UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Washington, DC 20460

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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: ORD review of comments on the IRIS Ethylene Oxide assessment contained in the ACC Request for Correction submitted regarding EPA's National Air Toxics Assessment.

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TO: Joseph Goffman
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ORD has examined the "Request for Correction under the Information Quality Act: 2014 National Air Toxics Assessment (NATA)", submitted to EPA by the American Chemistry Council (ACC) on September 20, 2018 (RFC 18003). This submission primarily presents ACC's arguments that EPA should not rely on the 2016 Ethylene Oxide (EtO) IRIS Assessment.

The purpose of the Request for Correction (RFC) process, under Section 515 of the Consolidated Appropriations Act (2001), known as the Information Quality Act, is to allow "affected persons to seek and obtain correction of information maintained and disseminated by the agency…". ORD has reviewed the ACC Request for Correction (RFC) and finds this document has not identified errors in the IRIS Assessment of EtO. Accordingly, ORD recommends that the RFC be denied. The RFC does not provide new scientific data bearing on the cancer risks of EtO. Rather, the RFC primarily re-presents issues that were identified in public comments during the development of the EtO IRIS assessment; EPA reviewed these issues at the time and did not concur with commenters' conclusions. ORD utilized extensive advice from the Science Advisory Board (SAB) in reaching its IRIS assessment judgements, including SAB advice on core components that constitute the ACC RFC. More specifically, the SAB was supportive of the suitability of the NIOSH cancer epidemiology study, and EPA closely followed SAB advice in the selection of appropriate dose-response models for analysis of the NIOSH study data (Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, 2015). ORD notes that the EtO IRIS Assessment was appropriately conducted with unusually extensive processes for the consideration of public comment and external peer review. ORD considers the 2016 assessment to still represent the best available scientific information regarding cancer risks from EtO.

1. **The RFC argues that EPA erred in relying on the NIOSH epidemiology study specifically due to perceived problems with assessment of EtO exposures to workers in that study.**

Response: ORD notes that the NIOSH epidemiology study and the exposure assessment developed for workers in that study were extensively discussed during public comment and external peer review of the IRIS EtO assessment. SAB (2015, page 16) states: "SAB supports the use of the NIOSH EtO worker cohort described in Steenland et al. (2004) and Steenland et al. (2003) as the primary data source for the modeling of cancer risk from EtO exposures. This is consistent with the support for the data source in the previous SAB (2007) review." Arguments presented in the RFC regarding the NIOSH study primarily recapitulate comments that EPA received and addressed during the development of the IRIS assessment. Additional claims presented in the RFC are insufficiently documented with data and do not indicate errors in the NIOSH study or its use by EPA.

a) **ACC claims that the NIOSH statistical model used to estimate occupational exposure was flawed in that it relied upon measurement data generated after 1978.**

Response: The stated purpose of the statistical exposure model developed in the NIOSH investigation was to allow estimation of exposures for those workers and time periods when direct measurement data were not available. The IRIS EtO assessment summarized the basis for the NIOSH exposure model on page 3-6 of the assessment. EPA further described the validation of the regression model (see page 4-65 and Section A.2.8 of Appendix A to the 2016 IRIS EtO assessment and further detail about the exposure estimates for the cohort in Section D.5 of Appendix D). The NIOSH study publications and the IRIS assessment were also transparent that measurement data on EtO levels in the studied plants were not available before the late 1970s. In reviewing this material, the SAB (2015, page 16) stated: "The support of the NIOSH data is founded on study documentation of the original exposure measurements, procedures for exposure estimation (Hornung et al., 1994) and historical modeling (prediction) of exposures that occurred before the time period in which actual exposure measurements were systematically collected." Further, the SAB stated that: "Appendix H [of the draft IRIS assessment] provides a comprehensive response on the issue of estimation of exposures prior to 1975 (in the absence of any sampling data prior to 1975). It addresses the implication of the original exposure prediction model assumption (Hornung et al., 1994) that calendar time effects (year) which were significant after 1978 but were absent prior to 1978 - allowing the predictions to pre-1978 exposures to be a function of the 1978 time effect (Figure 1 in Hornung et al., 1994) and additive effects of other predictors in the model of log exposure (exposure category, product type, product age, engineering controls, air volume of work area, etc.)." Additionally, EPA followed SAB's recommendations to expand discussion of exposure uncertainty in the final IRIS assessment.

b) **ACC faults the NIOSH exposure model for not including a time variable to account for potential changes in exposures in the years prior to 1978, noting that such a variable was used for the later years.**

Response: The NIOSH exposure data were generated in a period during which workplace exposures were being reduced due to health risk concerns about EtO. The measurement data allowed description of changes in air concentrations *during this period.* Thus, the NIOSH model incorporates a time variable to address changes in exposures levels during this period after the late 1970s. It would be technically incorrect to extrapolate this pattern of reduction of EtO workplace concentrations back to earlier times before concerns about health risks of EtO were prominent. The IRIS assessment is transparent about this methodology (e.g., see page 4-65) and use of the NIOSH study was extensively discussed and supported by the SAB. The preceding quotation from the SAB also addresses the use of the time variable in the model.

c) The RFC restates ACC's viewpoint that historical EtO exposures were likely underestimated by the NIOSH exposure model.

