Texas Commission on Environmental Quality
Responses to Comments Received on the

1,3-Butadiene Development Support Document
Original Dated August 2007 and
Revised Dated June 2008

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INTRODUCTION

Toxicology Excellence for Risk Assessment (TERA) supported the Texas Commission on Environmental Quality (TCEQ) by conducting an expert external peer review as a letter peer review of the *Development Support Document for 1,3-Butadiene, Proposed August 2007*. The review materials, including draft document, charge to reviewers, August 2007 public comments, and key references (available at http://www.tera.org/peer/TCEQ_1,3butadiene.html) were distributed to the panel in September 2007. Reviewers submitted written comments that addressed the charge questions in October 2007. These written comments represent the panel's review of the 1,3-butadiene (BD Development Support Document (DSD) and are available in the final peer review report. On October 30, 2007, *TERA* facilitated a follow-up conference call between the panel and TCEQ. Conference call materials (available at http://www.tera.org/peer/TCEQ_1,3butadiene.html), including a focused charge, a summary of the benchmark dose modeling, and additional reviewer comments were distributed prior to the call; members of the public were allowed to listen to the call. The purpose of this call was to allow TCEQ to ask the panel questions regarding their written comments and to allow the panel members to discuss issues on which there were divergent opinions in the written comments. Therefore, the final peer review report of the follow-up conference call, along with the written comments submitted by the panel, comprise the complete peer review of the BD DSD (December 21, 2007 *Peer Review of 1,3-Butadiene Development Support Document and Report of Follow up Conference Call*, available at http://www.tera.org/peer/TCEQ_1,3butadiene.html).

There were two public comment periods:

- There was a public comment period that ended August 29, 2007. The Texas Chemical Council (TCC) (Appendix A) and ISP Elastomers (Appendix B) submitted comments. These public comments were made available to the reviewers.
- Another public comment period ended March 10, 2008. The TCC (Appendix C), ISP Elastomers (Appendix D), and International Institute of Synthetic Rubber Producers, Inc. (IISRP) (Appendix E) submitted comments.

The August 2007 version of the DSD was revised based on panel member comments and public comments. Chapter 3 of the revised June 2008 version of the DSD describing the development of the health-based acute ReV and ^{acute}ESL was reviewed by Mr. Bruce Allen, Dr. George Daston, and Dr. Lynne Haber (TCEQ Contract # 582-7-80167-03). See Appendix F for the full comments of the reviewers. The Office of the Mayor, City of Houston, Texas, reviewed the revised June 2008 version of the DSD and submitted comments (Appendix G).

The Toxicology Section (TS) of the TCEQ appreciates the effort put forth by the panel members, TCC, ISP Elastomers, IISRP, and the City of Houston to provide technical comments on the proposed DSD for BD. The goal of the Toxicology Section and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. The panel member's comments, including the June-July 2008 comments of Mr. Allen, Dr. Daston, and Dr. Haber, are addressed first, followed by responses to TCC comments and City of Houston comments. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment. There were no specific issues that needed to be addressed in the comments from ISP Elastomers (Appendices B and D) or IISRP (Appendix E).

Panel Teleconference Comments

There were differing opinions expressed by the reviewers during the teleconference. For some issues, a consensus statement from a majority of the reviewers was provided, but for other issues there were

differing opinions and only a concluding statement was provided. When responding to the reviewers' comments, the TS has attempted to address the issues where consensus was reached or, if a consensus was not reached, the TS has attempted to address the statements in the concluding statement and other major issues. A comment statement, which is a summary of the panel, TCC or City of Houston comments, is presented followed by the TS response. Refer to the December 21, 2007 *Peer Review of 1,3-Butadiene Development Support Document and Report of Follow up Conference Call* or the Appendices for complete comments.

Panel Written Comments

The TS did not prepare responses to issues in the written comments that were previously addressed in the teleconference comments. Rather, only comments or major issues that were not discussed or resolved in the teleconference are addressed in these sections.

TCEQ-Initiated Changes to the DSD

The following changes were not suggested by the panel or in public comments, but changes to the DSD were made by the TS for the following reasons:

- In Section 4.2.3.2 *Dosimetric Adjustments*, occupational concentrations were converted to environmental concentrations for the general population using the ratio of 240 days/365 days in the proposed DSD. In the final DSD, the ratio of 5 days per week/7 days was used in order to be consistent with the ESL Guidelines (TCEQ 2006) and to be consistent with other final chemical-specific DSDs.
- Information on a recently released epidemiological study by Khalil *et al.* (2007) was included in the acute section, although the study was not used to develop an acute toxicity factor.
- A proposed mode of action for the reproductive/developmental effects of BD has been added to the DSD (Section 3.1.2.2 *MOA for Reproductive/Developmental Effects*) based on research conducted by Spencer *et al.* (2001) and Chi *et al.* (2002).

1. Cancer Weight of Evidence and URF

1.1 Panel Teleconference Comments

Issue #1, Page 4: 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?

1. **Comment:** The panel concluded that categorical approach decreases the impact of misclassification at the high end, but increases misclassification at the low end, where exposure estimates are likely to be better. The preferred model for risk assessment should use an exposure variable which is continuous and covariates which are categorical. However, in this case, either approach is adequate and both give similar values. (page 4)
   Response: After reviewing all the panel comments, the TS has decided that the preferred model for risk assessment should use an exposure variable that is continuous. The Cox regression analysis using continuous, untransformed data are preferred over models using mean-scored deciles (categorical data) because it uses the best estimate of cumulative BD ppm-years, uses individual data, and adjusts for the effects of age in an optimal way (in the Cox regression, age is the index variable and implicitly a covariate). The log-linear Cox regression analysis, with continuous data and mean-scored deciles and the linear Poisson regression analysis using mean scored deciles conducted by Seilken et al (2007) are included in the DSD for comparison purposes, but they are not the preferred model. All approaches provided values that were within a factor of five.

Issue #2, Pages 4-6: 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?

2. **Comment:** Peak exposures greater than 100 ppm are highly correlated with cumulative dose. Therefore, putting both variables in the same model results in a decreased estimate of the impact of each measure. (page 4, last paragraph)
   Response: The TS recognizes that there is concern about using two exposure variables that may be highly correlated in the same model. Cheng *et al.* (2007) conducted an analysis of the correlation between BD exposure variable (page 18):

   > "The three BD exposure variables were correlated, but in general correlations were weaker for continuous than for categorical variables. For example, the Pearson correlation coefficients for continuous BD variable were 0.30 for BD ppm-years and BD peaks . . . In contrast, correlation coefficients for categorical (deciles) BD variables were 0.80 for BD ppm-year and BD peaks . . ."

   Categorical BD exposure variables are highly correlated (i.e., 0.80). However, there is not a strong correlation between BD ppm-years and BD peaks if they are evaluated as continuous variables (i.e., 0.30). Therefore, the TS will evaluate # of HITs > 100 ppm (continuous) as a covariate with BD ppm-years as continuous, untransformed data. This analysis is included in section 4.2.5.2 *Estimating Risks for the General Population from Occupational Workers* but the preferred model does not include # of HITs > 100 ppm (continuous) as a covariate (response to Comment #1).

3. **Comment:** This reviewer expressed little confidence that the number of peaks was estimated accurately (page 4, last sentence). A panel member . . . raised questions regarding the accuracy of measuring the HITs. (page 6)
   Response: The DSD was not revised based on this comment. TCEQ staff participated in a teleconference on January 11, 2007 with Dr. Cheng and Dr. Delzell, and specifically asked if it was difficult to accurately measure the number of HITS > 100 ppm. They responded that they were more comfortable estimating the number of tasks that took place in high exposure than in estimating the area under the curve for cumulative ppm-years. Therefore, the TS considered the estimates of # HITs as reliable.

4. **Comment:** In addition, because HITS is not a confounder in the study, it is not appropriate to use in the dose response modeling. (page 5, third paragraph from the bottom of page)
   Response: The DSD was not revised based on this comment. The presence or absence of HITs "confounds" the impact of BD ppm-years (January 11, 2008 teleconference with Dr. Cheng and Dr. Delzell). Therefore, # of HITs was used and evaluated in the uncertainty section (Section 4.2.5.2 *Estimating Risks for the General Population from Occupational Workers).*

5. **Comment:** Another reviewer noted that arguments could be made for using both measures in modeling because there were clearly effects observed at high intensity exposure that are not seen at lower exposures. However, having both variables in the model would attenuate the effects of cumulative exposure. (page 5, last sentence to page 6, first sentence)
   Response: This statement is not correct because it has been shown by Sielken & Associates that including cumulative number of HITs does not necessarily attenuate the effect of cumulative BD exposure and it actually intensifies the effect of cumulative BD ppm-year for some endpoints other than leukemia. Thus, it is an unbiased approach to incorporating how HITs affect the impact of BD ppm-years. Therefore, # HITs was used and evaluated in the uncertainty section (Section 4.2.5.2 *Estimating Risks for the General Population from Occupational Workers).*

6. **Comment:** Two panel members concurred that mechanistically, it is appropriate to include a metric that captures high exposures. One reviewer agreed that the approach provides a degree of public health comfort, but was not sure that the difference between the worker population and the general population could be quantified appropriately. (page 5) On the other hand, using both variables in the model improves the model fit, and is a reasonable approach for extrapolating from workers to the general population . . . . (page 6)
   Response: The majority of the reviewers commented on the advantages of including BD ppm-years and # of HITs > 100 ppm in the model to estimate risks to the general population based on mechanistic reasons (i.e., dose-dependent transitions in toxicological mechanisms as presented in Slikker *et al.* 2004). The TS agrees with the reviewers who stated that using both variables (BD ppm-years (continuous, untransformed) and number of HITS > 100 ppm (continuous)) is a reasonable approach for estimating risk to the general population. This analysis is included in the uncertainty section (Section 4.2.5.2 *Estimating Risks for the General Population from Occupational Workers)*.

7. **Comment:** In conclusion, no consensus was reached on this issue. A panel member noted that it is statistically incorrect to include both continuous exposure and peak exposures in the dose-response model . . . (page 6)
   Response: Another panel member indicated that just because the cumulative number of HITS and cumulative BD ppm-years are somewhat correlated is not a justification for excluding the number of HITs from the model. The panel member indicated that epidemiological models adjust for variables that are correlated to cumulative exposure all the time (e.g., age, years-since-hire, calendar-year, etc.) so it is not statistically incorrect. Therefore, # HITs was used and evaluated in the uncertainty section (Section 4.2.5.2 *Estimating Risks for the General Population from Occupational Workers)*.

Issue # 3, Pages 6-7: Should excess risk be calculated using leukemia incidence rates or leukemia mortality rates?

