. After Sterigenics shut, a 'rapid drop' in toxins; EPA official: Air tests showed carcinogen lower in Willowbrook. *Chicago Tribune*, March 22. Online at *http://digitaledition.chicagotribune.com/tribune/article_popover.aspx?guid=073416be-94a1-445b-96ef-a26002c88331*, Accessed September 5, 2019.

[10] Illinois Department of Public Health. 2019. Cancer Incidence Assessment near Sterigenics in Willowbrook, IL, 1995-2015, March 29. Online at *http://www.dph.illinois.gov/sites/default/files/publications/sterigenicswillowbrookcancer-investigation-final.pdf*, Accessed September 5, 2019.

[11] EPA. 2016. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8), In Support of Summary Information on the Integrated Risk Information System (IRIS), December. Online at *https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf*, Accessed September 5, 2019.

September 26, 2019

Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Submitted electronically via tox@tceq.texas.gov

Re: Ethylene Oxide Carcinogenic Dose-Response Assessment, Development Support Document (Proposed, June 28, 2019) CAS Registry Number: 75-21-8

We appreciate the opportunity to submit these comments on behalf of Environmental Defense Fund ("EDF") on the Texas Commission on Environmental Quality's ("TCEQ") Ethylene Oxide Carcinogenic Dose-Response Assessment and proposed 4 parts per billion ("ppb") concentration as an air permit screening level for ethylene oxide ("EtO") and are appreciative of the extension of the comment deadline. EDF is a nonprofit organization representing more than 2 million members and supporters nationwide, including over 174,866 members and supporters in Texas. Since 1967, EDF has linked science, economics, and law to create innovative, equitable, and cost-effective solutions to urgent environmental problems. EDF and its members are deeply concerned about harmful air pollution, including the public health-threatening ethylene oxide emissions in Texas.

I. TCEQ should not reduce a risk threshold to EtO, a known human carcinogen

Ethylene oxide is harmful air pollutant and a known human carcinogen through an inhalation exposure pathway.[1] The United States Environmental Protection Agency ("EPA") has concluded that there is "strong evidence of an increased risk of cancer of the lymphohematopoietic system and of breast cancer" for workers in EtO-manufacturing facilities and in sterilization

[1] EPA, *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, In Support of Summary Information on the Integrated Risk Information System (IRIS)* at 2 (Dec. 2016) *available at* https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1025_summary.pdf

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facilities using EtO.[2] The deadly effects of exposure to EtO can also impact communities breathing air near these facilities. The public health issues related to EtO pollution recently attracted national attention when Willowbrook, Illinois began to experience extremely high rates of lymphatic cancers which was directly linked to high concentrations of EtO emitted into the air from a medical equipment sterilization plant. In the wake of this tragedy, Illinois enacted The Matt Haller Act, 415 ILCS 5/9.16, to regulate EtO emissions from sterilization plants and reduce further human exposure to EtO emissions.[3]

Fully aware of these risks, TCEQ now proposes to move in the opposite direction by raising the threshold for EtO exposure to 4ppb, a massive jump from the current air permit screening level of 1ppb. This change is further significant because of the volume of EtO Texans are already exposed to under the current limit[4] – Texas is responsible for around half of the EtO emissions in the United States.[5] TCEQ's proposal to quadruple the screening level for air permits runs counter to the agency's core mission to protect the public from dangerous air pollution. TCEQ is charged with "safeguard[ing] the state's air resources from pollution by controlling or abating air pollution and emissions of air contaminants, consistent with the protection of public health, [and] general welfare." Tex. Health & Safety Code Ann. § 382.002 (a). Accordingly, TCEQ should abandon its flawed approach in its proposed assessment and adhere to its clear mandate to protect public health and welfare.

II. TCEQ's Proposed Assessment for EtO is Flawed Scientifically

The most egregious scientific error in TCEQ's proposed assessment is the dose-response analysis using the Cox proportional-hazards model fit to these data by Valdez-Flores et al. (2010) (Valdez-Flores et al. 2010). In the analysis, TCEQ estimates the slope of the dose-response curve using the lowest exposure category rather than the 100 randomly matched unexposed individuals as done by Steenland et al. (2004) (Steenland et al. 2004). This is by far and away the most important difference between EPA's cancer risk analysis of ethylene oxide and the TCEQ analysis. The obvious place to see the effect of this assumption is on page 133 of

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[2] *Id.*

[3] Illinois Public Act Public Act 101-0022, SB1852 Enrolled, *available at* http://ilga.gov/legislation/publicacts/fulltext.asp?Name=101-0022

[4] Increased severe weather events also correspond to more frequent startup, shutdown, and malfunctions at industrial facilities, resulting in increased air emissions, such as the recent impacts from Tropical Storm Imelda in the Houston area which released large quantities of hazardous air pollutants including EtO. For example, rainfall from Imelda resulted in the "release of about 100,000 pounds of toxic air pollutants . . . includ[ing] 1,3 butadiene, benzene and ethylene oxide." The Associated Press, *Texas Agency Blames Imelda in Mass Release of Air Pollutants* (Sept. 25. 2019) Fort-Worth Star Telegram, *available at* https://www.star-telegram.com/news/state/texas/article235467067.html

[5] Editorial Board, *TCEQ's Dangerous Trade Off: Jobs Over Clean Air*, Houston Chronicle (Sept. 6, 2019) *available at* https://www.houstonchronicle.com/opinion/editorials/article/TCEQ-s-dangerous-trade-off-jobs-over-clean-air-14417795.php.

the TCEQ DSD document (Figure 22). It is clear that the dashed blue line used by TCEQ does not pass through 1 when the x-axis (15-year lagged ppm-days) equals zero, but instead almost passes through EPA's relative risk for the first quintile. This results in an over-estimation of the risk in the unexposed population quite dramatically, in fact treating this population as if the risk were the same as the risk in the first quintile. Because the relative risk climbs dramatically from the control response to the first quintile, using the first quintile as the denominator in the risk ratio for Cox modeling substantially reduces the slope, and thus the risk.

Surprisingly, TCEQ illustrates how bad their fit is relative to the control population in Figures 20 and 21 of the DSD. In these figures, rather than having the model run through the red dot for the first quintile, TCEQ's model (the blue solid line) is forced through the relative risk of 1 for the unexposed group. We illustrate this point by placing the blue line (now a black thick line) running directly through the first quintile red dot on the same plot in Figure 21. One can see the resemblance to the lines shown in Figure 23.

