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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.

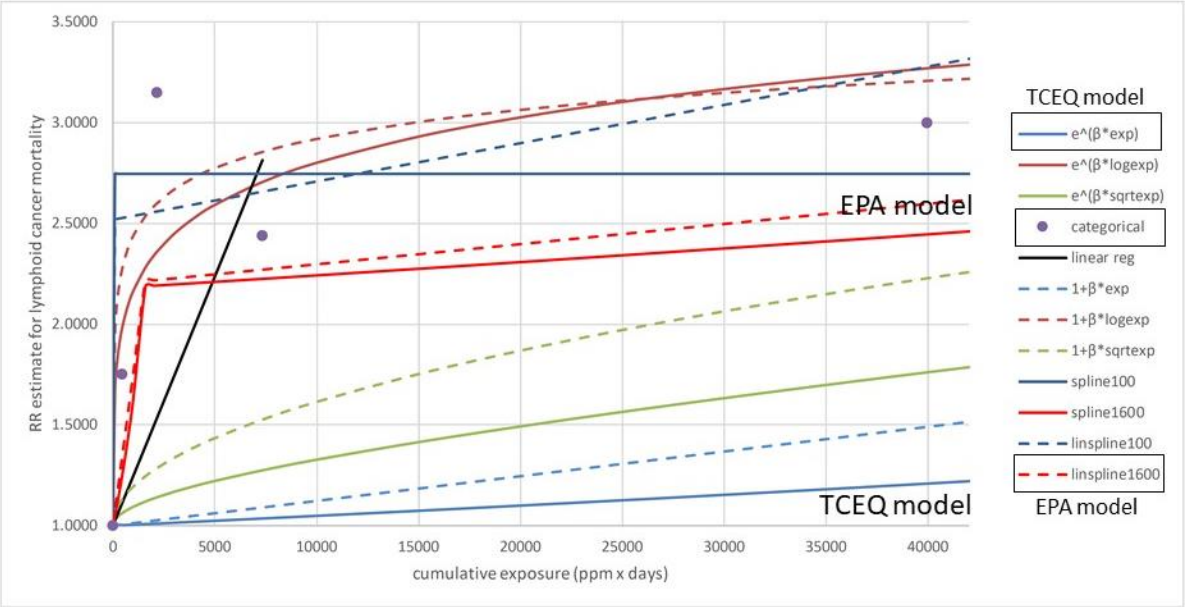
TCEQ's method for predicting the number of cases in the NIOSH cohort relies on a standardized mortality ratio (SMR) comparison.[52] As discussed in comment #10b, SMRs are notoriously deficient for analyzing occupational epidemiology data because workers often have background disease mortality rates below 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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