8. **Comment:** Another reviewer noted that the actual modeling can only be done using the leukemia mortality data since that is the only data available. The question to be addressed is whether the assessment should use background incidence or mortality rates for estimating the excess risk value. If modeling based on mortality data is used with background rates for incidence, it results in higher excess risk values (or lower exposures for a fixed excess risk), which is more conservative. Using mortality may underestimate the excess risk for leukemia incidence. (page 7)
   Response: The DSD was not revised based on this comment. It is not necessarily true that using mortality data underestimates the excess risk of leukemia incidence. While incidence occurs more frequently than mortality, the dose-response models are modeling the proportional increase in the response due to exposure. Thus, there is no guarantee that there is a greater proportional increase with exposure for incidence or mortality. If, for example, exposure does not change incidence but increases the rate of mortality among those with incidence, then mortality is the right endpoint and an excess risk calculation using incidence rates and the slope for the proportional increase in mortality would be a serious overestimate of risk. The TS did not use incidence rates to calculate excess risk using dose-response modeling based on leukemia mortality data, as discussed in detail in Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence*.

9. **Comment:** The panel unanimously concluded that TCEQ should evaluate/compare the results of both analyses (i.e., using mortality and using life table methods to extrapolate from incidence to mortality) before deciding which risk value to select. However, the panel noted that the choice should be made based on issues and uncertainties noted in the two analyses, not based on the final number. One panel member agreed that it is reasonable to follow both approaches, but expressed

a preference for incidence. Regardless of the approach taken, the uncertainties in both approaches should be discussed. (page 7) In written comments (page 47, lines 19-21), Reviewer #5 stated: The discussion implies that one could never do a lifetable (BEIR type) analysis given incidence rates or estimates of age- and dose-specific incidence risks.
Response: An assessment and comparison when mortality dose-response data in a BEIR-type analysis set up to evaluate mortality data (i.e., a mortality model) is used with total leukemia mortality rates or total incidence rates has been included in the uncertainty section. The BEIR equations were altered according to Appendix 8 so that a lifetable analysis could be evaluated if incidence dose-response data (i.e., an incidence model) and incidence rates were available (written comments from Reviewer #5). An assessment and comparison when the incidence model was used with the BD mortality dose-response data and incidence or mortality data was also completed.

The uncertainties in both approaches are discussed in Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence*. The TCEQ agrees with Reviewers 1 and 5 who stated in written comments page 46 (lines 11-16) and page 47 (lines 26-28), respectively: "R1: Ideally, one would want to calculate risk based on incidence rather than mortality, as it is the former that one wants to protect against. However, there are pragmatic limitations to this approach, which are well presented in Appendix 7 and have been published in the literature by others. Given these limitations and the inherent conservatism of the risk estimation procedure, it seems to me that a less-biased estimate of risk based on mortality is better than a more-biased estimate based on incidence." R5: "if one can only estimate mortality rates from the studies with exposure and response data, then one should not attempt to calculate lifetime cancer incidence risks." The TS did not use incidence rates to calculate excess risk using dose-response modeling based on leukemia mortality data.

Issue # 4, Page 7: 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?

10. **Comment:** The panel agreed that TCEQ should present both UCL and MLE and discuss the remaining uncertainties associated with each value, but should base the risk value on the UCL. (page 7)
Response: No revision of the DSD was necessary. Both the UCL and MLE were presented in the proposed DSD and both have been included in the final DSD. There is only a 1.4 fold difference between the UCL and MLE. The TS used the 95% UCL as the preferred potency estimate because the UCL on the risk is a standard health-protective measure and addresses statistical uncertainties. Refer to Section 4.2.5.4 *Dose-Response Modeling*.

Issue # 5, Pages 7-9: Discuss the most appropriate approaches for discussing/evaluating uncertainty in the cancer assessment.

11. **Comment:** One reviewer stated that the TCEQ URF is about 100-fold lower than the EPA value, and the document was not clear on what was done differently to reach such a different value. (page 8)
Response: A discussion of the different procedures used to develop TCEQ's URF compared to the procedures used to develop USEPA's URF is included in Section 4.2.6 *Comparison of TCEQ's URF to USEPA's URF*.

12. **Comment:** Other reviewers suggested possible approaches to quantifying uncertainty. (Page 8) These approaches include:

    - #1 Model averaging - used when the modeling included different statistical models with no clear biological choice of model to use. The average is weighted according to the

Response to bullet #1: The TS did not attempt to do model averaging because it is hard to decide which models to average and this practice has not yet obtained widespread acceptance in a regulatory setting.

- #2 Provide a range of risk values and discuss comparisons of the values in a section on uncertainty analysis. Improve the clarity and presentation of the uncertainty discussion.
  Response to bullet #2: The uncertainty section has been revised to improve clarity and presentation and a range of risk values and comparisons have been provided throughout the different subsections of Section 4.2.5 *Uncertainty Analysis*.

- #3 Address uncertainties in exposure assessment of the critical study with alternate modeling. The validation study reports more exposure mismeasurement at higher exposure levels. For example, Figure 1-b from Cheng *et al.* (2007) below shows the effect of dropping the top 5% of exposure expressed as ppm-years. Therefore, TCEQ could present modeling that shows how the risk value changes when the top 5% of data are excluded. The reviewers suggested that TCEQ add a discussion of what happens to the risk value as additional data are dropped off the top.
  Response to bullet #3: The TS now presents modeling that show how the risk value changes when the top 5% of the data are excluded, based on Cheng *et al.* (2007), but does not discuss what happens to the risk value as additional data are dropped off the top. Sielken *et al.* (2007) presents this analysis, and the DSD now references this analysis. One of the main reasons the TS chose to use BD ppm-years as mean deciles of exposure rather than continuous, untransformed data was "Compared to analyses that use continuous exposure variables, analyses using deciles (or other quantiles) of BD exposure . . . may reduce the influence of data at the extreme exposure values and, in particular, may reduce the impact of misclassification that some investigators have suggested might selectively affect the upper range of exposure estimates" (Cheng *et al.* 2007) (refer to discussion for Issue 1, page 4 above). However, the recommendation from the panel was the preferred model for risk assessment should use an exposure variable which is continuous. The TS feels it is important to address the uncertainty of sparse data and an erratic dose-response relationship at the high end of the exposure range. The URF derived from restricted data was more conservative and a policy decision was made to use the more conservative URF. The University of Alabama at Birmingham (UAB) group recommended the estimate of the dose-response relationship that is based on the continuous, untransformed form of BD ppm-years, age included as the index variable, and the full range of exposure data (2.9E-04 (β), 1.0E-04 (S.E.)). However, due to the high potential for distortion of the dose-response relationship as a result of exposure misclassification, Cheng *et al.* (2007) also recommended that an uncertainty analysis be incorporated into any risk assessment that uses these data. However, since the purpose of the TCEQ assessment is to calculate a health-protective 10^{-5}-risk air concentration for evaluation of air permits and ambient air monitoring data, the TS decided to use the more conservative results based on restricted data (i.e., when the top 5% of data are excluded) as the preferred model so that the sparse data and the erratic dose-response relationship at the higher exposure levels would be accounted for and because it was more conservative (see Section 4.2.4 *Potency Estimate Selected to Represent Excess Leukemia Mortality Risk* and response to Comment #18).

13. **Comment:** Panel members recognized that formal uncertainty analysis can be time intensive, but noted that presenting Cheng's data on the impact of dropping the high doses provides useful

Response: Cheng's data on the impact of dropping the high doses has been included and has been used as the preferred model, as discussed in the DSD. Qualitative statements about the use of an updated exposure assessment and validation of that assessment have been added to the DSD (e.g. "Based on the validation study of Sathiakumar *et al.* (2007), the updated exposure estimates of Macaluso *et al.* 2004 have a higher confidence than original exposure estimates."). Sielken & Associates completed a sensitivity study based on the Sathiakumar *et al.* (2007) exposure estimate validation study and this sensitivity analysis has been included in the DSD (Appendix 7 and Section 4.2.5.3 *Effect of Occupational Exposure Estimation Error*).

1.2 Panel Written Comments

Is the epidemiological evidence in Albertini *et al.* (2007) properly used in the characterization of chronic cancer risks?

14. **Comment:** R1: The data from this paper (i.e., Albertini *et al.* paper) does not appear to have been considered in the weight of evidence section. This section deals exclusively with the potential for BD to be a human carcinogenic hazard, whereas the Albertini work addressed the question of risk in humans. (page 42, lines 4-7). . . R6 The weight of evidence statement is appropriate. The Albertini study is a useful one, but it is not clear what conclusions TCEQ is deriving from this study in the overall context of the cancer evaluation. In particular, consideration of the "clear NOAEL" for gene mutation in the context of the calculated cancer risk would be useful (considering such issues as sample size and sensitivity). (page 42, lines 16-20)
Response: The DSD has been modified as suggested. (Section 4.2.1 *Carcinogenic Weight of Evidence and MOA*)

15. **Comment:** The finding that urinary BD metabolite levels were lower in females was not surprising, since females had lower exposures. But Albertini also noted that the metabolite levels were lower for the same butadiene exposure concentration compared to males. This latter finding is more significant, and does not appear to be mentioned in the DSD. (page 42, lines 27-29)
Response: The DSD has been modified as suggested. (Section 4.2.5.1 *Estimating Risks for other Potentially Sensitive Subpopulations*)

Was the dose metric selected, cumulative ppm-years, the most relevant and appropriate choice?

16. **Comment:** R5: Although ppm-years is the proper metric to use to relate population exposures to population risks, it may be more appropriate to consider a window of exposure (probably lagged by some number of years) as the measure to be used . . . (page 43, lines 30-36) (similar comments from R5 concerning window of exposure appear on page 45, lines 23-29).
Response: The DSD has been modified to include a statement that considering windows of exposure did not improve model fit (Section 4.2.3.1 *Beta coefficient (β) and Standard Error Based on Observed Data*).

Comment on the relevance of using penalized spline regression and restricting the data to the lower 95% of the exposure range of all subjects.

17. **Comment:** R5: Adoption of a parametric model in Cox regression should be done after examination of categorical and spline results, preferably conducted within the Cox model (not within Poisson regression) so have as much as possible comparability between categorical and purely parametric models. Categorical and spline results will provide minimally parametric graphical representation of the exposure-response shape and will guide choice of a simpler parametric model. Such results are provided in Cheng *et al.* (2007). It might be useful to

incorporate into the Texas risk assessment as a graph with the spline and the categorical points. (page 44, lines 22-29)
Response: Figures 1a and 1b from the Cheng *et al.* (2007) paper illustrating spline results from unrestricted data and restricted data, respectively, have been included in the DSD (Section 4.2.3.1 *Beta coefficient (β) and Standard Error Based on Observed Data*). A graph with spline combined with categorical points was not available. The dose-response relationship in the low dose region is fairly linear, and supports the use of the log-linear Cox regression model (continuous, untransformed data).