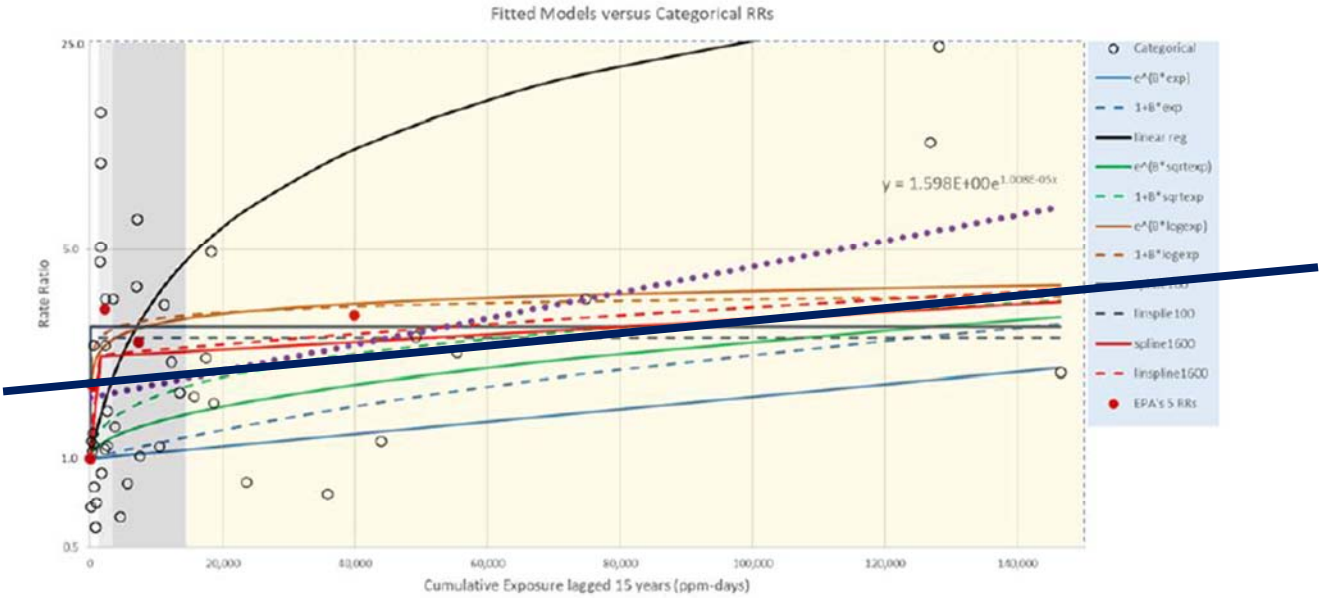


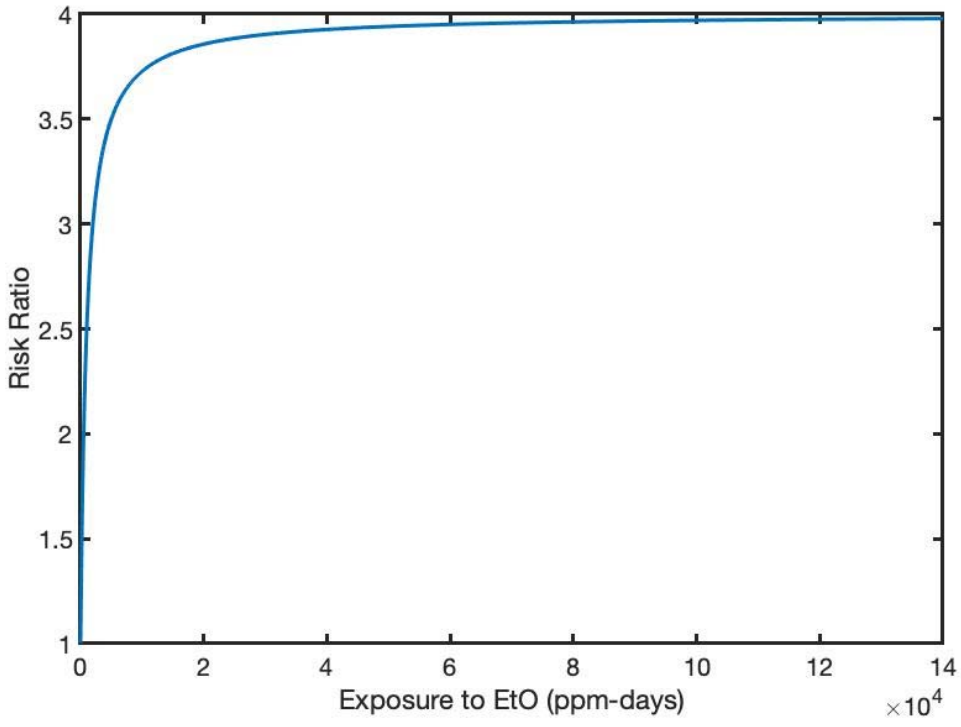
Figure 20: Lymphoid Cancer Death Categorical Rate Ratios (RRs) and Various Fitted Models for 15-Year Lagged Occupational Doses ≤150,000 ppm × days (NIOSH cohort)

Additionally, TCEQ's discussion of the fit of their model to quintiles 2-5 is very misleading because it does not mention the lack of fit of the model against the mortality expected in the unexposed population since the unexposed population has been ignored in the evaluation. Steenland et al. fit the Cox model to their data using the unexposed group as the referent population and did the same thing using log (dose+1) and present their results in Table 7 of their paper. They concluded the log(dose+1) model fit best with the 15-year lag. That model is

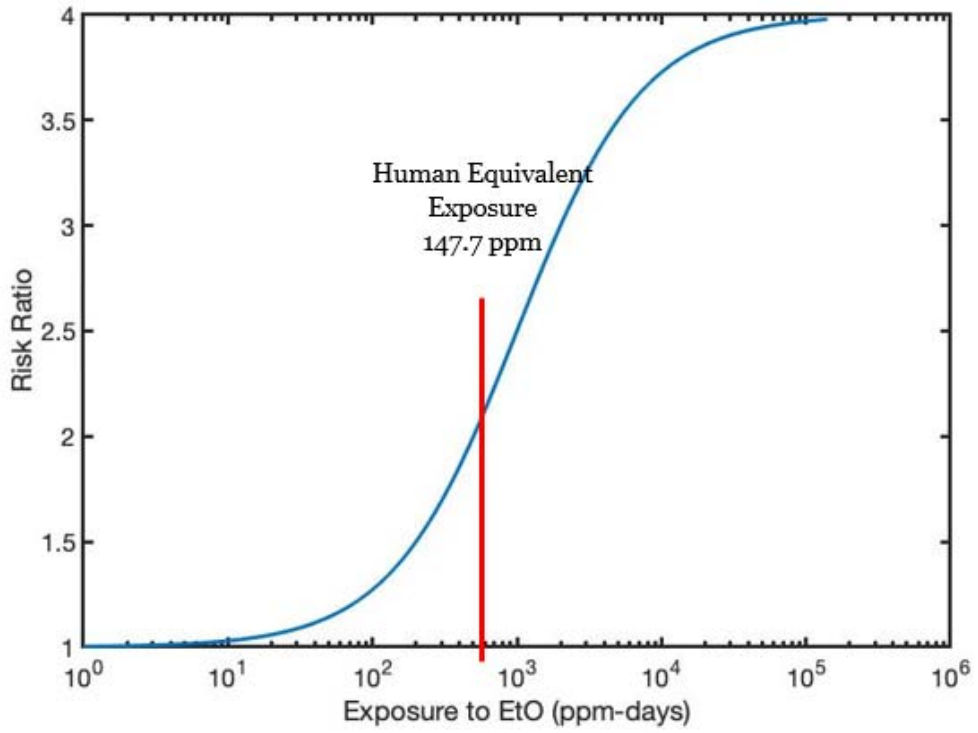
shown in the Figure above (it is the brown solid line). What is noted is the rapid climb from non-exposed to exposed that has been eliminated in the modeling used by the TCEQ because of the intentional decision to rely only on the modeling within the exposed groups. The EPA model (solid red line) accounts for the early rise in risk ratios then flattens out in the higher doses.

