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RE: Comments of the ACC EO Panel on EPA's Proposed New Source Performance Standards for the Synthetic Organic Chemical Manufacturing Industry and National Emission Standards for Hazardous Air Pollutants for the Synthetic Organic Chemical Manufacturing Industry and Group I & II Polymers and Resins Industry. Docket ID No. EPA-HQ-OAR-2022-0730, 88 Fed. Reg. 25,080 (April 25, 2023)

The American Chemistry Council's (ACC) Ethylene Oxide (EO) Panel respectfully submits its comments on the U.S. Environmental Protection Agency's ("EPA") proposed New Source Performance Standards for the Synthetic Organic Chemical Manufacturing Industry and National Emission Standards for Hazardous Air Pollutants for the Synthetic Organic Chemical Manufacturing Industry and Group I & II Polymers and Resins. EO Panel members include major producers and users of EO in North America.

ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.

The Proposed HON includes a description of technical measures to be undertaken to reduce facility source emissions and the residual health risk for the local public. The Proposed HON emphasizes that the IRIS inhalation URE (EPA, 2016) is the foundational scientific rationale underpinning the Proposed HON's intent "to ensure our standards provide an ample margin of

safety to protect public health" after implementation of proposed facility controls. Specifically, regarding facility ethylene oxide (EtO) emissions and health risk, the EPA states

"*Additionally, in 2016, the EPA updated the IRIS inhalation URE for EtO. In the first step of the CAA section 112(f)(2) determination of risk acceptability for this rulemaking, the use of the updated 2016 EtO risk value resulted in the EPA identifying unacceptable residual cancer risk driven by EtO emissions from HON processes. Consequently, the proposed amendments to the HON also address the EPA review of additional control technologies, beyond those analyzed in the technology review conducted for the HON, focusing on emissions sources emitting EtO that contribute to unacceptable risk"*.

Use of the IRIS inhalation URE for EtO to determine "risk acceptability" and "unacceptable risk" is extremely problematic as this EPA assessment has numerous flaws and lacks the biological plausibility to serve as a useful basis for risk management. We feel that it is essential to address the serious problems with the 2016 IRIS assessment and URE that the EPA previously failed to objectively address and discuss an alternative biologically plausible EtO assessment, the Texas Commission of Environment Quality risk assessment (TCEQ 2020), that would provide a scientifically sound and practical basis for managing EtO risk.

The EO Panel and others have identified critical flaws and weaknesses compromising the scientific reliability of the extremely conservative IRIS URE that currently underpins source control technology to reduce residual risk under the HON. Most critically, EPA estimated EtO cancer risk-based on its determination that cancer incidence in the EtO NIOSH occupational cohort was best characterized by use of a "supralinear" two-slope linear spline dose-response model that projects cancer risk increases sharply at low cumulative EtO exposures and less steeply at higher exposures.

The EO Panel noted that the justification of the IRIS dose-response model is based on flawed statistical analysis critical to the location of the "knot" in the two-slope model, i.e., the dose-dependent transition from the initial steep slope to a plateauing slope at higher exposures. ACC also noted faulty key assumptions that compromise EPA's assertion that a visual fit of plots of categorical risk ratios (RR) supported use of the 2-slope dose-response model. In contrast, ACC advocated that a more scientifically preferred and EPA policy-consistent modeling of NIOSH data is accomplished by use of a single-slope log-linear dose-response model (Cox Proportional Hazard, CPH).

Importantly, a published high-quality CPH-based alternative dose-response model (TCEQ, 2020) results in an approximate 3 order of magnitude decrease in EtO risk estimation (10^{-6} – 10^{-4} risk equated to 0.43 – 43 µg/m^3; 0.24 – 24 ppb) and more consistent predictions for the specific cancers at issue. The overall EtO experimental toxicology data (e.g., animal tumorigenicity, genotoxicity, toxicokinetics, mode-of-action) indicate the IRIS reliance on a two-slope IRIS dose-response model lacks an essential mechanistic foundation of biological plausibility, which the EPA Scientific Advisory Board proscribed as a key rationale necessary for justification of a scientifically plausible EtO dose-response model. The overall biological data thus offer no credible evidence supporting a conclusion that the EtO dose-response steeply increases at low

exposures with an ensuing plateau at higher exposures. In distinct contrast, an integrated consideration of the overall biological and epidemiological data suggest the EtO dose-response is far more plausibly modeled as low dose linear with transition to a steeper dose-response at higher exposures.