18. **Comment:** R1: The general question in my mind is whether it is reasonable to restrict the data set. Given the high uncertainty in the exposure assessment at the upper end of the distribution, I think it is reasonable to restrict the data set. Many of the model runs took other approaches to limit the impact of the high exposure estimates, particularly the models that clumped the exposures into deciles. Doing so resulted in potency estimates that appear to be more robust. (page 44, lines 34-39)
R7: Regarding analyses without the top 5% of the data, I believe such analyses are appropriate as a sensitivity analysis, particularly as the highest exposures are likely to involve greater mis-measurement. Such exposures can sometimes have a strong influence on the shape of the exposure-response curve. High exposures do appear to have a big influence here, as per page 19 of Chang *et al.* (2007), section 3.4. Texas might consider basing its risk assessment on the data excluding the top 5% of exposures, or some kind of average between the full data and the restricted data. These data appear to be linear in the low dose region as per Figure b on page 19 of Chang *et al.* (pages 44, lines 46-47 thru page 45, lines 1-8).
Response: Based on comments during the teleconference and the above written comments, the TS has revised the DSD to use the log-linear Cox regression model that uses restricted data as the preferred model to address concerns for the sparse data and the erratic exposure-response relationship at high exposure concentrations and to be conservative (i.e., a policy decision). The sensitivity study that Sielken & Associates conducted (Appendix 7) indicates that the β and SE calculated by Cheng *et al.* (2007) and Sielken *et al.* (2007) were conservative and did not underestimate potency estimates based on concerns about exposure estimation error.

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?

19. **Comment:** R1: No. The confidence intervals are indicators of the variability (and to some extent uncertainty) in the dose-response curve for mortality. They don't speak to the relative relationship between incidence and mortality. It can't be claimed that the UCL accounts for the difference. What can be said is that using the UCL adds conservatism to the estimate, and that by doing so it is probable that risk of incidence will be lowered. (page 46, lines 39-43)
R7: Use of the 95% UCL estimate is a common conservative practice which I believe is standard in this type of risk assessment, to allow for uncertainty of all types, including for example estimation of RRs for incidence based on mortality RRs. (page 47, lines 30-32)
Response: There was a lot of discussion on this topic. Strictly speaking, confidence intervals only provide a measure of the variability in the dose-response curve for mortality and to some extent uncertainty, as pointed out by Reviewer #1. However, it is standard practice for toxicologists to state that use of the 95% confidence limit somewhat accounts for other uncertainties in a risk assessment, as stated by Reviewer #7 (above) and reiterated by Reviewer #2 on page 47, lines 45-46 ("R2: Good idea! I would like to see both estimates considered. But the reason for using the 95% UCL is that there are some subpopulations that may be more sensitive to BD than others."). However, the DSD has been modified in Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence* to state: The confidence intervals are indicators of the variability, and to some extent, the uncertainty in the dose-response curve for mortality. The risk of incidence will be lowered

since using the URF (95% UCL) adds conservatism to the estimate.

The choice of response rate, 0.1% (in EC001 and LEC001) for linear extrapolation to lower exposures.

20. **Comment:** R1: As noted above, the estimates at this level are reasonably consistent from model to model. Furthermore, this value is not far from the death rate from leukemia in the study cohort (81 in approx. 16,000). Therefore, I believe this is a reasonable starting point for extrapolation. (page 49, lines 33-36). R7: . . . An alternative might be the 1% excess risk, which might be more within the range of the epidemiologic data used to estimate it. (page 50, lines 11-13)
Response: The DSD was not revised based on this comment. The TS will continue to use the 0.1% (in EC001 and LEC001) for linear extrapolation to lower exposures because it is within the range of the data, whereas the 1% excess risk is above the range of the mortality data.

Other Issues Related to the Cancer assessment

21. **Comment:** R2: What I find missing in the document is a good discussion of the uncertainty associated with the numbers you derive for the various standards. A whole section on this subject should be added. The values determined are estimates only and there are many sources of uncertainty associated with each value. It is particularly disturbing to see values such as those listed in Table 16 with 4 significant figures! . . . This gives the public the wrong impression of the degree of precision involved in risk assessments (page 50, lines 35-39 and lines 43-44)
Response: There are numerous places where alternative results (based on different models, different modeling, different assumptions, different covariates, etc.) are reported – explicitly quantifying uncertainty. An entire section of the proposed DSD was included to address uncertainty. However, the uncertainty section has been extensively revised based on the reviewer's comments.

    The DSD reports four significant figures because they reflect the calculations made and are provided for individuals trying to follow or reproduce the calculations rather than to indicate precision. At the end of all calculations, the URF is rounded to two significant figures, then the 10^{-5}-risk air concentration is calculated and it is rounded to two significant figures.

22. **Comment:** R6: A discussion and consideration of the relative toxicodynamic sensitivity of children vs. adults to chemical-induced leukemia would be of value, particularly in light of the public comment stating that susceptibility to leukemia of unknown origin appears to increase between younger and older children, and between older children and adults. This database is beyond my knowledge base. (page 51, lines 19-23)
Response: References have been included in the revised DSD that discuss the potential toxicokinetic and toxicodynamic differences between children and adults for chemical leukomogenesis. The last paragraph of Section 4.2.4.1 *Evaluating Susceptibility from Early-Life Exposures* has been revised.

23. **Comment:** R6: Note that the MOA is understood, and is identified as DNA reactivity and resulting mutagenicity. The **mechanism** of action is what is not known in sufficient detail to develop a BBDR. (page 51, lines 25-27)
Response: The DSD has been modified as suggested.

24. **Comment:** R7: It is not clear to me why Texas has chosen to calculate excess risk only through age 70 . . . (page 51, line 29)
Response: The DSD was not revised based on this comment. A lifetime exposure of 70 years is the default used by TCEQ for exposure analysis. This is clearly stated in the ESL Guidelines (TCEQ 2006) and in Section 4.2.3.3.1 *URFs and Air Concentrations at 1 in 100,000 Excess*

Cancer Risk. The TCEQ will use the 70-year default to be consistent between evaluations for different chemicals (i.e., the risk from different chemicals will be more comparable if the dose-response was evaluated using a consistent 70-year exposure analysis). The use of 85 years instead of 70 years has been criticized for a variety of reasons. The dose-response modeling was not done based on person-years corresponding to older ages. The dose-response model based on early ages and older ages may be very different. Furthermore, the relevance of the dose metric (cumulative BD ppm-years) may differ for older ages.

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

2.1 Panel Teleconference Comments

Issue # 6, Pages 9-10: Is ovarian atrophy in mice relevant for humans as the critical effect?

25. **Comment:** One reviewer strongly disagreed with using this endpoint in mice as the basis of the chronic ReV because none of the human epidemiology studies have reported reproductive effects . . . other reviewers disagreed, noting that ovarian atrophy is equivalent to premature menopause . . . (page 9) The reviewers agreed the mouse may not be a good model for human toxicity because it is clearly more sensitive to the reproductive effect than other species tested, and they suggested that TCEQ consider the suitability of non-mouse datasets as the basis of the chronic ReV one more time. However, the panel acknowledged that selecting a relevant endpoint in the most sensitive species is consistent with both TCEQ guidelines and accepted risk assessment practice, and the sensitivity of the mouse to these effects can be addressed with UF_A as discussed below. (Page 10)
    Response: The DSD was not revised based on this comment. The TS agrees with the panel members who stated that selecting a relevant endpoint in the most sensitive species is consistent with both TCEQ guidelines and accepted risk assessment practice, and the sensitivity of the mouse to these effects can be addressed with the UF_A.

Issue # 7, Page 10: Should the point of departure be based on a 5% or 10% increased risk of ovarian atrophy?

26. **Comment:** Overall, the reviewers did not express a preference for using either 5% or 10% increased risk as the point of departure. The panel agreed that this was a policy decision and that the most important consideration in choosing a value was consistency across risk assessments. One reviewer noted that the choice should not depend on the severity of the response being modeled. Another reviewer noted that the benchmark analysis process addresses issues related to study design.
    Response: The TS will use the 5% benchmark response for increased risk of ovarian atrophy as the POD because ovarian atrophy is considered a severe response. This is a policy decision discussed in the ESL Guidelines (TCEQ 2006) that will consistently be applied to all toxicity assessments for all chemicals (refer to response to comment # 86, General Written Comments). Although one reviewer noted that the choice should not depend on the severity of the response being modeled, other reviewers considered this defensible based on the ESL Guidelines (written comments from R6, page 37, lines 44-45 and R1, page 38, lines 9-12). The BMC_{10} and $BMCL_{10}$ are included in the BD DSD based on recommendations from USEPA (2000) since the BMC_{10} and $BMCL_{10}$ can be used for comparison to other chemicals in other risk assessments.

Issue # 8, Pages 10-11: Choice of dosimetric adjustments - Are there data to support a lowering of the animal to human UF to less than 1?

27. **Comment:** Another reviewer noted that data on the diepoxide metabolite levels in blood was available in rats, mice, monkeys (Thornton-Manning *et al.*, 1995, 1998).
    Response: Thornton-Manning *et al.* 1995, 1998 only provide data on metabolite concentration in

rats and mice. Data comparing epoxide metabolite levels in monkey, rat and mice have been published by Henderson *et al.* (1996), Henderson (2001), and Dahl *et al.* (1990, 1991). The TS has used the experimental data from these investigators in a new section entitled *Toxicokinetic Adjustments from Animal-to-Human Exposure* (Section 4.1.5.2). See additional comments below.

28. **Comment:** Although the panel discussed approaches for identifying a specific value < 1 for UF_A, the panel concluded that given the available data and practical regulatory considerations, it might be sufficient to determine an approximate bound (e.g., whether the number is < 1/3, < 1/10, 1/100) rather than a identifying a specific value.

    TCEQ pointed out that the chronic ReV is already 5x higher than the highest measured BD air concentrations in the State, so there is no effect on the regulatory impact by trying to reduce this uncertainty factor.

    Response: The TS has included a discussion of the available data that provides an approximate bound on the toxicokinetic portion of the animal to human UF (Section 4.1.5.2 *Toxicokinetic Adjustments from Animal-to-Human Exposure*).