TCEQ claims that there is no discernable pattern to the data based on risk ratios where the grouping only includes a single death in each group (circles with black edges in the Figure above). What TCEQ has not shown is that there is no confidence in these numbers and that the confidence bounds around the individual risk ratios will be overwhelming. The grouping done by Steenland et al. (red dots, effectively) is the standard epidemiological approach to dealing with these types of data (have enough deaths in an exposure interval to insure reasonable estimates of risk ratios).

Theoretically, the pattern noted here is not unexpected if the chemical investigated is additive to a process that already exists in the body. As an illustration, consider the usual model for Michaelis-Menten kinetics used for most enzymatic reactions in the body (adding 1 to make it range between 1 and 4). To match this to these data, we will use Vmax=4 (the maximum risk ratio), a KD of 1000 (about 8 times higher than the 147 ppm-days mean TCEQ is using for human equivalent air exposure for endogenous EtO) and plot this as a function of EtO ppm-days. After doing this, you get the figure below.



The graph illustrates a rapidly climbing curve reaching its maximum fairly quickly. Putting this on a log(dose) scale allows greater detail of the low-exposure region and provides the following graph:



Here, it is clear that starting from the presumed human background exposure of 147 ppm-days used by TCEQ, there is no curvature at all, but instead the rapidly climbing relative risk that would be expected. TCEQ argues that the amount that EPA is suggesting as protective of human health is far below the normal human range. This argument does not address the issue of additional human risk, but simply magnitude and associated error of their presumed human background exposure. The argument that the one-standard error estimate away from the estimated human background is much larger than EPA's proposal is confusing statistical noise with the effects in a population. That noise is a function of the response from the people included in the biomonitoring work (people who can clearly have some exposure to EtO, cigarette smoke, ethylene, and other agents in this metabolic pathway), instrument accuracy in calculating values in a urine sample, and the accuracy of the method used to back-calculate to the equivalent air exposure. It also does not mean that the concentrations seen in the population aren't already causing lymphatic cancers because it does not address that question. Additivity to background, as illustrated by the Michaelis-Menten kinetics example illustrated above, demonstrates how rapidly risk can change in the low-dose region for these reactions.

The risk-ratio data from Steenland et al. (2004) demonstrates a similar, rapidly-rising risk for low exposures.

By calculating the slope relative to the lowest exposure category (>0-1199 ppm days) instead of relative to unexposed, TCEQ has disregarded all of the increased risk at low external exposures in this data set and has calculated a slope factor that is meaningless. The arguments for the fit of the model are not convincing since TCEQ disregards the fact that their model is overestimating response in the unexposed group. Indeed, the fit of the TCEQ model as it is being used for risk calculations is the solid blue line passing through 1.0 in Figures 21 and 22. It is clear that the model used does not fit these data. Finally, TCEQ has ignored the fact that additivity to background is likely to lead to linear or supra-linear response.

III. Conclusion

TCEQ's proposal has the potential to inform policy nationally on a compound that has been identified as a significant contributor of cancer risk within the human population in the United States. Indeed, much of TCEQ's DSD references EPA's own risk analysis and evaluation. We respectfully request TCEQ to revise the development support document to increase its scientific rigor to ensure that the best science available is used in the assessment of one of the nation's most ubiquitous cancer-causing compounds.

Respectfully submitted,

Elena Craft, Ph.D.
Senior Director, Climate & Health

Chris Portier, Ph.D.
Senior Contributing Scientist

Environmental Defense Fund
301 Congress Avenue, Ste. 1300
Austin, TX 78701

REFERENCES

Steenland K, Stayner L, Deddens J. 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. Occupational and environmental medicine 61:2-7.

Valdez-Flores C, Sielken RL, Jr., Teta MJ. 2010. Quantitative cancer risk assessment based on niosh and ucc epidemiological data for workers exposed to ethylene oxide. Regulatory toxicology and pharmacology : RTP 56:312-320.

Jessica Myers

From: TOX
Sent: Friday, September 27, 2019 8:10 AM
To: Jessica Myers; Joseph Haney
Subject: FW: Comments on regulation for raising ethylene oxide threshold

From: Anuradha Pandey [redacted]
Sent: Thursday, September 26, 2019 10:28 PM
To: TOX <TOX@tceq.texas.gov>
Subject: Comments on regulation for raising ethylene oxide threshold

Hello,

I would like to submit my comments as a concerned Texas resident about the proposed change of threshold of long-term EtO exposure.

The most alarming thing about the proposed threshold change is that Texas already produces half of the country's ethylene oxide, and the rule change would no doubt lead to increased emissions in a time we are also experiencing hotter years. Ethylene oxide can be explosive when exposed to air and heated, so you can understand why a resident of an urban center would be concerned about an increase in toxic gas in the air.

The assessment that is cited in the paper on the commission's website is based on comparisons to 'endogenous values', the calculation of and data sources for which are never discussed. The value of 'endogenous' EtO is not at all a consensus value. The article by Kirman and Hays cited as the basis of the assessment throughout the document was commissioned by the industry trade group, the American Chemical Council, as cited in the conflicts of interest section toward the end of the article:

> "The analysis presented here was funded by the Ethylene Oxide Panel of the American Chemistry Council (contract 5478)."

The 'endogenous value' holding up the analysis has not been independently verified. The interests of the American Chemical Council, driven by nebulous 'market forces', and the interests of the general public, with which the TCEQ is entrusted, diverge in obvious ways. The American Chemical Council is entrusted with upholding the economic interests of its members, who are driven by the maximization of profit regardless of environmental impact. This is a story we have read many times.

The endogenous equivalent value is a calculation of the ambient ethylene oxide air concentration to which non-smoking test subjects were exposed in the months leading up to sampling. The value is a calculation of the baseline exposure of these test subjects and not the endogenous production of ethylene oxide, the two being distinct scientific concepts.

The 'endogenous values' based on reporting by Kirman and Hays reflect the baseline exposure of the study participants which has nothing to do with endogenous production at all. The value is an extrapolation of ambient EtO concentrations based on hemoglobin adduct quantitation, which does not discriminate between endogenous and exogenous exposure. To call this value 'endogenous' is to be factually incorrect and misleading to the public for the sake of profit at the expense of our health and environment.

The ethylene oxide assessment is also difficult to read because data are frequently presented in relation to the non-

consensus ‘endogenous values’ discussed above that are the linchpin of the assessment. To compare real values and examine the relationships the authors put forth, a reader must pull all the relevant originals and comb through them for the data to recreate the basis for the likely inaccurate conclusions in the paper. An average Texan who wants to be engaged in the processes of her government and have a say should not have to work so hard to understand what is scientifically proven and what is vapor. The authors are obfuscating their wrong assertions by massaging numbers and conflating concepts.