Response: In public comment during the SAB review, ACC identified certain plants where the NIOSH model had predicted higher concentrations in the late 1970s than in earlier years and ACC suggested this behavior indicated the NIOSH model was flawed. The final IRIS assessment reviewed this issue and noted that in the NIOSH model, sterilizer volume had a highly significant positive association with EtO concentrations. In the plants identified in ACC comments, sterilizer volume increased at certain times, and changes in predicted concentrations largely correlated with changes in sterilizer volume. This provided a reasonable understanding of the predicted time patterns of EtO concentrations in these plants. In the RFC, ACC objects to this EPA analysis as not proving that changes in sterilizer volume caused changes in EtO concentrations. ORD notes that this comment appears to not understand the nature of the statistical modeling being applied. The purpose of this modeling was to utilize statistical relationships in the observed data to predict levels that occurred in unobserved situations. The NIOSH regression modeling observed highly significant ($p < 0.001$) positive relationships between sterilizer volume variables and EtO concentrations. These observed relationships were appropriately incorporated when the statistical model was used for prediction. The strong relationship between sterilizer volume and concentration (along with other model variables) was reasonably utilized in the NIOSH predictive model. EPA responded to SAB's recommendations that EPA further evaluate patterns of EtO exposure in the NIOSH cohort with expanded analysis specifically including the examination of the effect of changes in sterilization volume size.

In the RFC, ACC also states that historical information and recent experiments conducted with one sterilizer indicate that EtO exposures would have been higher in earlier time periods before the availability of measurement data. However, ACC provides little specific information to support these statements. These contentions substantially rely on unpublished information and do not allow for critical review by ORD. ACC has not demonstrated the assumptions of the NIOSH exposure assessment to be in error.

2. ACC contends the occupational cancer data should not be modeled with the two-piece linear spline model used in the IRIS assessment and that instead a log-linear model, which is much flatter, should be used.

Response: EPA's decision to utilize the two-piece spline model relied heavily on SAB advice. The IRIS assessment's approach to model selection and consideration of potential alternative models were extensively described in the assessment and in the response to public comment contained in the assessment. ACC arguments in the RFC largely restate earlier comments provided during the assessment process; however, EPA and the SAB disagreed with the ACC comments. The RFC does not contain new information to indicate error in EPA's modeling of EtO risks.

a) ACC states EPA's choice of spline model is inappropriate as they believe it presupposes a steep "supralinear" response at low exposures.

Response: EPA gave particular attention to SAB (2015) recommendations in guiding model selection used in the finalized EtO assessment:

> "Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low-exposure range (e.g., spline models; these are preferred over more global functions, such as untransformed or log-transformed cumulative exposure, that give more weight to the high exposures in the estimated dose response)" (SAB, 2015, page 9)

The SAB also specifically noted the shape of the EtO dose response pattern:

> "From the comparisons, it is clear that these [NIOSH study] data suggest a general pattern of the risk rising very rapidly for low-dose exposures and then continuing to rise much more slowly for higher exposures. It is reassuring to observe that many of the fitted models reflect this pattern even though they have different sensitivity to local data." [Comments concerning breast cancer (SAB 2015, page 12)]

and

> "The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures." [Comments concerning lymphoid cancer (SAB 2015, page 14)]

ACC's repeated use of the term "supralinear" in referring to the two-piece spline model is misleading. The spline model applied in the IRIS assessment is linear at lower exposures and transitions to a second linear, but shallower, relationship at higher exposures. Under EPA's cancer guidelines, such a relationship – one that is linear in the low exposure range - is inferred as appropriate for DNA reactive mutagenic carcinogens such as EtO.

The IRIS assessment presents a consideration and rejection of the log linear model (also termed "standard Cox model") that ACC has used because that model does not fit with the observed results of the NIOSH study. Specifically, as fit to the EtO data, the cumulative dose Cox model fit indicates a shallow linear increase over most of the dose range while at high doses the model curves upwards. This log-linear model is mathematically incompatible with the pattern of the

NIOSH study results (as SAB advice discussed above) indicating that the dose-response for EtO increases more steeply at lower exposure concentrations.

b) ACC objects to a statistical approach used in the spline model fitting. Specifically, in the IRIS assessment the location of the breakpoints ("knots") in the spline models were selected in preliminary calculations and then model parameter estimates and statistics were calculated using the selected knot values.