29. **Comment:** One reviewer agreed with the choice of UF_A, but recommended a refinement to the presentation. This reviewer noted that all of the considerations addressed in the DSD reflect toxicokinetics – the tissue dose resulting from a given external exposure concentration. In contrast, a toxicodynamic metric would be some measure (e.g., an early precursor) related to the ovarian atrophy. In the absence of information on interspecies differences on toxicodynamics, the interspecies toxicodynamic subfactor would still be 3. However, TCEQ could make a valid argument that the toxicokinetic factor would be less than 0.3, and so an overall interspecies factor of 1 is still appropriate.
    Response: The TS has revised the DSD to indicate that available data indicate the toxicokinetic factor in the animal to human UF may be less than 0.3, but information on interspecies differences on toxicodynamics is not available so a toxicodynamic animal to human UF of 3 will be used. The resulting total animal-to-human UF is 1.

30. **Comment:** The available data support the concept that humans are less sensitive than rodents to the effects of butadiene. However the data are not sufficient to quantitatively state how much lower than 1 the UF_A should be. Therefore any attempt to do this in a regulatory context will not be supportable.
    Response: Refer to the new Section 4.1.5.2 *Toxicokinetic Adjustments from Animal-to-Human Exposure*.

2.2 Panel Written Comments

31. **Comment:** R2: I think it *(i.e.,* ovarian atrophy*)* is appropriate as a sensitive endpoint in the most sensitive species. Is it relevant to humans? No, as you have stated, this endpoint does not appear to occur in humans. Mice are known to have hematopoietic toxicities after chronic exposures (rats do not). I think you should consider using those data (page 36, lines 34-37).
    Response: The DSD was not revised based on this comment. Hematopoietic effects occur at higher concentrations in mice ($\geq$ 62.5 ppm in male mice and $\geq$ 200 ppm in female mice) than ovarian atrophy in female mice (6.25 pppm), after chronic exposure (USEPA 2002). Tsai *et al.* (2005) conducted a hematology surveillance study of petrochemical workers at two Shell facilities and reported there were no significantly increased abnormalities for any hematology parameter among exposed employees (404 exposed employees and 733 comparison employees). Therefore, hematopoietic toxicity may not be a relevant endpoint in humans. Information on the

findings of Tsai *et al.* (2005) has been added to the DSD. The TS will continue to use ovarian atrophy as the most sensitive endpoint and will consider it relevant to humans because there is no data to demonstrate it is not relevant to humans.

32. Comment: 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? (page 37, lines 24-25)
Response: The DSD did not need to be revised based on this comment. Differing opinions were expressed by two different panel members (R1 and R2). The TS will continue to use the 95% lower confidence limit of the benchmark exposure response of 0.05 because the UCL is a standard health-protective measure and addresses statistical uncertainties.

33. **Comment:** R1: As noted in an earlier comment, it is also possible to adjust for respiratory rate/ minute volume between mice and humans, which would improve the extrapolation. Doing this necessitates calculating a dosage instead of an atmospheric concentration, and therefore back calculating to an acceptable human concentration; however, given the concern expressed that the high respiratory rate of mice may be unduly influencing the reference value, it is worth considering. (page 38, lines 28-33).
Response: The DSD was not revised based on this comment. This would be an interesting research project, but the TS does not have the time or resources to conduct this study. A panel member (page 11, next to the last paragraph) commented that rate/minute volume differences between mice and humans play a more important role for acute exposures when steady state may be achieved for mice but not for humans. Following chronic exposure, both animals and humans would reach steady state, and so differences in the ventilation rate would not be relevant for animal to human extrapolation.

34. **Comment:** R1: it would be good if there were some way to indicate the large uncertainty associated with the huge difference in the dose of the diepoxide to the tissue in humans versus mice. (page 39, lines 21-24)
Response: No experimental data exists on diepoxide tissue levels in humans, although there is data on diepoxide tissue levels in rats and mice (Thornton-Manning *et al.* 1995). Section 4.1.5.2.2 *Estimate for the Toxicokinetic UF_A Based on Empirical Data* includes data indicating ranges in the differences between humans and mice, monkeys and mice, and rats and mice. An assumption is made that monkeys are adequate surrogates for humans and humans metabolize BD more similar to rats than mice. This provides some measure of the large uncertainty associated with differences between humans and mice.

35. **Comment:** R1: I think the uncertainty factor should really be less than 1, but you stated there are not procedures to do that. Perhaps Texas could be at the forefront to set up such procedures. (page 40, lines 20-23) . . . R2: My suggestion is for Texas to "take the bull by the horns" and come up with a way to use uncertainty factors less than one, when such are warranted. (page 40, lines 30-31) . . . I think that we have enough data now to no longer use the mouse reproductive toxicity data to estimate risk for humans, or if we use it, we should correct with a fractional uncertainty factor to reflect the fact that we know we are going to get an overestimate. (page 40, lines 42-46)
Response: The TS will use a BD-specific toxicokinetic UF = 0.3 (i.e., a fractional uncertainty factor) and the standard toxicodynamic UF = 3 because the key sequence of events and understanding of how DEB interacts in different species to produce ovarian atrophy is not available. The resulting total $UF_A = 1$ (Section 4.1.5.2.2 *Estimate for the Toxicokinetic UF_A Based on Empirical Data*). The toxicokinetic UF_A may range from less than 0.2 to 0.01 based on data discussed in Sections 4.1.5.2.1 to 4.1.5.2.3. There is uncertainty in these estimates since data on a more specific dose metric in humans and mice (e.g. area under the curve DEB blood

concentration) are not available. The information needed to derive a more quantitative estimate or a chemical-specific adjustment factor (CSAF) is not available.

36. **Comment:** R6: More of a critical analysis is needed of the molecular epidemiology study conducted by Albertini *et al.* (2007), particularly considering that it is the only human study that evaluated endpoints related to the critical effects for the acute and chronic noncancer ESLs. In particular, the power and sensitivity of the study should be considered, since no effect was seen on the reproductive endpoints. Is the study adequate to put a bound on the risk of reproductive effects? (page 41, lines 2-7)
Response: The TS does not feel that the study is adequate to put a bound on the risk of reproductive effects, but it is an important, informative study. Additional information has been added to indicate there were only a few subjects in the study and that this may limit the ability of the study to detect differences in the evaluated endpoints.

3 Health-Based Acute ReV and ^{acute}ESL

3.1 Panel Teleconference Comments

Issue # 9, Page 12: Is the choice of maternal extra-gestational weight gain relevant for human risk assessment? If not, what would be a more appropriate critical effect?

37. **Comment:** Reviewers agreed that the benchmark modeling should not be limited to those endpoints with the lowest NOAEL. It is possible that endpoints with a higher NOAEL will give a lower BMDL. Therefore, this panel recommended that TCEQ model all relevant endpoints and then select the endpoint with the lowest BMDL as the point of departure. (page 12)
Response: All maternal and fetal endpoints with a positive dose-response (i.e., doses statistically significantly different from controls) were modeled.

38. **Comment:** The fetal weights should be modeled as continuous data; TCEQ will need to make a decision about what degree of weight change will be defined as adverse (see discussion of Question 6, below). In response to one reviewer's suggestion in written comments that the data be modeled using the nested model of BMDS, another reviewer noted that the current version of the nested model software can only model quantal (dichotomous) data, not continuous endpoints such as body weight. (page 12)
Response: There were five maternal and five fetal toxicity endpoints with a positive dose-response and the data from all endpoints were continuous data. The TS did not change continuous data into dichotomous data, but modeled continuous data with continuous BMC models. The current version of the quantal nested model software, therefore, was not used. See Section 3.1.4.1 *Critical Effect Size* for a discussion of the percent of change in mean response were compared to the control mean response that was defined as adverse.

Issue # 10, Page 12: Should the analyses of Hackett *et al.* data in Appendix 1 adjust for litter size and percent of males in litter?

39. **Comment:** Several reviewers noted that the analyses presented in Appendix 1 of the DSD are related to identifying a NOAEL. As discussed below for question 3, for doing dose response modeling, it does not matter what the NOAEL is. (page 12)
Response: The DSD was not revised based on this comment. The TS believes it is important to identify the correct study NOAEL for each endpoint. If the data from an endpoint cannot be modeled with confidence, USEPA (2000) recommends that the study NOAEL be used as the appropriate POD.

40. **Comment:** One reviewer suggested that the approach depends on the endpoint. For effects on

Response: Appendix 1 contains the results with and without adjustments for the litter size and the percent of males, and presents the results for male and females combined, only females, and only males. The adjustment for the percent of males also impacts analyses for only female and only male.

Issue # 11, Page 12: In conducting the benchmark modeling for the acute ReV, was the output from the most appropriate model selected?

41. **Comment:** One reviewer commented that the Hill model is not the best choice for estimating the dose-response in the lower end of the data because it inherently gives too much weight to the higher doses, compromising the fit to the lower doses. (page 12)
    Response: The TS did not use the Hill model and provided the reasons why the Hill model was not used in Section 3.1.4.2 *Benchmark Concentration Modeling*.

42. **Comment:** This reviewer recommended that TCEQ should use either the restricted polynomial or the unrestricted power models. However, another reviewer disagreed with use of the unrestricted power model because the steep slope in the low-dose region drives the BMDL toward 0. However, other reviewers suggested that in this case, it appears that the unrestricted power model gives the best fit. (page 13)
    Response: The unrestricted power model does provide the best fit for some endpoints when all four exposure concentrations are included for some endpoints. In his email (Appendix 2 *Benchmark Modeling Results Using the Power Model (11/19/07 Email from Bruce Allen)*), Bruce Allen recommended that one standard deviation be selected as the most appropriate critical effect size or benchmark response when using the unrestricted power model because the steep slope in the low-dose region drives the BMDL toward 0. Not all endpoints could be adequately modeled with confidence with the unrestricted power model, so a linear model was used when necessary. For example, mean fetal body weight could not be modeled with confidence using the unrestricted power model, but when the highest concentration of 1000 ppm was deleted, a linear model fit the data adequately and the $BMCL_{05}$ from the 3-dose linear model was used as the POD for reduction in fetal body weight.

43. **Comment:** This reviewer also suggested that the TCEQ DSD provide the p values and chi^2 values in the tables so that readers can more easily visualize the model fit. (page 13)
    Response: For those endpoints that were adequately modeled with confidence and results were acceptable based on the trend test, the p values and information on chi^2 values (i.e., scaled residuals) are included in Table 7. *BMC Modeling Results for Maternal/Developmental Toxicity* and Appendix 2.

44. **Comment:** The panel also agreed that, while dropping the high dose(s) is an accepted approach for improving the fit in the low-dose region, this approach is not needed for the data sets of interest. (page 13)
    Response: All four exposure concentrations were modeled in the unrestricted power model for extragestational weight gain. It was not possible to exclude the highest concentration for the unrestricted power model since the power model requires four exposure concentrations to model data with confidence. Not all endpoints could be modeled with confidence with the unrestricted power model so the linear model was used. If the endpoint could not be modeled with four concentrations for the linear model, then the highest dose was dropped to see whether the endpoint could be modeled with confidence. For those endpoints that could not be modeled with

confidence with the unrestricted power model, the results from the linear model were used.