The evaluation is also based on mortality from the cancers examined. Mortality rates vary as medical advances reduce mortality compared to incidence. Therefore, basing a calculation on mortality is muddying the waters. Incidence, however, directly correlates exposure with human impact. Cancer treatment itself is a significant medical expense and personal trauma that should not be discounted.

Furthermore, the time frames of the studies make a mortality comparison questionable because the relationship between incidence and mortality was much closer in the older Union Carbide study than the more recent NIOSH study. NIOSH would be expected to have lower mortality rates due to medical progress over time in improving the survival rate of cancer incidence. In short, mortality is a measure of medicine and incidence is the true measure of toxicity.

Finally, the assumptions and key evaluations chosen by the authors betray the purpose of re-evaluating the allowable limits in the draft assessment provided by the TCEQ, which appears to be to justify increased emissions by businesses located in Texas. In contrast, the US EPA IRIS report for ethylene oxide released in 2016 establishes throughout the document that its purpose is to develop a protective risk assessment that takes into account not only worker safety, but sufficient margins of protection for the general public and children.

For ethylene oxide in particular, the consequences of local emissions are reflected globally in increased baseline levels that in turn influence cancer rates locally, nationally, and globally.

The TCEQ has a responsibility to the American people because Texas-based businesses produce the bulk of the country’s EtO. The nationwide consequences of this rule change must be taken into account. In the end, Texans will be closest to the increases toxic gases in the air. Please kill this regulation change for the good of all Americans.

Sincerely,
Anuradha Pandey
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EOSA The Ethylene Oxide Sterilization Association, Inc.
Managed by B&C® Consortia Management, L.L.C.

September 26, 2019

Via E-mail

Mr. Joseph Haney, Jr., M.S.
Toxicology Division, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
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Re: Comments Regarding Proposed Development Support Documents for Ethylene Oxide Carcinogenic Dose-Response Assessment

Dear Mr. Haney:

On behalf of its members, the Ethylene Oxide Sterilization Association, Inc. (EOSA)[1] appreciates the opportunity to submit these comments in response to the Texas Commission on Environmental Quality (TCEQ) Proposed Development Support Documents (DSD) for Ethylene Oxide (EO) Carcinogenic Dose-Response Assessment. In general, EOSA supports the inhalation-based unit risk factor (URF) derived by TCEQ for EO. EOSA believes the TCEQ carcinogenic dose-response assessment is more scientifically defensible than the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Assessment for EO.

The TCEQ URF Based on Lymphoid Cancer

The URF for EO based on lymphoid cancer derived by TCEQ is 2.5E-6 per parts per billion (ppb) (1.4E-06 per µg/m^3) and results in a risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000.[2] This value is much more realistic and defensible than the EPA IRIS URF of 9.1E-3 per ppb (5.03E-3 per µg/m^3), which yields a 1 in 100,000 risk concentration of 1 part per trillion (ppt).

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[1] EOSA is a nonprofit organization that represents EO suppliers, contract sterilizers, sterilization equipment manufacturers, medical device manufacturers, analytical equipment and systems suppliers, and laboratories. EOSA works to educate industry, regulators, and the public on the uses and benefits of EO sterilization. EOSA also works to improve safety standards, foster industry communications, and provide a forum for many subjects related to EO sterilization.

[2] TCEQ, 2015. Guidelines to Develop Toxicity Factors. RG-442: Texas Commission on Environmental Quality.

EOSA agrees with TCEQ that the EPA IRIS assessment is not adequately supported by current scientific data. The EPA IRIS assessment should not be used as the basis for the exclusion of other estimates of cancer risk that are based on other robust studies and modeling methodologies with more representative exposure estimates. Reliance on the flawed, overly conservative, and outdated EPA IRIS assessment would result in disastrous consequences to the healthcare industry and public health in the United States. Decisions on how best to protect public health cannot be made on such demonstrably flawed science. Though EOSA supports TCEQ's statements regarding the inaccuracies of EPA's modeling approach, the non-threshold effects screening level (ESL) of 4 ppb is overly conservative when you consider endogenous and background ambient EO levels.

EPA's December 2016 IRIS assessment relies exclusively on a National Institute of Occupational Safety and Health (NIOSH) epidemiology study of sterilizer workers. The NIOSH study used a model to estimate exposures prior to 1978 because there were virtually no measured EO concentration data for sterilization workers prior to 1978. The NIOSH exposure model estimates job exposures that were lower than levels observed from 1978 and later. This would be an unusual pattern of historical exposure, based on industry experience with sterilization operations. This unusual pattern was also noted by the EPA Science Advisory Board (SAB) during its review of the IRIS assessment.

Without independent verification, the NIOSH model predicted that the EO exposures were lower in the earlier periods of the study than in the later periods. This assumption underpredicted the potential exposures. This issue is important because, in general, underestimation of exposure can result in overestimation of risk. This estimate was largely driven by the assumption that sterilizer chamber volumes were lower in the earlier periods of the study, and researchers inexcusably ignored the evolution of EO sterilization technology, equipment, and industry practices. As indicated by the SAB in its comments to EPA in 2015, these initial assumptions used to develop model exposure scenarios, which included the trend of decreasing exposures backward in time from the late 1970s to the late 1930s, when no data were available to validate the NIOSH exposure estimates, is counterintuitive, flawed, and scientifically indefensible.

By assuming that low doses of EO are more potent than high doses for causing cancer, EPA significantly overpredicted the cancer incidence observed in the NIOSH cohort study. EOSA agrees with TCEQ on this point and supports its use of a mathematical dose-response model, rather than the supralinear spline model relied on by EPA. Furthermore, the mathematical dose-response model is the standard and conventional risk assessment method used in this instance.

The IRIS assessment concludes that levels below those that occur naturally in the environment or as part of normal human metabolism can cause cancer. EOSA agrees with

TCEQ's determination that, using EPA's IRIS assessment, the background levels of EO in the population would be predicted to cause more lymphoid cancer than is observed in the general population. Clearly, setting cancer risk levels below background levels conflicts with scientific observations of EO exposed humans and animals. This problem supports the TCEQ conclusion that the modeling used by EP overestimates the cancer potency of EO.

EO Sterilization Is Critical for Today's Healthcare Industry

EO is primarily used as an important "building block" chemical in the production of numerous everyday products, including detergents, adhesives, antifreeze, plastics, textiles, pharmaceuticals, and other items, but it is also used by members of the healthcare community to sterilize a wide variety of medical devices and equipment. EO sterilization of medical devices and equipment in the healthcare industry accounts for less than one percent (1%) of the overall EO usage in the United States, yet it is critical to eliminating microbial contamination (*e.g.*, sterilization). Although this represents a limited amount of overall EO use, it supports a critical step required by the U.S. Food and Drug Administration (FDA) in the manufacturing process of medical devices and equipment that are labeled as sterile. This step allows the healthcare industry to provide sterile products that protect patient safety.

