Executive Summary

- Ethylene oxide (EtO) is a chemical with many industrial applications and is particularly useful as a sterilant for medical devices.
- Because EtO is emitted in Texas and has been determined to be a carcinogen, the TCEQ undertook a carcinogenic dose-response assessment and derivation of a unit risk factor (URF) and an effect screening level (ESL) for this chemical.
- Review of the EtO literature demonstrated that EtO operates by a direct-acting mutagenic mode of action (MOA) and suggests that the EtO cancer dose-response should be no more than linear overall with sublinearity expected by both the TCEQ and USEPA (2016) at endogenous levels and below.
- In addition, EtO is produced endogenously, and an ambient air concentration of ≈1.3 ppb would be required to increase the internal dose of EtO by 1 standard deviation. Therefore, ambient EtO concentrations significantly less than 1 ppb (e.g., USEPA's acceptable air concentrations of 0.0001-0.01 ppb) would not be expected to produce biologically meaningful internal doses considering the range of normal endogenously-produced background EtO levels.
- Consistent with TCEQ guidelines (TCEQ 2015), recently derived toxicity factors and guideline air levels were reviewed to determine if there is a toxicity factor or guideline air level that is suitable for adoption by the TCEQ. As such, the USEPA's recently completed Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (USEPA 2016) was reviewed. The USEPA derived a URF of 7.1E-3 per ppb, which corresponds to a 1 in 100,000 excess cancer risk air concentration of 0.001 ppb.
- The human data available for deriving an EtO toxicity factor came from two very high exposure occupational cohorts (Union Carbide Corporation (UCC) and National Institute for Occupational Safety and Health (NIOSH)) that provide no information about the shape of the dose-response curve at low (i.e., environmentally-relevant) EtO concentrations. The TCEQ agrees with USEPA's determination that in the low-dose range a sublinear dose-response is "highly plausible," based on the MOA and information about endogenous production of EtO.
- In contrast to their determination that the low-dose region of the EtO dose-response curve is highly plausibly sublinear, USEPA ultimately chose to model EtO-induced lymphoid cancer with an overall supra-linear two-piece spline model that has a very steep linear slope in the low-dose region.
- The TCEQ evaluated USEPA's URF and overall supra-linear (i.e., linear two-piece spline) modeling choice in the context of the available observed data to determine the validity of the modeling and URF:
    - <u>Endogenous Levels of EtO</u> – USEPA's URF estimates that ambient concentrations of EtO > 0.01 ppb would produce an unacceptable increased cancer risk of greater than 1 in 10,000. This estimated ambient EtO concentration corresponds

to an internal dose that is over 30 times lower than the 1st percentile of normal endogenous background levels (non-smokers), which is highly unlikely to be biologically meaningful and is inconsistent with the assessment of excess risk.

- Population-Level Lymphoid Cancer Risk – Using measured concentrations of a biomarker of internal EtO exposure (an EtO-specific protein adduct in blood), it can be estimated that the mean amounts of endogenous EtO levels would be equivalent to ambient concentrations of EtO of 1.9 ppb in non-smokers and 18.8 ppb in smokers. Accordingly, at measured endogenous levels of EtO, the USEPA's URF would predict a population-wide lymphoid cancer incidence rate of 3.8% (in the absence of any exogenous EtO exposure or other potential causes of lymphoid cancer). By contrast, the USEPA-cited lymphoid cancer background incidence rate (which would have many contributing factors, not just a single chemical) is 3%, demonstrating that USEPA's URF overestimates observable lymphoid cancer risk based on endogenous levels of EtO alone.
- Lymphoid Cancer Risk from Cohort Studies – The UCC cohort shows no statistically significant increased risk of lymphoid cancer with EtO exposure. The NIOSH cohort shows statistically significant increased risk of lymphoid cancer mortality at relatively high cumulative exposures. These data are not consistent with USEPA's selected model assessment (i.e., upper bound on the linear two-piece spline model) because that model assessment would predict statistically increased risks at even the lowest EtO cumulative exposures (see below).
- Model Fit with Observed Data – USEPA conducted their EtO cancer dose-response modeling using the NIOSH cohort data. To verify that USEPA's final selected model assessment (i.e., upper bound on the linear two-piece spline model) properly fit the original data, it was used to predict the expected number of lymphoid cancer deaths based on the same NIOSH individual exposure data as USEPA used for modeling. *Whereas 53 lymphoid cancer deaths were observed* in this cohort of 17,530 workers, *USEPA's selected dose-response model assessment predicted 141* (95% confidence interval (CI) of 108, 188) lymphoid cancer deaths in this same cohort. Similarly, USEPA's final selected model assessment statistically significantly over-predicts lymphoid cancer deaths in every cumulative exposure quintile and indicates that statistically increased lymphoid cancer mortality should have occurred in every exposure quintile (including the lowest), when in fact this did not occur. This demonstrates unequivocally that USEPA's selected model assessment cannot be validated by the data that was used to derive it, and this model is not appropriate to use for estimates of population risk.

