Charge Questions

TCEQ Ethylene Oxide Development Support Document (DSD)

1. The TCEQ conducted a systematic review of the literature relevant to the derivation of an inhalation unit risk factor for ethylene oxide (EtO) (see DSD Appendix 1). Are you aware of any additional literature or studies that should be considered and if so, how might they impact the assessment?

2. The TCEQ adopts the EPA conclusion that the weight of the evidence supports a direct-acting mutagenic mode of action (MOA) for EtO carcinogenicity (DSD Sections 3.3 and 3.3.1). Section 3.3.1 of the DSD presents summary information from the EPA (EPA Section 3.4.3) relevant to the MOA determination. Do you agree with the MOA determination? Please explain.

3. The TCEQ adopts EPA's MOA analysis (DSD Section 3.3.1) and considers MOA as information relevant to the likely or expected shape of the dose-response (DSD Sections 3.4.1 and 3.4.1.1) as specified by the TCEQ guidelines for developing toxicity factors (TCEQ, 2015). What is your opinion on whether and how the MOA should inform the likely or expected shape of the dose-response curve, overall and in the low-dose range (e.g., at environmentally-relevant concentrations); and whether and how the MOA should inform the choice of dose-response model for estimating human carcinogenicity risk? Please comment on TCEQ's reasoning on the implications of the MOA for the shape of the dose-response and its relative importance amongst their other model choice considerations (summarized in DSD Section 3.4.1.4.2). Are the TCEQ conclusions concerning implications of the MOA scientifically defensible?

4. The TCEQ conducted an evaluation of EtO's carcinogenic classification (DSD Section 3.3.2), and also evaluated breast cancer risk in humans as a potential cancer endpoint (DSD Appendix 6; Response to Dr. Kyle Steenland, Comment 1 in Response to Public Comments Document). What is your characterization of the overall weight of the evidence for or against EtO increasing the risk of breast cancer in humans at occupational concentrations (past or present) and at environmentally-relevant concentrations?

5. While it is in the interest of public health to protect against cancer *incidence*, available epidemiological studies often only provide cancer *mortality* data for dose-response modeling. What is your opinion on the accuracy of using a dose-response model based on cancer <u>mortality</u> data (e.g., lymphoid cancer mortality) to predict cancer <u>incidence</u> (e.g., lymphoid cancer incidence)?

6. The TCEQ's DSD discusses a problem with key USEPA AIC and p-value calculations used as criteria in determining model fit, and the TCEQ recalculated these values (DSD Section 3.4.1.3 and Appendix 4). Please explain what you think the appropriate approach should be for accounting for the number of estimated parameters in the modeling and the associated calculation of the AIC and p-values. Given that appropriate AIC and p-values are available for models fit to *individual* data, what role should visual fit to *categorical* estimates play in model selection (Response to University of California at San Francisco, Comment 6 in Response to Public Comments Document)?

7. Please comment on the biological and mechanistic support for and against use of an overall supralinear model to estimate risk of lymphoid cancer from exposure to EtO at occupational levels and at environmentally-relevant concentrations.

8. As summarized in DSD Section 3.4.1.4.2, the TCEQ used MOA, model predictiveness reality checks (both for the NIOSH cohort and the general population), biological plausibility, and statistical model fit criteria for model selection. Have these considerations been clearly described and are they scientifically appropriate given the available data?

9. In DSD Sections 3.4.1.4, 3.4.1.5, and 3.4.1.6, the TCEQ describes their modeling choices and assumptions, and calculates an inhalation unit risk factor (URF), ultimately applying age-dependent adjustment factors (ADAFS) in DSD Section 3.4.2. Do you disagree with any of the modeling choices and assumptions or calculations made by TCEQ in the dose-response assessment? Please discuss any issues or concerns you have with the inhalation URF derivation.

10. Based on biomarker data, various sections of the DSD (e.g., Section 3.4.1.2.1, Section 3.4.1.4.2 number "4.", second to the last paragraph of Section 3.4.1.6.2) discuss air concentrations corresponding to endogenous and background EtO levels and also compare these levels to acceptable air concentrations derived from URFs (either the TCEQ's or EPA's). Such a discussion is also included in the Response to Public Comments document (e.g. Response to Dr. Kyle Steenland, Comment 3). Please comment on whether the information and context provided by the discussion of endogenous/background EtO levels is clear and is scientifically appropriate.

11. Please provide comments on the overall accuracy, objectivity, and transparency of the presentation of information in the revised DSD. Are the assumptions, data, and analyses described completely and clearly? Please identify any sections that need revision or improvement and describe in detail, to the extent possible, how they should be revised.

12. The TCEQ solicited public comments on a June 2019 proposed DSD and has prepared a response to those comments (See Response to Public Comments Received on the Ethylene Oxide Draft Development Support Document, January 2020). Has the TCEQ appropriately addressed the critical scientific questions and issues raised by the public commenters in the Response to

Comments and/or revised DSD? Are the responses to public comments presented clearly and completely? Please explain.

13. Please discuss any additional relevant comments or issues. Are there any additional questions or concerns that you would like fellow peer reviewers to address?