Since its discovery as a uniquely effective sterilant in the 1930s, EO has played a critical role in the sterilization of medical devices and pharmaceutical products that protect the general public. Decades later, EO is now used to sterilize more than 20 billion healthcare products each year in the United States alone. This number represents more than 50 percent of all medical devices sterilized annually. EO sterilization is critical in the safe delivery of sterile devices to the healthcare field and is essential to a functioning and effective healthcare system.

Hundreds of thousands of medical, hospital, and laboratory processes rely on EO to sterilize devices and equipment to protect millions of patients from the real risks of infectious diseases caused by bacteria, viruses, and fungi. For the majority of these healthcare products, EO sterilization is the most effective and efficient, and often the only viable, sterilization technology. The extensive compatibility and nature of EO allows for the sterilization of many critical healthcare product and devices that would otherwise be destroyed and rendered unusable by other sterilization methods. Although there are some alternative sterilization techniques, such as steam and irradiation, many medical devices cannot be sterilized with these options, leaving EO sterilization as the best and, in many cases, the only sterilization alternative.

EO sterilization of medical devices and equipment in the healthcare industry is critical and essential to eliminating microbial contamination, which in turn allows the healthcare industry to provide sterile products that protect patient safety and save lives. The elimination or significant restriction on the use of EO as a sterilant could immediately compromise the U.S. healthcare system's ability to provide a consistent and safe supply of sterile medical devices and

cause a public health crisis. A lack of sterile medical supplies to operating rooms would result in delayed or even canceled procedures, which would pose grave risk to those in urgent medical need. Medical supplies sterilized with EO are used in virtually every surgical procedure performed.

For the reasons noted above, EOSA supports the TCEQ derived URF and strongly supports that it not adopt the EPA IRIS assessment URF for 1 in 100,000 of 1 ppt. EOSA is concerned that the TCEQ risk-based air concentration of 4 ppb is overly conservative when considering endogenous and background ambient EO levels; if, however, the flawed IRIS assessment is used to establish limits for EO, there will certainly be disastrous consequences to the healthcare industry and public health in the United States.

The industry takes seriously the importance of controlling emissions of EO. It is our belief that the flawed method of the IRIS assessment does not reflect real-world EO emission concerns, and for that reason the benefit of limiting EO emissions to an unnecessary level does not outweigh the risks of delaying and disrupting access to sterile medical devices and, in turn, critical care to public health. The IRIS risk value should be viewed as invalid until the assessment is revised to reflect the best available science.

If you have any questions, please contact me at [redacted]

Sincerely,

Jake Vandevort
Executive Director,
The Ethylene Oxide Sterilization Association, Inc.

TEXAS CHEMICAL COUNCIL

1402 Nueces Street • Austin, Texas 78701-1586 • (512) 646-6400 • Fax (512) 646-6420

September 26, 2019

Dr. Michael Honeycutt
Director, Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality
12100 Park 35 Circle
Austin, TX 78753

RE: TCEQ Proposed DSD for Ethylene Oxide

Dear Dr. Honeycutt:

The Texas Chemical Council (TCC) submits the following comments on the proposed Development Support Document (DSD) for Ethylene Oxide (EtO). TCC appreciates the opportunity to submit these comments on the DSD for EtO and supports the findings made by the Texas Commission on Environmental Quality (TCEQ) in your research for this DSD.

TCC represents approximately 70 companies who own or operate more than 200 manufacturing and research facilities across the state of Texas. Our members have invested more than $150 Billion in physical assets in the state, directly employ more than 75,000 Texans and indirectly employs over 500,000 Texans. TCC member companies pay more than $1.5 Billion in state and local taxes each year and represent the state #1 non-energy Texas export with over $45 Billion in exports annually.

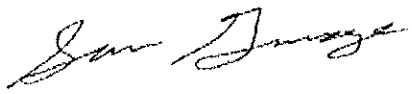
TCC supports the DSD proposed by TCEQ on June 28, 2019. In the DSD proposal, your division utilized robust science-based reasoning for setting the effect screening level (ESL) at 4ppb and thoroughly reviewed the level used by The United States Environmental Protection Agency (EPA).

We appreciate the review of the supra-linear model used by EPA in their assessment of EtO emissions. In your review, you point out that the EPA supra-linear method over-estimates the cancer potency of EtO by assuming that low doses of EtO are more potent than high doses for causing cancer. To that point, your research demonstrates that the EPA assessment improperly suggests that ambient background levels of EtO in the population are more likely to cause cancer than what is actually occurring in the general population. This is counterintuitive and as stated in your DSD, "suggests a scientifically unreasonable unit risk factor."

TCC appreciates the thorough research conducted by TCEQ in establishing a science-based ESL for Ethylene Oxide. We urge the TCEQ to adopt this DSD with the 4ppb ESL and urge EPA to carefully consider the data included in the TCEQ's DSD and reconsider their proposed standard.

We appreciate your consideration of our comments. If you have any questions, please do not hesitate to contact me at [redacted]

Respectfully,



Sam Gammage
General Counsel

CITY OF HOUSTON

Houston Health Department

Sylvester Turner

Mayor

Stephen L. Williams, M.Ed., MPA
Director
Houston Health Department
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September 26th, 2019

Texas Commission on Environmental Quality
Toxicology Division, MC 168

Re: Opposition to Texas Commission on Environmental Quality Proposed Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document

The Houston Health Department opposes the approval of the Texas Commission on Environmental Quality Developmental Support Document for Ethylene Oxide which conflicts with and presents a lower toxicity value for ethylene oxide than that used by the Environmental Protection Agency (EPA). According to the 2014 EPA National Air Toxics Assessment (NATA), ethylene oxide is of grave concern for Houstonians. Not only is ethylene oxide the cancer risk driver for the highest risk census tracts in Houston/Harris County, census tract 343100 has the 7th highest cancer risk from ethylene oxide and the 11th highest total cancer risk in the nation (Table 1, Figure 1). In fact, ten census tracts in Harris County are in the top one hundred highest ethylene oxide cancer risks in the nation, out of a total of 76,727 census tracts (with another census tract just outside the top one hundred). **Lowering the toxicity value will remove pressure from understanding and mitigating exposure to this pollutant**.

In general, the Houston Health Department advocates for consistency of toxicity values with the EPA. In this case, we are especially concerned with the departure from the use of the EPA toxicity values because the proposed value is less protective, and many residents are potentially affected. There is a high degree of uncertainty in understanding the toxicity of individual chemicals on humans, but even more so in Houston, where residents are exposed to mixtures of other toxic chemicals. The health of Houstonians is better protected with the current EPA toxicity value.

