Peer Review of
1,3-Butadiene Development Support Document
Charge Questions

The Toxicology Section (TS) of the Chief Engineer's Office, Texas Commission on Environmental Quality (TCEQ) has prepared a Development Support Document that outlines the hazard assessment and dose-response processes used to derive Effects Screening Levels (ESLs), Reference Values (ReV), and Unit Risk Factor (URFs) for 1,3-Butadiene (Cas. No. 106-99-0). The toxicity values were developed using RG-442 *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (TCEQ 2006). ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. ESLs are used in the evaluation of air permit applications as well as proposed rules and regulation (e.g. Permits by Rule). ReVs and URFs, used as the basis of ESLs, are used in the evaluation of air monitoring data and in the development of Protective Concentration Levels for remediation sites.

The TCEQ document relies on the US EPA *Health Assessment of 1,3-Butadiene* (EPA/600/P-98/001F), released in October 2002, to provide detailed information on the following topics for 1,3-butadiene: overview of exposure, pharmacokinetics, mutagenicity, reproductive and developmental effects, toxicity in animals, epidemiologic studies of carcinogenicity, hazard characterization, and pharmacokinetic modeling. However, TCEQ has incorporated new data and statistical analyses not available to US EPA in 2002, and therefore, has derived new dose-response assessments for 1,3-butadiene.

General Issues

Please consider all aspects of the butadiene DSD and evaluate strengths and weaknesses of the procedures used to develop acute and chronic toxicity factors based on the specific questions described below. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Please try to avoid emphasizing minor technical details or making tutorial comments. Reviewers should identify scientific uncertainties and suggest ways to reduce or eliminate those uncertainties.

- Were procedures outlined in the ESL Guidelines followed by the TCEQ to perform butadiene's toxicity assessment? If references to accepted procedures in federal, state, or other appropriate guidance documents were made in the ESL Guidelines, were those accepted procedures followed?

- Does the butadiene DSD clearly describe the approaches used by TCEQ to perform the toxicity assessment (i.e., hazard identification and dose-response assessment).

Health-Based Acute ReV and ^{acute}ESL

The 1,3-Butadiene DSD describes the approaches used to derive the health-based acute ReV and acute ESL in Section 3.1 (page 8). Appendix 1 (page 66) describes the statistical analysis of data from the critical study. Appendix 2 (page 101) describes the benchmark concentration modeling conducted for estimating the point of departure. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision.

The key decisions and some specific issues to consider are listed below. Please indicate if there are other issues specific to developing acute toxicity factors that have not been adequately addressed in the document.

- The choice of Hackett et al. (1987b) as the critical study
- The statistical re-analyses of the data from the Hackett (1987b) conducted by Green (2003) and Sielken et al. (Appendix 1 *Statistical Analyses of Developmental Endpoints*).
    - Are these re-analyses a more appropriate basis for risk assessment than the statistical analyses conducted by Hackett et al. (1987b)?
    - Should the analyses of Hackett et al. data in Appendix 1 adjust for litter size and percent of males in litter?
    - Should the analyses of Hackett et al. data in Appendix 1 use mean data or individual data to determine the NOAEL?
- The choice of maternal extra-gestational weight gain, which occurs at a NOAEL of 40 ppm, as the critical effect.
    - Is this endpoint relevant for human risk assessment? If not, what would be a more appropriate critical effect.
- The choice of point of departure based on a 5% reduction in extragestational weight gain and reduction in maternal weight gain (GD 11-16) (i.e., $BMCL_{05}$) (see Appendix 2 *BMC Modeling for Acute ReV*).
    - Was the output from the most appropriate model selected? Should these models be monotone?
    - Should the POD be based on the maximum likelihood estimate or the 95% lower confidence limit of the reduction of weight gain?
    - Was the appropriate benchmark response selected (5% vs 10% reduction of weight gain)
    - Should the POD be considered to be a NOAEL or a LOAEL? Explain your reasoning.
- The choice of dosimetric adjusments
- The choice of uncertainty factors.
    - Have all of the appropriate uncertainty factors been considered and are the values assigned to the uncertainty factors clearly justified and defensible?
    - Would you make recommendations for a different approach to select uncertainty factors to calculate the acute ReV?

Welfare-Based Acute ESL

The welfare-based acute ESLs are described in Section 3.2 (page 22) of the 1,3-butadiene DSD. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision. The key decisions and some specific issues to consider are listed below. Please indicate if there are other issues specific to developing welfare-based ESLs that have not been adequately addressed in the document.

- The choice of the Nagata (2003) study as the basis of the acute ESL for odor.
- The decision to not derive an acute ESL for vegetative effects.