Response: ORD notes that it followed SAB (2015) advice regarding the two-step process for fitting the spline models. SAB noted that:

> "…the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." (SAB, 2015, page 12)

Additionally, the two-step approach to knot selection and model fitting was clearly presented in the draft IRIS assessment materials reviewed by the SAB. ORD continues to view the approach in the IRIS assessment as reasonable. EPA's (and the SAB's) key conclusion was that the spline model was capable of representing the local shape of the dose-response for EtO, particularly in the low exposure region, while the log-linear model, preferred by ACC, was not capable of representing the shape of the results. This conclusion is not dependent on the particular approach used for knot selection in the modeling.

c) ACC objects to EPA's use of comparisons of fit between the dose-response models of the worker data and "categorical" estimates of cancer risk averaged over defined sub-intervals of the occupational exposure range.

Response: This issue was addressed during SAB (2015) peer review, where the SAB noted consistency of model fits and categorical results in supporting inference about dose response for EtO: "The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures." (SAB, 2015, page 14) EPA has also addressed this comment in the context of responding to ACC comment during the Miscellaneous Organic Chemical Manufacturing (MON) rulemaking:

"… the commenter broadly contends that it is not appropriate to compare the categorical estimates of relative risk for EtO with relative risk predictions from continuous models. In this regard the EPA notes that: (1) Plotting of fits of models in comparison with categorical breakouts of the data is a very useful and commonly used tool in epidemiology as it allows examination of the behavior of the parametric continuous models versus unstructured information on disease within ranges of the independent variable (exposure); (2) The categorical response predictions and continuous model fits were appropriately developed from the same individual level data on cancer; (3) The categorical and continuous results compared utilize the same referent group –

individuals who have no estimated exposure after taking into account the lag period of the modeling; (4) Both categorical and continuous model results are utilizing proportional hazard methodology to estimate the relative risk of worker exposures compared to the same reference group and this relative risk is a well-defined quantity. Thus, the categorical results and predictions of a valid continuous model need to be in general agreement." (Response to Comments, Section 4.3.3 Dose-response model selection. https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0200)

3. **ACC argues that the EtO risk assessment needs to incorporate information on endogenous biological sources of EtO and that a proposed analysis indicates that environmental EtO exposures are small by comparison.**

Response: The IRIS assessment contains a substantial discussion of what is known about endogenous exposures to EtO (Section 3.3.3.1 and with implications discussed in Section 4.5). The potential for endogenous exposures to EtO and the IRIS Assessment's handling of such exposures was discussed in public comment and SAB peer review of the assessment.

It is important to recognize that the IRIS risk estimate for EtO represents the increased cancer risk due to exposure to EtO emissions – above any potential existing risks from endogenous or ambient background levels of EtO exposure. The occupational exposures in the NIOSH study represent workplace EtO levels these workers experienced – and are in addition to any endogenous or broad population background exposures to which the workers may also have been exposed. Similarly, the relative risk estimates for workers are made in comparison to risks to individuals in the absence of occupational exposure – but these reference individuals would also have exposure to population background and endogenous EtO. Thus, methodologically, the levels of endogenous exposures (and baseline population level risks that may result from these exposures) have been accounted for in the EtO IRIS dose-response assessment.

SAB (2015 page 24) stated: "Based on the discussion presented in the assessment and considering the weight of the evidence from human and animal studies, the SAB finds EPA's conclusion on endogenous exposure to EtO to be supported. Nonetheless … it appears that recognizing this source of metabolic EtO and briefly expanding on its relevance to the assessment would complete the description of sources of endogenous EtO and their relative importance for adduct formation."

In response to this SAB comment, the relevance of endogenous EtO exposure to the assessment received expanded discussion in IRIS Section 4.5 in the context of low-dose extrapolation which was linked to the discussion of endogenous EtO exposure in IRIS Section 3.3.3.1.

In the RFC, ACC also submitted additional analysis and modeling of previously published studies of EtO associated hemoglobin adduct levels (based on Kirman and Hayes, Regul Toxicol Pharmacol. 2017, 91:165-172). This report, published after the SAB peer review and finalization of the IRIS EtO assessment, uses a previously published relationship from occupational hygiene studies to infer what it terms "equivalent" inhaled air concentrations that would theoretically be

associated with endogenous adduct levels. While the math involved is simple, this calculation amounts to a major and unvalidated change in the interpretation of the industrial hygiene relationship which specifically correlated *increases in adduct levels above background* with substantial occupational exposures to EtO. ACC does not reference any direct measurements of endogenous EtO levels nor analysis to validate the application of this calculation to endogenous adduct levels. As discussed in the IRIS assessment, several biological processes that can produce some amount of endogenous EtO have been identified, however little quantitative information on these sources appears to be available. For these reasons, EPA does not regard ACC's comparisons of airborne EtO concentrations with their proposed calculated "endogenous equivalents" as factually substantiated.

ORD also notes that ACC's argument implicitly suggests that endogenous levels of EtO do not themselves contribute to background rates of cancer. Such an assumption may not be correct, as no quantitative analysis has been presented to define how much of the background risk of lymphoid tumors or breast tumors (or other tumors) might be related to endogenous or background exposures to EtO.

Conclusion

ORD concludes that the content of the ACC RFC does not demonstrate any errors in the EtO IRIS assessment as regards available scientific information about potential levels of endogenous and background EtO.