- The TCEQ determined that USEPA's use of an overall supra-linear dose-response model (i.e., the upper bound of the linear two-piece spline model) to derive their URF: 1) is not justified by the MOA data (which support a no-more-than linear dose-response); 2) is not consistent with predicted population risk from endogenous EtO for lymphoid cancer; and 3) statistically significantly over-estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. **Therefore, the**

TCEQ found that USEPA's EtO inhalation URF is not adequately supported by scientific data and the TCEQ did not adopt it for this evaluation.

- The TCEQ conducted a systematic review for studies that could inform the derivation of a cancer URF for inhalation exposures to EtO. This review identified key epidemiological data from two cohorts of occupationally-exposed workers, and Cox proportional hazards modeling was conducted to model the EtO-cancer dose-response.
- The TCEQ ultimately chose lymphoid cancer mortality as the critical cancer endpoint, using a 15-year EtO exposure lag with results for NIOSH males being more conservative, to calculate a **URF of 2.5E-6 per ppb (1.4E-6 per ug/m^3)** and a ^{chronic}**ESL**$_{nonthreshold(c)}$ **of 4 ppb (7 ug/m^3)** at an excess cancer risk level of 1 in 100,000.
- As with USEPA's URF, the TCEQ's URF was evaluated in the context of the available observed data to determine the validity of the modeling and URF:
    - Endogenous Levels of EtO – Compared to endogenous EtO levels, the TCEQ's ESL of 4 ppb would produce an internal exposure equivalent to between the 90th-95th percentile of the normal endogenous range and could biologically plausibly be associated with excess risk above and distinguishable from normal endogenous EtO contributions to background risk.
    - Population-Level Lymphoid Cancer Risk - At measured endogenous levels of EtO, the TCEQ's URF would predict a population-wide lymphoid cancer rate that is appreciably lower than the cited background population cancer rate of 3%.
    - Lymphoid Cancer Risk from Cohort Studies – The standard Cox proportional hazards model of lymphoid cancer mortality did not show a relationship with EtO exposure that was statistically significantly different from zero. Therefore, by assuming a significant positive slope in the EtO-cancer association, the TCEQ is making a conservative decision to assume that EtO is causing lymphoid cancer in the exposed workers in the NIOSH cohort. Adding to this conservatism is the TCEQ's decision to use an upper confidence limit on the slope.
    - Model Fit with Observed Data – To verify that the TCEQ's model properly fit the original data, the expected number of lymphoid cancer deaths based on the individual exposure estimates for the NIOSH cohort (also used by USEPA) were calculated. Whereas *53 lymphoid cancer deaths were observed* in this cohort of 17,530 workers, *the TCEQ's selected dose-response assessment (i.e., upper bound of the Cox proportional hazard model) predicted 59* (95% CI of 45, 78) lymphoid cancer deaths. Similarly, TCEQ's selected assessment neither significantly over- or under-estimated lymphoid cancer deaths for any exposure quintile. This demonstrates that the TCEQ's model selection provides a superior fit to the observed number of lymphoid cancer deaths in the NIOSH cohort.
- The TCEQ determined that the use of Cox proportional hazards models to derive a URF for inhalation EtO cancer risk: 1) is justified by the MOA data showing EtO to be a direct-acting carcinogen whose effects, particularly at doses near the endogenous range, would be buffered by cellular repair mechanisms; 2) is consistent with population background risk considering background endogenous EtO levels (i.e., does not

overestimate population risk for lymphoid cancer mortality); and 3) accurately estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. **Therefore, the TCEQ's EtO URF has a sound scientific basis and will be adopted for review of air concentration data and for use in air permit reviews.**