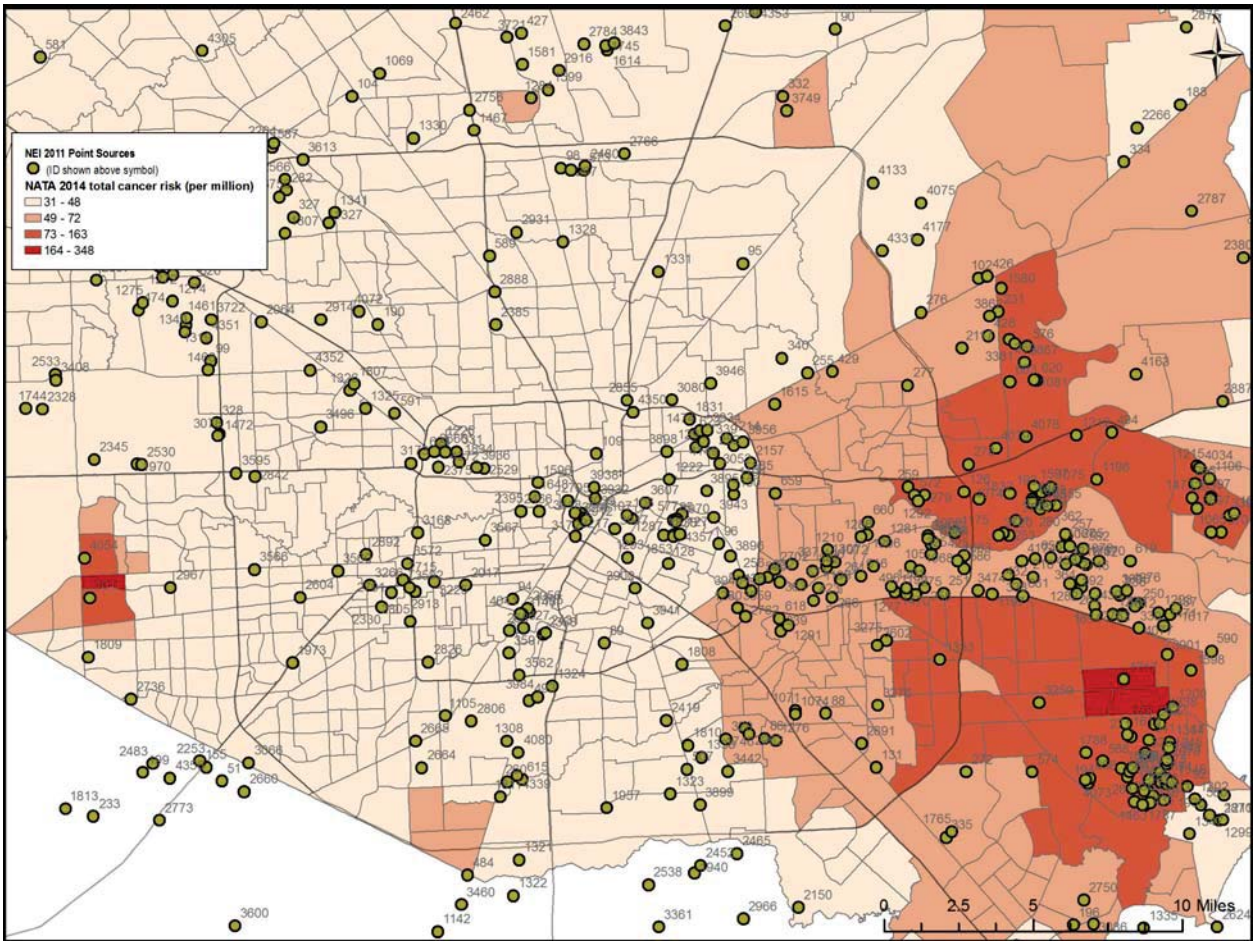
Table 1: Ethylene Oxide Cancer Risk, Total Cancer Risk, and Risk Rank in Harris County Census Tracts.

County	Tract	Population	Total Cancer Risk (per million people)	Total Cancer Rank in US	Ethylene Oxide Risk (per million people)	Ethylene Oxide Risk Rank in US
Harris	343100	4,629	348.2016	11	311.6273	7
Harris	343200	4,944	296.1831	16	249.5291	11
Harris	451700	3,407	224.4594	32	193.1012	24
Harris	343302	4,763	223.5143	33	183.7526	29
Harris	343000	7,423	162.8309	43	129.9362	43
Harris	343301	4,452	155.5736	46	119.0901	47
Harris	342800	8,854	119.3042	74	84.6718	69
Harris	342900	5,437	111.8229	87	78.5844	76

Harris	252600	7,552	120.1101	72	77.6732	77
Harris	340203	4,035	101.8035	106	71.1365	92
Harris	451800	4,744	94.2705	121	62.9828	107

76,727= total number of census tract in NATA 2014
Rank of 1= highest risk

Figure 1: Total Cancer Risk in Harris County Census Tracts.



Reference: United States Environmental Protection Agency. (24 August 2018). 2014 National Air Toxics Assessment. Retrieved from https://www.epa.gov/national-air-toxics-assessment

Thank you

Stephen L. Williams, M.Ed., MPA
Director

Vince Ryan
Harris County Attorney

September 26, 2019

Via tox@tceq.texas.gov
Toxicology Division, MC 168
Texas Commission on Environmental Quality
12100 Park 35 Circle, Building F
Austin, Texas 78753

Re: Harris County Comments on Texas Commission on Environmental Quality (TCEQ) Ethylene Oxide: Carcinogenic Dose-Response Assessment

Dear Sir or Madam:

Thank you for the opportunity to review and comment on the proposed TCEQ Ethylene Oxide: Carcinogenic Dose-Response Assessment (DRA). Harris County, home to over 4 million people, is the third largest county in the United States and home to the second largest industrial complex in the United States. Industrial air emissions are a critical component of the many environmental challenges faced by Harris County. Our nonattainment status for ozone is a testament to our air quality challenges. Recent emission events from fires at the ITC Deer Park Facility, KMCO Facility, Exxon Baytown Refinery, Exxon Baytown Chemical Company Olefins Plant, and many other recent emission events highlight the need for careful consideration of impacts from all air pollutants. Due to these concerns, on September 10, 2019, Harris County Commissioners Court authorized the submission of comments to the TCEQ on behalf of Harris County.

In November 1953, Harris County began regulating air quality when Harris County Commissioners Court established the Harris County Stream and Air Pollution Control Section, as a part of the Harris County Health Unit. It was the first joint air and water pollution control agency in the Nation. Today, the successor department, Harris County Pollution Control Services Department (HCPCSD), investigates and issues violations of environmental laws and rules, including air quality regulations and refers cases for civil or criminal prosecution. Given Harris County's years of experience in protecting air quality, Harris County submits the following comments to the TCEQ.

Ethylene oxide, a hazardous air pollutant, is a known human carcinogen, mutagen, and neurotoxin and is especially dangerous to children. Constant, low level exposure over several months to a few years may cause nausea, headaches, bronchitis, miscarriages, pulmonary edema, memory loss and numbness. Harris County is home to the majority of ethylene oxide facilities in the State of Texas, twelve of which report ethylene oxide emissions to the United States Environmental Protection Agency's (EPA) Toxic Release Inventory (TRI). Eleven of these facilities are located in East Harris County. In 2017, of the eleven facilities located in East Harris County, there were approximately 13,800 pounds (lbs) of ethylene oxide emissions reported to the TRI. Two facilities in particular – Celanese Clear Lake Plant and Equistar's

Bayport Chemicals facility – reported the highest ethylene oxide emissions of 6,282 lbs and 5,033 lbs, respectively.