Health-Based Chronic ReV and $^{chronic}ESL_{noncancer}$

The 1,3-Butadiene DSD describes the approaches used to derive the health-based chronic ReV and chronic ESL for noncancer in Section 4.1 (page 24). Appendix 3 (page 125) describes the benchmark concentration modeling conducted to estimate the point of departure. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision.

The key decisions and some specific issues to consider are listed below. Please indicate if there are other issues specific to developing chronic toxicity factors that have not been adequately addressed in the document.

- The choice of NTP (1993) as the critical study.
- The choice of ovarian atrophy as the critical effect.
    - Is the selected endpoint relevant for humans?
- The choice of point of departure based on a 5% increase incidence of ovarian atrophy in female mice (i.e., $BMCL_{05}$) (Appendix 3 *Statistical Analyses of Reproductive Endpoints*)?
    - Were the ovarian atrophy data in mice correctly modeled?
    - Should the highest dose group be included or excluded in the time-to-tumor model?
    - Should the POD be based on the maximum likelihood estimate or the 95% lower confidence limit of the benchmark exposure concentration for an extra risk of 0.05?
    - Should the POD be based on the benchmark exposure concentration for an extra risk of 0.05 or some other extra risk level, e.g., 0.10?
    - Is the POD considered to be a NOAEL or a LOAEL?
- The choice of dosimetric adjustments
- The choice of uncertainty factors.
    - Have all of the appropriate uncertainty factors been considered. Are the values assigned to the uncertainty factors clearly justified and defensible?
    - Was the Swenberg et al. (2007) data on differences between occupationally-

exposed workers and mice and rats if the formation of hemoglobin adduct used properly to characterize the animal to human toxicodynamic uncertainty factor?
    - Would you make recommendations for a different approach to select uncertainty factors to calculate the chronic ReV?

Cancer Weight of Evidence and Unit Risk Factor (URF)

The 1,3-Butadiene DSD describes the approaches used to evaluate carcinogenicity and derive the URF and chronic ESL for cancer in Section 4.1 (page 24). Cheng et al. (2007), Sielken et al. (2007) and Appendix 4 (page 133) describes the statistical approaches used to calculate the cancer potency estimate. Appendix 5 (page 136) describes the leukemia mortality and survival rates. Appendix 6 (page 138) describes the approaches used to estimate age-specific adjustment factors. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision.

The key decisions and some specific issues to consider are listed below. Please discuss other issues specific to developing unit risk factors for carcinogenic effects that have not been adequately addressed in the document.

- The weight of evidence statement
    - Is the epidemiological evidence in Albertini et al. (2007) properly used in the characterization of chronic cancer risks?
- The statistical and modeling approaches used for selecting different butadiene cancer potency estimates: Cheng et al. (2007): Sielken et al. (2007); and Sielken et al. (Appendix 4 *Additional Cox Proportional Hazards Models*).
    - Was the dose metric selected, cumulative ppm-years, the most relevant and appropriate choice?
    - Are there reasons to prefer Cox regression modeling over Poisson regression modeling or vice versa?
    - Comment on the relevance of using penalized spline regression and restricting the data to the lower 95% of the exposure range of all subjects.
    - Are exposures in the distant past and the immediate past equally biologically relevant? Are lags or windows of exposure biologically relevant?
    - Was endpoint selected as the basis of the potency estimates, "all leukemia", the most appropriate and relevant choice?
    - Should excess risk be calculated using leukemia incidence rates or leukemia mortality rates? Comment on Appendix 7 (page 145) *Calculating Excess Risk when Specified Response is Mortality versus Incidence*.
    - Does using the 95% UCL estimate instead of the central estimate somewhat account for the uncertainty that leukemia incidence rates are higher than leukemia mortality rates?
    - Would best estimates (maximum likelihood estimates) of excess risks be more appropriate than estimates based on 95% upper confidence limits given that the estimates are based on human epidemiological data?

    - Did the approach used adequately address the potential impacts of exposure misclassification? Would use of exposure deciles have been more appropriate than using continuous exposure?
    - Were the appropriate covariates used in estimating cancer potency? Have the results using alternative covariates been properly weighted?
    - Have the results considering the number of high intensity tasks (number of HITS) been properly weighted?
    - Would the consistency of the Cox regression results using continuous untransformed exposure data be reason to emphasize these results?
- The choice of response rate, 0.1% (in EC_{001} and LEC_{001}) for linear extrapolation to lower exposures.
- The application of ADAFs to the slope factors using life table analysis and the BIER IV methodology (NRC 1988) to address susceptibility from early-life exposure to butadiene (Appendix 6 *Calculating Excess Risk with Age-Dependent Adjustment Factors).*