The EtO IRIS URE is one of the most conservative cancer risk standards of all evaluated IRIS compounds, i.e., estimating risk specific concentrations (RSCs) of 0.0001- 0.01ppb = 10^{-6}-10^{-4} risk. These RSCs are so small that they are well below the analytical sensitivity and precision of presently available EtO measurement methods, as well as background concentrations that everyone is exposed to daily. Thus, the IRIS RSCs provide no practical utility in managing the residual risk posed by facility EtO emissions. These small RSCs have contributed to risk communication problems in the past regarding the substantial background exposure that derives from human metabolism (endogenous) and from breathing ambient air from natural and unregulated sources (exogenous) and may well also do so in describing residual risk associated with source controls.

Although the HON appears to limit health risk considerations to specific source control measures and describes a strictly technical basis for the fenceline monitoring program for other sources to be implemented after individual measures, a credible health risk basis would likely have eliminated the need for a fenceline monitoring program (the rationale for the fenceline monitoring is challenged in the associated technical comments). Because EPA guidance on background states that an Action Level should have a health basis, we also propose an approach to developing a health risk-based Action Level for managing residual EtO risk from emission sources.

The Proposed HON itself indicates a reasonable scientifically plausible resolution to the lack of utility of the IRIS URE in managing residual EtO risk, stating:

> "For residual risk assessments, we [EPA] generally use UREs from the EPA's IRIS. For carcinogenic pollutants without IRIS values, we look to other reputable sources of cancer dose-response value, often using California EPA [CalEPA] UREs, where available. In cases **where new scientifically credible dose-response values have been developed in a manner consistent with EPA guidelines and have undergone a peer review process similar to that used by EPA, we may use such dose-response values in place of, or addition too (sic), other values."** [emphasis added]

Although this statement specifically applies to chemicals without IRIS values, the lack of utility of the IRIS URE and associated RSCs in managing EtO residual risk indicate that the option of relying on an alternative plausible dose-response assessment consistent with EPA guidelines is warranted. The TCEQ published a "new" (post 2016-IRIS) "scientifically credible" and peer-reviewed dose-response model that is importantly based on the same occupational cohort as that relied on by IRIS for its URE (TCEQ, 2020). The TCEQ CPH-based dose-response model estimates an EtO cancer risk that is approximately 3 orders of magnitude greater than IRIS. Although EPA has challenged the TCEQ URE as a reasonable alternative cancer dose-response model, the EO Panel HON comments extensively document how the TCEQ URE indeed

represents a higher-quality and more "scientifically credible" characterization of EtO risk compared to the EPA IRIS and would serve as more scientifically sound and practical basis for managing EtO risk. Should EPA continue to use the EO IRIS value and not recognize the TCEQ alternative value, then it should initiate a revision of the IRIS value incorporating all recent information.

In December 2022, EPA (2022) provided responses for the reconsideration of the 2020 national emission standard for hazardous air pollutants: miscellaneous organic chemical manufacturing residual risk and technology review. EPA (2022) challenged the TCEQ URE as a reasonable alternative cancer exposure response model and responded to ACC's comments. EPA (2022) included new flawed analyses and new responses to ACC comments. EPA's (2022) response to comments include new information and analyses that are directly relevant to any EPA rule based on the IRIS assessment, and are important to respond to as part of our comments on the proposed HON.

The new EPA (2022) responses reveal an important misunderstanding of ACC's comments, although it is possible that EPA (2022) mischaracterized ACC comments in the process of summarizing multiple comments together from different commentors and thereby conflated different comments in a manner that lost the emphasis of ACC comments. EPA's new analyses of animal toxicity data perpetuate EPA's visual methods of eyeballing data and indiscriminately present a large amount of data without any consideration of which data is most relevant for addressing the biological plausibility of the epidemiological exposure-response models. In other cases, EPA responses dismiss ACC's comments for reasons that were far more problematic in the EPA IRIS or NIOSH study or reinterpret the emphasis of EPA IRIS (2016) or EPA SAB reports.

These issues are readily apparent in the EPA (2022) consideration of the TCEQ peer reviewers evaluation of the TCEQ's correction of the EPA IRIS (2016) statistical analysis and visual fit. When the two TCEQ peer reviewers with statistical modeling expertise clearly disagree with the IRIS assessment of statistical results, EPA brushes off the statistical error aside as a matter of opinion: "it does not disagree that some modelers would follow an alternate process where the knot location is handled as a fully adjustable model parameter and uncertainty in the parameter. . .If followed, this process would lead to some increase in the calculated fit statistic (AIC) and model p-values."

What EPA (2022) dismissively describes as "some increase" is in fact a substantive difference between what EPA describes as nearly significant p=0.07 to a clearly non-significant p=0.14. Had both the statistics and visual fit comparisons been accurately presented in the EPA IRIS, the EPA SAB likely would have reached very different conclusions. This is apparent in the EPA (2019) sensitivity analyses which selected models based solely on incorrect p-values and visual fit criterion, as well as in public comments, including those by the former chemical manager of the IRIS (2016a), that based their comments on these incorrect statistics and flawed comparisons of visual fit along the y-axis.