The EPA Unit Risk Factor (URF) model for ethylene oxide, referenced in the DRA, is clearly a more conservative approach to determine a health based screening value than the method proposed by TCEQ. The TCEQ Cox Proportional Hazard method uses a very different approach and results in a level that is higher and may not be protective of human health. The proposed TCEQ health based screening value is 4,000 times less protective than the EPA value. When human health is at risk, and sensitive populations are at risk of exposure, increasing a health-based value by over three orders of magnitude must be supported by ample scientific data. Harris County requests that TCEQ coordinate with the EPA and reach a concurrence prior to the determination of a final value.

Currently, due to a lack of data, the impact of ethylene oxide on the residents in the area of exposure in Harris County is not well understood as background data has not been collected and evaluated. Also, Section 3.4.2 of the DRA notes that there is a lack of chemical specific data on susceptibility from early-life exposures and as a result, the TCEQ utilized default ADAF numbers. Therefore, Harris County urges the TCEQ to conduct a study to determine the actual background ethylene oxide concentrations in Harris County and impacts of ethylene oxide on children and pregnant women. This data is necessary to understand our residents' chemical burden and health impacts.

This TCEQ proposal is a matter of great concern to Harris County and many members of our community. Harris County requests that the TCEQ hold a public meeting to explain to the public the scientific process utilized in this determination as well as to present supporting data.

Thank you for the opportunity to provide comments on the DRA. If you have any questions, please contact Dr. Latrice Babin, Interim Director, Harris County Pollution Control Services Department at [redacted].

Sincerely,

VINCE RYAN
Harris County Attorney

Sarah Utley

Sarah Jane Utley
Managing Attorney
Environmental Practice Group

cc: Danielle Sullivan, Policy Advisor, Pct. 1
Kristen Lee, Senior Policy Adviser, Pct. 2
Carole Lamont, Administrative Aide, Pct. 3
Cheryl Guenther, Chief of Staff, Pct. 4
Aaron Dunn, Policy Analyst, County Judge's Office
Rock Owens, Special Assistant—Environmental Affairs, HCAO
Dr. Latrice Babin, Interim Director, HCPCSD

NATURAL RESOURCES DEFENSE COUNCIL

September 26, 2019

Texas Commission on Environmental Quality
Toxicology Division, MC 168

Submitted by email: tox@tceq.texas.gov

Comments from the Natural Resources Defense Council (NRDC) Opposing The Texas Commission on Environmental Quality (TCEQ) Proposed Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document

In April 2019, in a strongly worded letter to EPA, thirty scientists, medical professionals, and environmental health experts recently wrote EPA to support the findings and conclusions of the EPA Integrated Risk Information System (IRIS) ethylene oxide (EtO) assessment.[1] These experts have devoted their professional lives to identifying preventable causes of human diseases and deaths. They wrote because EtO is such a concerning chemical pollutant, associated with cancers of the brain, breast, lung, and blood.[2] EtO also poses non-cancer risks including brain and nervous system damage, respiratory irritation and damage to the nose and throat, lung damage, skin irritation, and eye irritation. [3]

The EPA IRIS program uses standard well-accepted scientific methods to conduct rigorous, transparent, peer reviewed scientific chemical hazard assessments that are used across federal agencies, by states and local governments, and in countries around the globe to set emissions limits and clean up levels for toxic chemical. Its EtO assessment was developed in a transparent public process, and has been through two public Science Advisory Board (SAB) reviews.

[1] Comments submitted by J. Sass (NRDC), M. Mabson (Earthjustice) and 29 health scientists on the EPA Proposed Rule: National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review. April 26, 2019. EPA-HQ-OAR-2018-0417-0132

[2] Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Managing Hazardous Materials Incidents. Volume III - Medical Management Guidelines for Acute Chemical Exposures: Ethylene Oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=734&tid=133

[3] Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Managing Hazardous Materials Incidents. Volume III - Medical Management Guidelines for Acute Chemical Exposures: Ethylene Oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=734&tid=133

Unfortunately, the TCEQ proposed factor is three orders of magnitude less protective than the factor developed by EPA scientists. TCEQ's factor, if applied, would ignore serious cancer risk from air pollution to which Texans are exposed and lead to more incidence and death from cancer for generations of Texans.

TCEQ process violates EPA peer review requirements

EPA's process for developing its EtO IRIS assessment was consistent with its peer review requirements as described in the EPA Peer Review Handbook (4th Edition, 2015), and the Final Information Quality Bulletin for Peer Review (OMB, 2004).[4] In stark contrast, TCEQ's EtO assessment and proposed risk estimate has not been vetted by an external scientific advisory committee or any other appropriate scientific peer review committee, and has not undergone any public peer review, scientific scrutiny, or public comment before this comment period.

The peer review process that TCEQ should undertake should be transparent, include EPA input, and be accountable to the recommendations that arise from that process. The Handbook and Bulletin require documents that are "highly influential," "novel, controversial, or precedent-setting," or have "significant interagency interest" to undergo peer review before being implemented. EPA has done this, while TCEQ has not.

TCEQ fails to address all cancer and non-cancer risks

TCEQ narrowed the focus of its assessment to lymphoid cancers only, disregarding the elevated breast cancer incidence in female workers. This results in an underestimate of the risks posed by EtO, and is one of the most significant differences between the TCEQ assessment and the EPA IRIS assessment, which included breast cancer data.

TCEQ fails to address environmental racism in cancer death rates

TCEQ disregarded EtO-associated breast cancer risks in women workers by conducting assessments based only on morbidity, that is, deaths from breast cancer. Because many women that are diagnosed with breast cancer can survive it, this make is seem as if the risk is negligible. In addition to underestimating risks by counting only women that die of breast cancer, TCEQ's approach also underestimates risks to women of color more than white women. This is because cancer survival depends on access to quality health care, routine medical screening procedures, and medical insurance to allow timely and effective treatments – all of which have significant racial bias. That is, although over time there has been a decline in deaths from breast cancer, not all women have benefited equally. This is evidence by the striking divergence in mortality trends between black and white women beginning in the early 1980s.[5] As treatment for breast cancers has improved, the racial disparity widened; in 2015, breast cancer death rates were 39% higher in black than white women. This is particularly relevant for

[4] OMB Final Information Quality Bulletin for Peer Review. M-05-03. December 2004

[5] See Report of the American Cancer Society. Breast Cancer Facts & Figures 2017-2018. Atlanta: American Cancer Society, Inc. 2017. Fig 6b. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf

EtO and other contaminating facilities that are disproportionately co-located in areas of Texas such as the Houston Ship Channel communities that are predominantly low-income and communities of color.[6]

TCEQ mis-represents endogenous exposures

Understanding the endogenous exposures is a scientifically critically important component of the EPA's EtO assessment, whereas it is mis-represented by TCEQ in its assessment. Although the body produces EtO endogenously (through cellular metabolic processes), it has some defense mechanisms, albeit imperfect ones, to deal with some level of endogenous exposure. Given that both breast and lymphoid cancers are fairly common, it is possible that some may be due to endogenous EtO levels, suggesting that the body's defense mechanisms may be largely overwhelmed by additional exogenous EtO from preventable industrial sources, especially when considered across the whole population. While EPA has addressed this in its more sophisticated and scientifically accurate assessment, the TCEQ assessment simply 'zeroes out' the cancer risks at lower exposures as if they do not exist, and – even more flawed – that the body's cellular defense mechanisms will make additional cancer risks 'go away'. This makes as little scientific sense as it sounds, and even less when considered across a diverse population that includes sensitive individuals.