45. **Comment:** In addition, the panel discussed differences in modeling approaches used by TCEQ and one reviewer who submitted the unrestricted power model modeling results shown in Appendix A. Parties had very different results, and the panel agreed that the reviewer and TCEQ they should resolve the issue in a separate discussion following the conference call. (page 13)
Response: All issues were resolved between the reviewer and TCEQ. Refer to Appendix 2 *Benchmark Modeling Results Using the Power Model (11/19/07 Email from Bruce Allen)*.

46. **Comment:** The panel concluded that the Hill model should not be used to model the data. (page 13)
Response: The Hill model was not used to model the data and the reasons why it was not used is discussed in Section 3.1.4.2 *Benchmark Concentration Modeling*.

47. **Comment:** Having a monotone model is important because a non-monotone model is not biologically relevant. Restriction is reasonable if it is necessary to get a monotone response. (page 13)
Response: Use of the unrestricted polynomial model produce a non-monotone model for the endpoints that were modeled and is not included in the updated BD DSD as discussed in Section 3.1.4.2 *Benchmark Concentration Modeling*. When the polynomial model is restricted, it becomes a linear model, which was used to model the data.

Issue # 12, Page 13: 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?

48. **Comment:** As discussed above, the panel agreed that only monotone models should be used, and that the 95% lower confidence limit on dose should be used. (page 13)
Response: The TS will not use the unrestricted polynomial model because is not monotone as explained in Section 3.1.4.2 *Benchmark Concentration Modeling*. All other models were monotone. The TS will use the 95% lower confidence limit (BMCL) and not the maximum likelihood estimate, although both estimates will be presented.

Issue #13, Pages 13-14: Was the appropriate benchmark response (BMR) selected (5% vs. 10% reduction of weight gain)?

49. **Comment:** In addition, the panel disagreed with TCEQ that the choice of response level cannot be below the observed responses, and with the approach of defining the BMR based on the response in the range of the data. However, the panel agreed that the choice is a policy decision. (page 13)
Response: The DSD was not revised based on this comment. The TCEQ did not mean to suggest that the choice of response level cannot be below the observed responses, only there is less uncertainty due to model choice when the benchmark response is not far below the observed range of responses.

50. **Comment:** One reviewer noted that the choice of 5% or 10% only applies to quantal data, and that several of the endpoints to be modeled are continuous data (page 13). . . . Another reviewer noted that if there are data on the degree of change that is considered abnormal, then those data should be used rather than change relative to the standard deviation. (page 14)
Response: All data from the ten endpoints that were modeled were continuous data. In order to distinguish continuous data from dichotomous data, Dekkers *et al.* (2001) recommended the term "critical effect size" (CES) be used instead of BMR, since for continuous data the effect measure is expressed on a continuous scale. Modeling results for a CES of 1 standard deviation are also provided for comparison purposes, following guidance in USEPA (2000).

51. **Comment:** In the case of body weight changes, risk assessors consider that a 10% body weight change is adverse. Other reviewers agreed, noting that a 10% change in extragestational weight gain and a 5% change in fetal weight would also be considered adverse. (page 14)
Response: A 10% change in extragestational weight gain and a 5% change in fetal weight were chosen as the critical effect size. Please refer to Section 3.1.4.1 *Critical Effect Size* which discusses the critical effect sizes selected for the ten different endpoints and the relevant scientific article that supports the choice of the critical effect size. The panel's suggestions are consistent with information in the scientific article.

52. **Comment:** Reviewers suggested that a hybrid approach would be appropriate for modeling these data. . . .(page 14)
Response: A brief discussion of the hybrid approach is included in Section 3.1.4.2.6 *BMC Modeling Results from USEPA (2002).*

53. **Comment:** TCEQ asked the panel to clarify that a point-of-departure based on a 5% change in extragestational weight gain would be considered not adverse and would be a good NOAEL surrogate. One reviewer noted that the lower bound on a 10% change is comparable to a NOAEL. Although reluctant to call the value a "NOAEL surrogate", the panel agreed that using this approach, TCEQ would not need to apply an additional uncertainty factor for using a LOAEL. In addition, it is always possible to choose a benchmark response such that an additional uncertainty factor is not needed. (page 14)
Response: For extragestational weight gain, a 10% change relative to control mean was initially chosen as the critical effect size (Section 3.1.4.1.2 *Critical Effect Size for Maternal Endpoints – Linear Model*) based on panel suggestions. For the unrestricted power model, the CES of one standard deviation was a more relevant choice because it avoids the steep-slope region (Appendix 2 *Benchmark Modeling Results Using the Power Model (11/19/07 Email from Bruce Allen*) and corresponds to USEPA's guidance (2000). The TS did not apply an additional uncertainty factor.

Pages 14-15, Issue #14. What is the appropriate approach for extrapolating to a 1-hour acute value from the experimental data?

54. **Comment:** One panel member indicated that for developmental toxicity studies when exposure occurs during gestation, that rationale is incorrect. (page 14)
Response: Since the endpoints with the lowest PODs were a decrease in extragestational weight gain and decrease in fetal body weight, and the PODs were so similar, the effects were considered developmental effects and not strictly just a maternal effect, so an adjustment from a 6-h exposure duration to a 1-h exposure duration was not conducted because the ESL Guidelines (TCEQ 2006) states that for developmental endpoints, such as decreased fetal body weight, an extrapolation from a 6-hr exposure duration to a 1-hr exposure duration will not be conducted. The revised acute ReV and ^{acute}ESL are for a 6-h exposure duration.

55. **Comment:** The panel disagreed with the TCEQ rationale and approach for extrapolating the results to a 1-hour exposure. Some panel members disagreed with the use of n=3 in the ten Berge (1986) extrapolation procedure, which was derived from lethality data. However, the use of n=3 is more precautionary than using n=1 in extrapolating experimental results to shorter exposure durations. (page 14)
Response: The DSD has been revised and the most relevant endpoints are reduction in extragestational weight gain and reduction in mean fetal body weight and are considered developmental endpoints. Therefore, an extrapolation from 6 h to 1 h was not conducted. For endpoints that are not developmental endpoints, the ESL Guidelines state that a validated physiologically based pharmacokinetic model (PBPK), if available, is used preferentially to

conduct duration extrapolations. If a PBPK model is not available, then Haber's rule as modified by ten Berge *et al.* (1986) is used with a chemical-specific value for "n". If a chemical-specific value for "n" is not available and it can be determined that concentration and duration both play a role in toxicity, then Haber's rule as modified by ten Berge *et al.* (1986) with a default value of "n" = 3 is used to adjust the concentration at a specific exposure duration of > 1 h to 1 h. This is a conservative default procedure since it results in a slow increase in concentration.

3.2 Panel Written Comments

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. (page 24)

56. Comment: R2: No, it is not. To follow standard guidelines, one must choose the most sensitive endpoint, RELEVANT TO HUMANS, in the most sensitive species. In this case, there is no indication that this endpoint has anything to do with the hazard to humans of exposure to 1,3-butadiene. My suggestion would be to examine endpoints in mice (the most sensitive species) having to do with adverse effects on the lymphohematopoietic system. (page 24, lines 32-36)
Response: The DSD was not revised based on this comment. Subchronic and chronic adverse effects on the lymphohematopoietic system have been documented (refer to response to comment #31, but acute adverse effects on the lymphohematopoietic system have not. The TS will continue to consider reduction in extragestational weight gain as a sensitive endpoint and will consider it relevant to humans. Refer to Section 3.1.2.2 *MOA for Reproductive/Developmental Effects*.

Issues Relating to BMC Models

57. **Comment:** The document also shows a lack of understanding of the use of the AIC. In the first and second paragraphs of p. 18, there are comparisons of AICs from different models. But the comparison is erroneous first because the 3-dose and 4-dose results cannot be compared on the basis of the AIC; the AIC must be used to compare models fit to the same data, and the 3-dose and 4-dose analyses are not of the same data. (page 27, lines 12-19). . . . (similar comments are found on page 27, lines 37-39).
Response: The revised DSD has been revised based on panel comments and does not compare the AICs from a 3-dose model to a 4-dose model.

58. **Comment:** Finally, in the DSD discussion regarding publications on the choice of BMR, it was not clear how the analyses were done. Note that the BMCL05 and BMCL10 for maternal body weight refer to a 10% change in the mean, not a 10% change in the percent of animals affected. (For a normally distributed population, 50% of the animals would have a 10% change or larger if the mean is changed by 10%.). (page 29, lines 32-36)
Response: In order to avoid confusion, the term critical effect size (CES), as recommended by Dekkers *et al.* (2001), is defined and will be used instead of the term benchmark mark response (refer to Section 3.1.4.1 *Critical Effect Size*). The CES refers to a percentage change relative to the mean value.

The choice of dosimetric adjustments (page 30)

59. **Comment:** R1: These were appropriate and follow established guidelines. As noted in an earlier comment, (*TERA*: comment copied again below) it is also possible to adjust for respiratory rate/ minute volume between mice and humans, which would improve the extrapolation. Doing this necessitates calculating a dosage instead of an atmospheric concentration, and therefore back calculating to an acceptable human concentration; however, given the concern expressed that the

high respiratory rate of mice may be unduly influencing the reference value, it is worth considering. The reference values presented in the DSD were derived using practices that are in line with the ESL guidelines, and are consistent with procedures used by other state and federal regulatory agencies. (page 30, lines 9-19).
Response: No change to the DSD was made based on this comment. This would be a very interesting research project, but the TS does not have the resources to conduct this study. We agree with the reviewer that "The reference values presented in the DSD were derived using practices that are in line with the ESL guidelines, and are consistent with procedures used by other state and federal regulatory agencies."

60. **Comment:** Throughout the document (examples on page 14, lines 30-31; page 16, lines 38-39), it is suggested that "Uptake of BD in mice is faster than rats and may account for the increased susceptibility of mice compared to rats." This is absolutely not true and should be deleted. (page 30, lines 41-44)
Response: The statement that uptake of BD in mice is faster than rats has been deleted in the revised DSD.

61. **Comment:** Extrapolation of concentration to a shorter exposure duration is estimated by the ten Berge procedure (ten Berge *et al.*, 1986), not Haber's Rule as incorrectly stated on Page 20, Line 4. (page 31, lines 27-29)
Response: The DSD has been corrected based on this comment.