EPA distracts from the main argument of EPA's error in p-values by citing the TCEQ peer reviewer (anonymous "Expert 5") who supported TCEQ's view about estimation of the knot parameter statement but also felt that health protectiveness becomes a salient factor. This point is irrelevant to the fact that the p-values are incorrect. This expert is merely saying, all things being equal this expert would pick the more conservative protective one. But as discussed in ACC's comments, all other things are not equal. When one focuses on the full body of epidemiological evidence and biological plausibility, the IRIS model's fundamental flaws are evident. ACC's comments provided ample information that the weight of the biological and epidemiological evidence supports the TCEQ model over the IRIS model.

EPA (2022) highlights a TCEQ peer reviewer's quote indicating a lack of understanding of the draft TCEQ figures as proof that the final TCEQ (2020a) URE is based on flawed visual analysis. EPA (2022) neglects to explain that the TCEQ figures in question were visual illustrations of the EPA (2016) warning in the footnote that comparisons along the y-axis should not be made. Contrary to EPA (2022) incorrect claim, TCEQ (2020a) did in fact make a very important change to the figure legends for the y-axis to address the confusion.

EPA criticizes TCEQ's demonstration of a lack of a clear exposure-response pattern of the underlying data because the graphs don't reflect the very wide confidence intervals, but then emphasize the pattern of a few categorical estimates on EPA IRIS figures that also don't show the wide confidence intervals as the basis for selecting the EPA's model. EPA (2022) gives the incorrect impression that by not addressing the peer reviewer's question and presenting confidence intervals, the TCEQ (2020a) basis for selecting the standard CPH model is flawed. In fact, TCEQ (2020a) specifically states that visual fit comparisons are not the basis for comparing the fit of the model and is not part of the main body of TCEQ (2020a). TCEQ (2020a) clearly considers biological plausibility, corrected statistics, and a more objective approach to check whether the model can predict the actual number of cases as the basis for selecting the CPH model.

A new approach EPA (2022) uses to dismiss ACC's comments is to distract from the main scientific arguments by reinterpreting the history of the EPA SAB deliberations and stretching the meaning of the EPA SAB comments. For example, EPA (2022) argues that the EPA IRIS must be correct in ignoring the knot as a parameter in the statistical analyses because ACC didn't comment on this point earlier. EPA's responses regarding past ACC comments are irrelevant to the key point that there is general consensus among statisticians that the statistical calculation is in error.

Ironically, EPA (2022) dismisses comments that were made during the EPA SAB deliberations as already addressed by EPA IRIS, but equally dismisses any comments that were not made at the time as if they must not be real errors if ACC had not previously commented on them prior to 2016. In this specific example, EPA (2022) ignores valid scientific arguments even when the evidence overwhelmingly indicates EPA IRIS is based on a flawed statistical analysis. This flawed statistical analysis had a major impact on EPA IRIS priority of accepting models, as well as the EPA SAB review.

EPA reinterprets the EPA SAB report by claiming incorrectly that the SAB advice to de-emphasize AIC and p-values as a rigid selection as proof that such "technical changes" would not have led to different model selection decisions. The EPA SAB advice was given in the context of EPA rejecting the statistically significant log cumulative models and selecting the knots for the spline models applied to the breast cancer and lymphoid cancer data.. EPA (2022) now revises the record to be advice specific to new concerns expressed by ACC after 2016, which EPA correctly notes was not a major comment made by ACC prior to 2016.EPA IRIS relied heavily on p-values and AIC to make decisions about priority of different types of models including the log cumulative model, and it was a major reason to reject the standard CPH model over the spline model.

EPA (2022) presents new analyses to support the conclusion that the biological evidence from genotoxicity and cancer bioassays cannot be used to address biological plausibility for any model. This new "analysis" is a crude visual inspection of a line drawn between the lowest and highest dose level and eyeballing whether the mid doses are below or above the line without consideration of statistical significance or the conclusions of the published studies. The studies are indiscriminately selected without consideration of whether they are the most relevant to the cancers of interest, the putative genotoxic mode of action and the exposure levels and duration.

For example, sister chromatid exchanges (SCE) are no longer considered as reflective of investigating genetic damage (Wilson and Thompson, 2007). Essentially, EPA (2022) uses this visual display to ignore EPA SAB's (2015) emphasis on biological plausibility. EPA SAB stated that "any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data."