Conclusion

NRDC supports the calls of Texas residents and others in calling for TCEQ to simply adopt the U.S. EPA scientists' determination and cancer risk factor for ethylene oxide, finalized by the IRIS program in 2016. The EPA IRIS determination reflects the best available science.[7]

NRDC supports the following comments to TCEQ for this comment period:

- Coalition comments submitted by the Sierra Club, Texas Environmental Justice Advocacy Services, Air Alliance Houston, Coastal Alliance to Protect our Environment, Environment Texas, Public Citizen's Texas Office, Texas Campaign for the Environment, Earthjustice, and Environmental Integrity Project;
- Comments from the UCSF Program on Reproductive Health and the Environment and supporting scientific experts.

NRDC attaches for inclusion comments submitted by J. Sass (NRDC), M. Mabson (Earthjustice) and 29 health scientists on the EPA Proposed Rule: National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review. April 26, 2019. EPA-HQ-OAR-2018-0417-0132

Respectfully,

Jennifer Sass, PhD
Senior Scientist, NRDC

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[6] See Coalition comments submitted by the Sierra Club, Texas Environmental Justice Advocacy Services, Air Alliance Houston, Coastal Alliance to Protect our Environment, Environment Texas, Public Citizen's Texas Office, Texas Campaign for the Environment, Earthjustice, and Environmental Integrity Project.

[7] Coalition comments submitted by the Sierra Club, Texas Environmental Justice Advocacy Services, Air Alliance Houston, Coastal Alliance to Protect our Environment, Environment Texas, Public Citizen's Texas Office, Texas Campaign for the Environment, Earthjustice, and Environmental Integrity Project

Jessica Myers

From: Bridgette [redacted]
Sent: Thursday, September 26, 2019 9:55 PM
To: TOX
Cc: Harold Dutton
Subject: TCEQ Proposed Ethylene Oxide DSD

Re: Comments opposing TCEQ's Proposed Ethylene Oxide Carcinogenic Dose-Response Assessment Development Support Document, and seeking external scientific peer review and adequate time for public notice and comment.

On behalf of Achieving Community Tasks Successfully dba ACTS which is an environmental, health, and environmental justice organizations, we submit the following comments to raise serious concerns about public health.

ACTS is a non profit community based organization in a community 2.2 miles from Port Houston. Our residents live, work and play near industrial facilities in Texas (and, in some instances, across the United States) that emit ethylene oxide. We urge the Texas Commission on Environmental Quality (TCEQ) to follow the best available science and not to weaken protections for the thousands of Texans exposed to the carcinogen ethylene oxide. We respectfully request that TCEQ not finalize the proposed Development Support Document (DSD),1 and instead adopt the robust, final, peer-reviewed cancer risk factor that the Integrated Risk Information System (IRIS) of the U.S. Environmental Protection Agency (EPA) finalized in 2016.

Again we urge TCEQ not to finalize the proposed ethylene oxide carcinogenic dose-response assessment Development Support Document and instead to use the 2016 EPA IRIS value. We ask that TCEQ seek external scientific peer review and provide adequate time for public notice and comment, if it continues to consider the proposed DSD.

Please feel free to contact our organization with any questions

Bridgette Murray
Founder/Executive Director ACTS
1403 Laurentide
Houston, TX 77029
[redacted]

Cc: The Honorable Harold Dutton, State Representative District 142

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AdvaMed
Advanced Medical Technology Association

September 26, 2019

Toxicology Division
Texas Commission on Environmental Quality

Toxicology Division:

The Advanced Medical Technology Association (AdvaMed), the national association of medical technology providers, supports the Texas Environmental Quality Commission's (Commission) reasonable, risk-based approach to the exposure assessment for ethylene oxide and we also support the Commission's rejection of the faulty Integrated Risk Information System (IRIS) approach.

AdvaMed member companies produce the medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed encourages public policies that assure patient access to the benefits of medical technology.

We support the Commission's comprehensive approach to the updated exposure risk assessment that follows well-established, traditional scientific measurements of exposure risk used by the US Environmental Protection Agency (EPA). Generally, we also appreciate the honest acknowledgement that naturally occurring or other non-industrial sources of ethylene oxide create background levels of the chemical that far exceed limits contemplated by new assessment methodology, such as the IRIS approach.

We oppose using the EPA's new and unproven IRIS assessment approach. We fully share in the concerns raised by the American Chemistry Council's (ACC) EO Panel and the Ethylene Oxide Sterilization Association, Inc. (EOSA). We are deeply concerned about the reliability and accuracy of the IRIS assessment and the potential negative impact the assessment could have on the healthcare industry and, most importantly, patient health and safety.

Although medical device sterilization accounts for less than 1% of the overall EO usage in the U.S., it is probably the chemical's most critical use, as our members currently sterilize hundreds of millions of medical devices each year in the U.S. with EO. Many of these devices cannot be sterilized in any other way because of the sensitive nature of the device materials, the components, or the complexity of design. The majority of these devices are not resistant to damage caused by moist heat, radiation, and other modes of sterilization. Examples of devices that can only be sterilized using EO include implantable devices containing electronic components and batteries, anesthesia products, combination products (devices that contain

drugs), MRI conditional/safe devices and IV devices. For a number of other types of products, our members utilize other modes of sterilization, such as gamma irradiation and electron beam sterilization when possible, but for many devices there is currently no viable alternative technology to EO.

The direct impact of any elimination or severe restriction on the use of EO as a sterilant would compromise the U.S. healthcare system. At best, inventory shortages would likely result, and at worst, many life-sustaining medical devices such as pacemakers and implantable cardioverter/defibrillators would no longer be available to patients. It should also be noted that changes in sterilization processes and methods would require clearance or approval by the FDA prior to implementation. Supporting evidence would have to be provided by the manufacturer demonstrating that the new sterilization process does not adversely affect the device and that the same level of sterility is achieved.

Delivery of excellent patient care, particularly for those facing life-threatening disease states, including cancers, motivates everything the medical technology community does. Ensuring sterility of safe and effective medical products and preventing introduction of dangerous infectious diseases, including multidrug resistant organisms like methicillin-resistant Staphylococcus aureus (or MRSA) is also an important consideration that requires the use of powerful tools like ethylene oxide sterilization until viable alternatives can be developed.

Given the importance of sterilized devices for providing necessary healthcare to the patient community, decision-making about an important sterilizing agent like EO which is integral to providing life-saving treatment, must be grounded in supportable fact-based assessments like the Commission in order to avoid unintended negative consequences for the healthcare system. We applaud the Commission's work to engage in fact-based, scientifically rigorous decision-making.

Please contact me if you have any questions.

Sincerely,

Fielding Greaves
Director, State Government & Regional Affairs