62. **Comment:** R6: At the least, more explanation is needed to explain the rationale for the exposure duration adjustment. First, it is not clear whether the authors considered the study to be a subacute study or a developmental toxicity study for the purposes of identifying the approach for extrapolation, although it appears that it was considered to be a subacute study, since the endpoint is systemic maternal toxicity. For such exposures, the guidelines appear to recommend that the DSD authors should compare ESLs developed based on the data with ESLs developed using the approach(es) for chemicals with minimal data, to ensure that the value derived is not over-conservative; it appears that such a comparison was not done for butadiene. This consideration may have a quantitative impact on the acute ESL. (page 32, lines 34-43)
Response: Since the critical effects were reduction in extragestational weight gain and reduction in fetal body weight, which are considered developmental effects, Section 3.1.5.1 *Critical Effect and Default Exposure Duration Adjustments* has been revised to state an exposure duration from 6 h to 1 h was not conducted, based on guidance in the ESL Guidelines (TCEQ 2006). Although it is not appropriate to compare a 6-h acute ESL to a 1-h generic ESL, the DSD has been modified to include a comparison using approach(es) for chemicals with minimal data (Section 3.1.6 *Comparison of ^{acute}ESL to Generic ESL*).

Choice of uncertainty factors

63. **Comment:** R4: I am in complete agreement with the choice of uncertainty factors by TCEQ. The use of the default UF of 3 for animal-to-human pharmacodynamics, as opposed to the use of a UF of 1 for the ovarian atrophy, is justified because of the lack of mode-of-action evidence tying the weight gain effects specifically to DEB. (page 32, lines 13-16) . . . R2: I consider the UF_A of 3 to be highly conservative for the reasons stated on page 21, lines 19-22. It is well known that humans are much less sensitive to BD than mice and a much smaller UF or even a fractional UF should be considered. (page 33, lines 15-17).
Response: We agree with reviewer #4. A discussion of the proposed MOA of BD's reproductive/developmental effects has been added to the DSD (Section 3.1.2.2), and additional discussion has been added to Section 3.1.6. *Adjustments of the POD_{HEC}*.

64. **Comment:** R6: I agree with the choice of uncertainty factors, with one specific comment. I agree with a database UF of 1, but recommend a clarification of the justification. The acute database for butadiene meets the minimum database requirements for a high confidence acute ReV, not the minimal database for an acute ReV. (page 33, lines 28-31)
    Response: The DSD has been modified as suggested.

Other comments on the health-based acute ESL (page 34)

65. **Comment:** R6: P. 12, second paragraph: Early resorptions were lower in the exposed groups. Thus, regardless of the statistical approach used to analyze the data, no adverse effect was observed, and there should be no LOAEL for this endpoint. The identification of the LOAEL appears to be an error by TCEQ, but if TCEQ believes that this effect was adverse, additional explanation should be provided. However, this consideration does not affect the ESL. (page 34, lines 36-40)
    Response: The DSD has been modified as suggested.

3.3 Comments from Reviewers #1-3 on Health-Based Acute ReV and ^{acute}ESL (June 2008 version of the BD DSD)

66. **Comment from reviewer #1:** My main criticism with the revision is with its organization. It is organized around the statistics, rather than around the biological effects and risk assessment . . . I recommend that it be organized by effect, not dose-response model.
    Response: The DSD has been modified so that it is organized by biological effects rather than different dose response models.

67. **Comment from reviewer #1:** I agree with the decision not to use extra ribs as the critical effect. There is disagreement in the field as to whether these are really adverse or are non-adverse variations of the norm and/or non-specific manifestations of generalized toxicity. Using decreased fetal weight as the critical effect would protect against other effects, including extra ribs, produced at the same or higher dose levels.
    Response: The DSD has been modified as suggested.

68. **Comment from reviewer #1**: On p. 26, I disagree with the use of the section title of "Preferred Modeling Results" because different models might be preferable for any given endpoint. Likewise, the first sentence under this section is misleading because it suggests that the power model is best regardless of which endpoint.
    Response: The section titled "Preferred Modeling Results" has been deleted. After careful evaluation of the comments from reviewers #1, #2 and #3 on fetal weight modeling, the TS has decided that it is appropriate to use BMC modeling results from the 3-dose linear model for fetal body weight as opposed to stating the unrestricted power model is preferred.

69. **Comment from reviewer #1:** P. 9, the last sentence (and carrying over to p. 10): I would delete this sentence. You can (and do) deal with the subject of differential sensitivity of different species later in the document. It is confusing to try to introduce it in the first sentence of a section on Human Studies.
    Response: The DSD was revised as suggested by the reviewer.

70. **Comment from reviewer #1:** P. 19, last sentence: I think this should be worded differently. One would want to select a critical effect because it is adverse, biologically plausible (e.g., consistent with the proposed MOA, dose-responsive), and is among the effects occurring at the lowest levels

of exposure. This will probably still be the lowest POD, but the rationale is much more palatable and correctly reflects the thought you have put into this assessment.
Response: The DSD was revised as suggested by the reviewer.

71. **Comment from reviewer #1:** P. 21, the long paragraph after the bullet points: This seems more like a discourse on benchmark dose methods than anything having to do specifically with butadiene. I found it out of place and I recommend deleting it.
Response: The DSD was revised as suggested by the reviewer.

72. **Comment from reviewer #2:** I agree that it is reasonable to choose the NOAEL for fetal body weight as the basis for the acute ReV, but found the documentation for that choice not fully transparent. The discussion of the linear model in Section 3.1.4.2.2 gives the impression that the linear model for fetal body weight with 3 doses gives an adequate fit to the data. The visual fit is fine, and the g-o-f p value is acceptable, although not ideal. No other issues are noted with this modeling, and Section 3.1.4.2.4 gives the impression that the linear model for fetal body weight is not chosen for the point of departure only because the power model is preferred overall.
Response: After careful evaluation of the comments from reviewers #1, #2 and #3 on the fetal body weight modeling, the TS has decided that it is appropriate to use BMC modeling results from the 3-dose linear model for fetal body weight as opposed to stating the unrestricted power model is preferred. The DSD has been revised to use the $BMCL_{05}$ of 54.7 pppm as the POD for fetal body weight. The rationale for that choice is documented in the final version of the DSD.

73. **Comment from reviewer #2:** However, based on the data in Table 2D of Appendix 2, it appears that the linear model was rejected based on the results of test 3, but that was not stated explicitly. What was the reason for rejecting the linear model? I would not expect that choosing the power model for other endpoints would be sufficient reason to reject the results of the linear model for fetal body weight. On the other hand, failing test 3 may not require that the model be rejected, if the variance is fit adequately in the range of the BMR. It was also noted that test 3 failed for the power model for placental weight, but the power model results were reported in the main text for this endpoint.
Response: The TS did not reject the 3-dose linear model for fetal body weight because of the results of test 3, which provides information on variance. Both a nonhomogeneous and homogeneous variance were used to model the data. The scaled residuals for a nonhomogeneous variance were slightly smaller in the low-dose region of the dose response curve, so the results from a nonhomogeneous variance are reported. This statement has been included in Sections 3.1.4.2.2 *Decreased Placental Weight* and 3.1.4.2.3 *Decreased Fetal Body Weight*.

74. **Comment from reviewer #2:** While it is not necessary to rework the butadiene document, I found it a bit confusing to organize the modeling results by model, rather than by endpoint. . .
Response: The DSD has been modified so that it is organized by biological effects rather than different dose response models.

75. **Comment from reviewer #2:** The text regarding the hybrid model looks as though it may have been added in response to a reviewer question. I'm not sure that the text is really needed, since the text that appears to have prompted the reviewer comment/question has been changed/clarified. . .
Response: The indicated text has been deleted based on the reviewer comment.

76. **Comment from reviewer #3:** I think that there is still too much strict reliance on and maybe misinterpretation of the results of the tests reported by BMDS. Appendix 2 shows that the modeled variance does not adequately characterize the variation when the linear model is fit to

the 3-dose data. There are ways around that (especially if you are going to use the 1-sd definition for the BMDL) that involve adding a constant to the means until a good characterization of the variation is found. If that is the only reason for saying that the modeling is not adequate for the fetal weight endpoint, this is not very satisfying. . . As long as the control group variance looks about right and the dose-response for the means is good (Test 4 suggests that it is fine), then the BMD can be used without untoward concern.
Response: The TS did not reject the 3 dose linear model for fetal body weight because of the results of test 3, which provides information on variance. Both a nonhomogeneous and homogeneous variance were used to model the data. The scaled residuals for a nonhomogeneous variance were slightly smaller in the low-dose region of the dose response curve, so the results from a nonhomogeneous variance are reported. This statement has been included in Sections 3.1.4.2.2 *Decreased Placental Weight* and 3.1.4.2.3 *Decreased Fetal Body Weight*. See response to comment #73.

77. **Comment from reviewer #3:** In general, here and in other of my comments, you will see that I much prefer any option that allows dose-response modeling rather than reliance on NOAELs. In fact, I would do my utmost to use PODs that do not depend on NOAELs.
Response: After careful evaluation of the comments from reviewers #1, #2 and #3 on fetal weight modeling, the TS has decided that it is appropriate to use BMC modeling results from the 3-dose linear model for fetal body weight as opposed to stating the unrestricted power model is preferred. The DSD has been revised to use the $BMCL_{05}$ of 54.7 pppm as the POD for fetal body weight. However, Section 3.1.4.2.1 *Data Not Amenable to Modeling* was not revised based on this comment because of the reasons in response to comment #78.

78. **Comment from reviewer #3:** The response to Comment 8 includes the sentence, "It was not possible to exclude the highest concentration for the unrestricted power model since the power model requires four exposure concentrations to model data with 95% confidence." I would not agree with this. . . I definitely think there are some situations where you have rejected the linear model fit to the 3-dose data that would benefit from fitting the power model even though the statistical evaluation of the fit would not be possible. The cases I am thinking of are the non-monotonic cases like reduced ossification and supernumerary ribs. In those cases, the linear model is not going to fit that well because it is going to have to split the difference between the first two doses to get the linear trend that hits the response at the high (3^{rd}) dose. The power model can have a flatter low-dose shape that might better approximate what is going on at the low dose and still curve up to hit the response rate for the 3^{rd} dose. This is what you want and will give a better value of a BMD and BMDL.
Response: The DSD was not revised based on this comment. For the BD DSD, the TS utilized standard BMD modeling software and procedures that are commonly accepted as scientifically-defensible by the scientific and regulatory risk assessment communities. Statisticians and BMD modelers may have various suggestions for improving BMD modeling software and procedures. However, expert opinions on improving and refining BMD modeling procedures or when statistical evaluations of model fit are necessary may vary and lack consensus. These differences in expert opinion may be best resolved, for example, as part of a workgroup providing input on updates to the various BMD modeling softwares and guidance documents. While the TS is interested in scientifically-defensible BMD modeling procedures and considerations which deviate from current regulatory guidance and software, such procedures may not have yet achieved widespread acceptance by the scientific and regulatory communities.