In contrast, TCEQ began their quantitative risk assessment approach with biological plausibility as the basis for selecting the standard CPH model over the spline model. However, they grounded their analysis in correct statistics and much more objective methods to verify the fit of the model compared to EPA's subjective visual fit comparisons that treat point estimates of categorical estimates of data as the actual data modeled. Our previous comments supported TCEQ's approach by further augmenting the analyses of biological plausibility and explanations of the validity of the prediction analyses. EPA has largely ignored ACC's specific comments on biological plausibility by stating that all these studies have been evaluated by EPA and so, therefore, are not new information that impact the IRIS assessment.

What EPA failed to do that ACC's new comments address is to properly integrate the biological and epidemiological evidence in the selection of the model. The epidemiological and biological evidence does not support selection of a log cumulative, spline or any of the multiple statistical models that attempt to mimic the shape of the log cumulative model. The categorical estimates of the data are not the individual data modeled, and the original peer reviewed Steenland et al (2004) publication did not combine males and females together in the categorical analyses because the patterns of effects are distinctly different.

EPA's (2022) responses also address breast cancer. However EPA (2022) failed to address the substance of ACC's comment: "Although breast cancer outcomes should be considered as part of the weight of evidence for cancer assessment, breast cancer incidence in the full cohort or subcohort should not be used for quantitative cancer risk assessment because of the high potential for bias in the lower exposure range due to under ascertainment of cases in the full cohort, most likely among workers who have shorter employment period and are harder to find (Steenland et al. 2003)." Instead of responding to this ACC comment, EPA (2022) focused on the question of whether breast cancer should be considered as part of the weight of evidence for cancer assessment.

In addition, EPA (2022) lists many statistically significant findings for breast cancer including the standard mortality ratios (SMRs) and standard incidence ratios (SIRs) from Steenland et al. (2003, 2004), but EPA did not address ACC (2020) comments that the SIR and SMR patterns support a CPH and not EPA's 2-slope. EPA (2022) also omits the statistically significant standard CPH model for breast cancer incidence (p=0.02 for CPH vs. the corrected p=0.04 for IRIS 2-slope spline model). This error of omission suppresses important information that supports the use of the standard CPH model. EPA (2022) correctly notes that the breast cancer mortality data is fully ascertained.

If EPA feels compelled to include breast cancer, then breast cancer ***mortality*** is more appropriate for quantitative risk assessment purposes because breast cancer mortality is fully ascertained (e.g. no missing data) and is publicly accessible. Based on EPA IRIS (EPA, 2016a, Table 4-11) application of the standard CPH model for breast cancer mortality, the central and lower-bound unit risk estimates for the cancer slope factor are 0.019[1] and 0.035[2] per ppm respectively, at the POD of 1/100[3] extra risk not including the EPA's age-dependent adjustment factor (ADAF). This is in contrast to the application of the 2-piece spline model for the under-ascertained breast cancer incidence of 0.72[4] and 1.5[5] per ppm for the central estimate and upper bound (see also EPA, 2016a, Table 4-15, not including ADAF). These data can then be used to derive a corrected URE based on the fully ascertained breast cancer mortality.

ACC extensively documents in these comments why the TCEQ URE represents a higher-quality and more "scientifically credible" characterization of EtO risk compared to the EPA IRIS, and would serve as more scientifically sound and practical basis for managing EtO risk. In addition, ACC includes recent responses to California OEHHA which addresses new issues and publications raised by OEHHA in support of the IRIS assessment.

[1] EPA IRIS (EPA, 2016a) Table 4-11 EC01(ppm) = 0.5305, not including ADAF

[2] EPA IRIS (EPA, 2016a) Table 4-11 LEC01 (ppm) = 0.285, not including ADAF

[3] Note: EPA IRIS provided no justification for applying the POD of 1/100 extra risk. An appropriate POD should be selected to ensure it is appropriately in the lower range of the experimental data.

[4] EPA IRIS (2016) Table 4-15 EC01(ppm) = 0.0138, not including ADAF

[5] EPA IRIS (2016 Table 4-15 LEC01(ppm) = 0.00675, not including ADAF

Thank you for your consideration of these comments. Please feel free to contact me at bill_gulledge@americanchemistry.com if you have questions or need more information.

Sincerely,

Bill Gulledge

Bill Gulledge

Senior Director, CPTD

The following attachments to this letter support our comments:

Attachment 1: ACC EO Panel Comments on HON Proposal (2023)

Attachment 2: ACC EO Panel Additional Comments on MON (2020)

Attachment 3: ACC EO Panel Comments on California OEHHA Draft NSRL for Ethylene Oxide (2023)

Attachment 4: ACC EO Panel Comments on California OEHHA Draft IUR for Ethylene Oxide (2023)