79. **Comment from reviewer #3:** The response to Comment 17 says, "…the CES of one standard deviation was most predictive for the unrestricted power model." I do not know what "predictive means here. The definition of the CES is just a choice, it is not predicting anything specific to a

model. . . .
Response: The DSD and the response to comment was revised as suggested by the reviewer.

80. **Comment from reviewer #3:** In the revised document, in the discussion of the hybrid approach (p. 21, paragraph below the bullet items), it says, "Another major disadvantage is that it is difficult to define a cutoff that is considered adverse for each endpoint." . . . I would not cite this as a reason to avoid the hybrid approach. . . .
Response: The paragraph discussing the hybrid approach has been deleted based on comments from all reviewers (see response to comments #71 and #75).

81. **Comment from reviewer #3:** In the revised document, p. 22, right below the bullet items, it says, "However, the variance for these data sets was not nonhomogeneous either, as defined by the BMD software (i.e., in BMDS 1.4.1c, the nonhomogeneous variance model assumes that the variance in each dose group is proportional to the magnitude of the mean raised to a power)." It cannot be right to say that the variances are not homogeneous and not nonhomogeneous!
Response: The DSD was revised and the statements about homogeneous and nonhomogeneous variance were removed in the indicated section.

82. **Comment from reviewer #3:** The beginning of section 3.1.4.2.2 (p.22) does not sit right. I know this is just for the linear model results, but it really leaves the impression that modeling was not very useful for your analysis. One thing I would suggest is that rather than organizing your report by linear model vs. power model, why not just show the modeling for each endpoint, . . .
Response: The DSD was reorganized by endpoint rather than by model. Therefore, the beginning of section 3.1.4.2.2 was revised.

83. **Comment from reviewer #3:** Moreover, I disagree with the statement in that first paragraph of section 3.1.4.2.2 that says the visual fits of the linear model to the two data sets called out were not very good. They look perfectly fine to me.
Response: The statements concerning fit of the data based on visual inspection have been removed.

84. **Comment from reviewer #3:** Bottom line: I think not enough has been done to get modeling results that can be used. Table 8 in particular is bothersome as it shows so few model-based results and so many NOAELs.
Response: Table 8 has been revised to include modeling results from the unrestricted power model and the linear model (i.e., all appropriate PODs considered when selecting a critical effect), but only NOAELs are presented for the endpoints discussed in Section 3.1.4.2.1 *Data Not Amenable to Modeling*, because the data were not amenable to modeling. Refer to response to comment #78.

85. **Comment from reviewer #3:** I would not exclude from analysis the endpoints with no trend – your statistical analyses have shown there to be trends (NOAELs less than the highest dose), so go ahead and model them – they will give BMDLs that are way high and can be ignored. Don't worry if BMDS says no trend – you have done other analyses that lead you to want to consider them and the test reported by BMDS (Test 1) has no bearing on the ability of the models to fit and describe a dose-response relationship (even if it appears to be very flat).
Response: The DSD was not revised based on this comment. Refer to response to comment #78.

4. General Written Comments

86. **Comment:** The potential downside to the use of benchmark dose methodology is that there are still relatively few risk assessments using it. As a consequence, the opinions of the risk assessment community are still coalescing around the details, such as using a 5% or 10% effect level, a central tendency vs. a lower confidence limit, and for continuous variables such as body weight changes, how much of a change constitutes an adverse effect. Until there is more consensus on how to handle these issues, any decision will be open to criticism. The DSD handles this potential pitfall in the best way, by clearly providing the basis for each decision in the process. (page 20, lines 16-23)
Response: We agree with the reviewer that the best way to deal with varying opinions from the scientific community on what the benchmark response should be is to clearly provide the basis for each decision, and whether the data being modeled is dichotomous or continuous. We have attempted to do this whenever benchmark dose modeling has been conducted.

87. **Comment:** The only other minor weakness that I noted was the heavy reliance on other sources to provide critical review of the hazard data. Two of the major uncertainties in the assessments were the relative sensitivity of mice to BD, and the range of genetic variability in the human population. Some additional critical analysis of the data pertaining to these two points would improve the DSD, particularly given that new information has been published since the 2002 EPA assessment on which the DSD relies. It is probable that the new data are still insufficient to support any additional modification in the uncertainty factors for animal-to-human or intrahuman extrapolation, but it would be an exercise in completeness to be state that the new data were considered in the sections that assign values to each uncertainty factor. (page 20, lines 44-47 thru page 21, lines 1-6)
Response: The DSD is a summary document so TS staff can quickly find and interpret information. Instead of detailed discussions on topics, references to sources containing additional information are provided. However, additional information concerning the uncertainty factors for animal-to-human (refer to Section 4.1.5.2.2 *Estimate for the Toxicokinetic UF_A Based on Empirical Data*) or intrahuman extrapolation (Section 3.1.2 *Mode of Action (MOA) Analysis* and Section 4.1.6 *Adjustments of the POD_{HEC}*) have been added.

88. **Comment:** Page 5, Table 1. It would be extremely useful to state that ESL = 0.3 x ReV.
Response: The DSD was modified as suggested.

89. **Comment:** Page 7, Figure 1. Consider adding TCEQ cancer ESL 28 ppb.
Response: Figure 1 of the DSD has been modified to include the updated TCEQ cancer ESL of 9.1 ppb.

5. Texas Chemical Council Comments

Supplemental Comments of Texas Chemical Council on Texas Commission on Environmental Quality's Public Comment Draft of Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors

5.1 August 28, 2007 Comments

Texas Chemical Council Comments Regarding the 1,3-Butadiene Effects Screening Level Development Support Document

90. **Comment:** Issue #1.0 The statement (page 16) that some humans might be as sensitive as mice is not supported by the current literature, which is quite extensive.

    Response: The DSD has been modified to state "Activation rates in humans exhibit a high degree of variability and appear to span the range of activation rates between mice and rats as investigated with in vitro systems measuring enzyme kinetics, but other in vitro and in vivo molecular epidemiological studies indicate the range of increased sensitivity due to human genetic polymorphisms is approximately two- to four-fold (Smith *et al.* 2001; Fustinoni *et al.* 2002; Albertini *et al.* 2001; Albertini *et al.* 2007)."

    The information provided by Dr. Albertini was very detailed and helpful. Since the DSD is a summary document, it is not possible to include all relevant information, just major concepts. References to research papers are provided.

91. **Comment:** Issue #2.0 The Chronic ReV and ESL based on ovarian atrophy in mice includes an interspecies uncertainty factor of 1. While this is directionally correct with respect to the use of a data based alternative to default uncertainty factors, in this instance a factor of less than one would be supported by available literature.
    Response: Please refer to Panel Comments #27-30 and response to comments.

92. **Comment:** Issue #3 The available evidence would not support the inclusion of an early life correction factor for 1,3-Butadiene.
    Response: The information provided by TCC on toxicokinetic and toxicodynamic sensitivity of children to chemical leukogenesis was very helpful. The DSD has been revised to refer to these studies. Please refer to Panel Comment #22 and response to comment.

93. **Comment:** Issue #4 The Development Support Document overstates cancer risk by using the upper confidence level instead of the most likely estimate.
    Response: Please refer to Panel Comment #10 and response to comment.

5.2 March 10, 2008 Comments

Texas Chemical Council Comments Regarding the document entitled "Peer Review of 1,3-Butadiene Development Support document and Report of Follow up Conference Call," dated December 21, 2007

94. **Comment:** TCC Supports TCEQ's Decision to Adjust the Risk Assessment to Account for the

Effects of High Intensity Tasks (HITS)

Response: Please refer to Panel Comments #2-7 and response to comments.

95. **Comment:** TCC Believes that the Excess Risk Calculations Were Appropriately Based on Leukemia Mortality

    Response: Please refer Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence* and to response to comments #8 and #9.

96. **Comment:** TCEQ Should Use the Maximum Likelihood Estimate Rather Than the Upper Confidence Level in Its ESL Support Document

    Response: Please refer to Panel Comment #10 and response to comment

97. **Comment:** TCEQ Should Base Its Choice of UCL or MLE and Incidence or Mortality on Its Analysis of Issues and Uncertainties

    Response: Please refer to Panel Comment #10 and response to comment to address issue relating to choice of UCL or MLE. Please refer to Panel Comments #8 and 9 and response to comments to address issues related to incidence or mortality.

98. **Comment:** TCEQ Should Base the Acute ESL on Maternal Body Weight

    Response: Although reduction in maternal body weight gain was an effect that was consistently observed in studies in rats and mice (IISRP 1982; Hackett *et al.* 1987a 1987b; and ACC 2003), there is experimental evidence that BD exposure causes a reduction in serum progesterone which may result in maternal effects as well as fetal/placental effects as discussed in Section 3.1.2.2 *MOA for Reproductive/ Developmental Effects.* It would not be appropriate to base the acute ESL on maternal body weight alone without evaluating all maternal and fetal effects. The revised DSD provides an benchmark dose analyses of all maternal/fetal endpoints with a positive dose-response relationship. The critical effects chosen by the TS are decreased extragestational weight gain with a POD of 51.3 ppm and reduced fetal body weight with a POD of 54.7 ppm, which would also be protective of potential teratogenicity as suggested by increased incidence of supernumerary ribs in mice.

99. **Comment:** TCC agrees with the opinion expressed in the peer review report that it is important to adjust for litter size. "For effects on fetal weight, one should adjust for litter size because the size of the litter affects the weight of the fetuses." (TERA, 2007, page 12).
Response: Sielken and Associates did adjust for litter size in Appendix 1 when determining the NOAEL for fetal body weight (refer to comment #39 and response to comment). For BMC modeling for fetal body weight, a continuous model was used and fetal body weight was modeled as continuous data (refer to comment #38 and response to comment). Benchmark Dose Modeling (BMDS) Software (Version 1.4.1c) using continuous models does not have the capability to perform a nested design that takes into account litter size for continuous models.

100. **Comment:** The Chronic ReV and ESL Based on Ovarian Atrophy In Mice Includes an Interspecies Uncertainty Factor of 1. An Interspecies Uncertainty Factor of Less Than 1 Is Supported by Available Literature

Response: The toxicokinetic UF_A has been reduced to 0.3 and the toxicodynamic UF_A is 3, for a total UF_A of 1. Please refer to response to Panel Comments #27-30.

6. City of Houston, Texas Comments (June 2008 version of the BD DSD)

1) Important local research indicates 1,3-butadiene is posing an unacceptable cancer risk in Houston.

101. **Comment:** The most important reason that the City advocates a lower, more conservative ESL consistent with the EPA is that recent epidemiological data indicate that the high concentrations found in the Houston Ship Channel (HSC) area are strongly correlated with increased incidence of certain childhood leukemias.

Response: The recent epidemiological data referred to is Walker *et al.* (2006):

> "A preliminary investigation of the association between hazardous air pollutants and lymphohematopoietic cancer risk among residents of Harris County Texas." University of Texas Health Science at Houston, School of Public Health, http://www.houstontx.gov/health/UT-main.html.

This is an ecological study which is a preliminary epidemiological study. This type of study can be useful in suggesting directions for future research but is of inadequate study design to quantify the dose-response relationship between exposure to BD and leukemia or to demonstrate that children are more sensitive than adults to leukemia. Basing regulatory decisions on these types of studies is generally inappropriate, and the design of this study in particular (e.g., inadequate control for racial differences in background cancer rates, a flawed method of estimating ambient 1,3-BD concentrations, no information on other exposures experienced by residents) further weakens the value of its conclusions.

There are three other epidemiological studies (Loughlin *et al.* 1999; Albertini *et al.* 2001, 2007) and an analysis of the updated University of Alabama at Birmingham (UAB) retrospective cohort study of styrene-BD occupational workers (Sielken *et al.* 2007) that indicate that exposure to low concentrations of BD does not increase leukemia mortality or biomarkers of effect:

- A retrospective cohort mortality study of 15,403 students conducted by Loughlin *et al.* (1999) evaluated cancer rates in graduates of the Port Neches-Grove High School located downwind of a styrene-BD manufacturing facility for the school years 1963-64 to 1992-93. This study did not find evidence of an excess of lymphatic and haematopoietic cancer mortality due to an environmental effect. There were flaws in this study (i.e., no BD exposure estimates, incidence data was not available, etc.), just as there are flaws in the UTSPH report, although a retrospective cohort study is a much better epidemiological study design than an ecological study design such as the UTSPH study. The Loughlin *et al.* (1999) study is not referenced in the UTSPH study.

- A molecular epidemiology study conducted by Albertini *et al.* (2001, 2007) reported that an initial study of workers in the Czech Republic demonstrated a clear no-observed-adverse-effect level (NOAEL) for biomarkers of effect (hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutations and chromosome aberrations) at mean BD exposure concentrations of 800 ppb.

  This NOAEL reflects the maximum average exposure level experienced by these workers and was based on extensive external exposure assessments and a comprehensive series of biomarker responses, which included urine metabolites (M1 and M2) and hemoglobin adducts of epoxybutene (N-[2-dihydroxy-3-butenyl]valine = HB-Val) and EBD (N-

[2,3,4-trihydroxybutyl]valine = THB-Val), HPRT mutations, sister-chromatid-exchange frequencies and chromosomal aberrations determined by traditional methods and chromosome painting (fluorescence *in situ* hybridization). Both the urine metabolite and hemoglobin adduct concentrations proved to be excellent biomarkers of exposure. A second study of Czech workers was conducted at this same facility to compare biomarker responses in female and male employees (Albertini *et al.* 2007). Mean BD exposure concentrations were lower in this second study than in the first, being 180 ppb and 370 ppb for females and males, respectively. Again, there were no BD-associated elevations of HPRT mutation or chromosome aberration frequencies above background in either sex.

- Sielken *et al.* (2007) examined the results of progressively restricting the data to lower concentrations (i.e., < 1338, 1000, 500, 400, 300, 200, and 100 ppm-years) in the updated UAB study of the styrene-BD occupational cohort. These analyses showed the absence of a statistically significant low-dose risk for cumulative BD exposure less than 300 ppm-years occupational exposure, which is equivalent to an environmental lifetime concentration relevant for the general population of 1,500 ppb.

102. **Comment:** These data approximately translate into the following concentration and incidence rates per 1 million people shown in Table 2 . . . From these estimates, concentrations above 1.15 ppbv result in an increased incidence of **15 cases per million children, or risk of $15x10^{-6}$ (1.5×10^{-5} / (ug/m^3)) from 1,3-butadiene alone**. . . . In a simple extrapolation of the UTSPH data regressed for all leukemia cases as related to 1,3-butadiene, it is possible that 1,3-butadiene concentrations at 4.5 ppb would result in over 60 excess leukemia cases in children (age < 20 years) in a million people . . . Although this extrapolation is based on limited data and some key assumptions . . .

Response: The UTSPH report did not contain the results presented in the comments provided by the City of Houston (data in Table 2, Table 3 and Figure 1). The UTSPH study is an ecological design that used group data rather than individual data and did not adjust for race/ethnicity differences in background cancer rates. The study is a preliminary epidemiological study and should be viewed as such. It is not scientifically defensible to develop an inhalation unit risk (IUR) of 1.5×10^{-5} / (µg/m^3) based on the study results or state that the increased incidence of leukemia in children observed in the UTSPH study is due to BD, much less due to BD alone. The study does not causally demonstrate that the increased incidence of leukemias was due to BD exposure as the study only demonstrates associations. In addition, the study does not demonstrate that children are more affected than adults by BD exposure as the study does not demonstrate a causa-and-effect relationship, only associations.

103. **Comment:** The UTSPH report was not referenced by the TCEQ in the DSD. Although the findings are on a pilot study level, a more comprehensive UTSPH study funded by the National Institutes of Health (NIH) and supported by the City of Houston is currently being conducted.

Response: The UTSPH report was not referenced by the TCEQ in the DSD because it is an ecological study design, is flawed, and, as far as the TS can tell, has not been peer-reviewed. It also does not provide the level of analyses and detail needed for quantitative risk assessment. When the more comprehensive UTSPH study funded by the NIH becomes available, the TS will review it. Hopefully, this study will be submitted for publication in a peer-reviewed journal. The BD DSD will be revisited if compelling new data become available.

2) EPA advocates the use of a lower more health protective value and use of a different level introduces inconsistency within the state.

104. **Comment:** The state is proposing to use a different 1,3-butadiene air standard than that used and advocated by the EPA. The state's value is: less conservative than the EPA's . . . Neither EPA IRIS nor EPA OAQPS has plans to change the 1,3-butadiene IUR values . . .

Response: The EPA IUR (inhalation unit risk) is outdated because it is based on an older epidemiological study with less accurate BD exposure estimates (Delzell 1995, 1996). The TCEQ IUR is based on the updated epidemiological studies conducted by the UAB researchers. Refer to Section 4.2.2 *Epidemiological Studies and Exposure Estimates* for a discussion of the advantages of the updated epidemiology study. All the external expert peer reviewers commented that the updated epidemiological studies conducted by the UAB researchers were superior to the outdated epidemiological studies used by EPA (Delzell 1995, 1996). In addition, refer to Section 4.2.6 *Comparison of TCEQ's URF to USEPA's URF*.

On January 19, 2007, the North Carolina Science Advisory Board recommended that North Carolina's acceptable ambient level (AAL) for BD be increased from 0.17 µg/m^3 to 1.28 µg/m^3 at a risk level of 1 x 10^{-6} risk (http://www.ncair.org/toxics/risk/sab/ra/1-3-butadiene_final.pdf) using the updated UAB epidemiological studies. USEPA's 1 x 10^{-6} risk air concentration is 0.03 µg/m^3 (http://www.epa.gov/iriswebp/iris/subst/0139.htm#carc). TCEQ's 1 x 10^{-6} risk air concentration would be 2.0 µg/m^3 based on the IUR in the final BD DSD, which is similar to North Carolina's AAL level.

Science and risk assessment continuously advance. The lack of an updated carcinogenic assessment by USEPA should not prevent TCEQ (or North Carolina) from deriving a more scientifically-defensible IUR based on a comprehensive, up-to-date, and external expert peer-reviewed scientific assessment of the carcinogenic potential of BD, using established scientifically-defensible procedures.

Use of a lower air concentration is not necessarily more health protective as risk calculations are based on theoretical risk at exposure levels significantly less than those at which increases in cancer known to be due to chemical exposure have actually been observed in epidemiological studies, and the actual risk at environmentally relevant concentrations may be as low as zero.

105. **Comment:** The state's value is: . . . not based on local cancer incidence

Response: There are no scientifically-defensible epidemiological studies on local cancer incidence available that can be used to perform dose-response analyses and develop an IUR for BD. The UTSPH report is a pilot study, is flawed, and is inadequate for use in quantitative risk assessment.

106. **Comment:** The state's value is: . . .will result in inconsistent regulation within Texas

Response: It is common to find different toxicity values for the same chemical among the federal and state agencies that develop them. The consistency that the Toxicology Section (TS) strives to achieve is that of always using the best available science in the derivation of toxicity values.

107. **Comment:** The 1,3-butadiene concentration corresponding to the EPA IUR is, for risk level of 1x10^{-5}, is 0.15 ppb and the TCEQ proposes to use 4.5 ppb at the same risk level. The proposed TCEQ number is 30x less conservative than what EPA advocates.

Response: The proposed TCEQ carcinogen-based ESL is 9.1 ppb based on a risk level of $1x10^{-5}$. The value of 9.1 ppb will be used to evaluate ambient air monitoring data. The noncarcinogenic $^{chronic}ESL_{nonlinear(nc)}$ of 4.5 ppb is used for review of air permits (HQ = 0.3), but is not used to evaluate monitoring data. The cancer risk level corresponding to the noncarcinogenic $^{chronic}ESL_{nonlinear(nc)}$ concentration of 4.5 ppb (protective of reproductive effects) is 5×10^{-6}.

The TCEQ's carcinogen-based ESL of 9.1 ppb is based on more recent, scientifically defensible epidemiological data. Please refer to Section 4.2.2 *Epidemiological Studies and Exposure Estimates* for a discussion of the advantages of the updated epidemiology study. All the external expert peer reviewers commented that the updated epidemiological studies conducted by the UAB researchers were superior to the outdated epidemiological studies used by EPA. The EPA IUR is outdated because it is based on an older, less well-conducted epidemiological study. The reasons for the differences between the TCEQ's and EPA's IURs (i.e., unit risk factor (URF)) are discussed in Section 4.2.6 *Comparison of TCEQ's URF to USEPA's URF*. The TCEQ number is scientifically defensible and is appropriately less conservative than EPA's value because it is based on better data which indicate that BD is not as potent a carcinogen as predicted by the older epidemiological studies with less accurate BD exposure estimates used by EPA (2002).

108. **Comment:** In addition, EPA Superfund sites within the state will be assessed using the IUR from EPA IRIS and OAQPS of $3x10^{-5}$ b/($\mu g/m^3$) but at the screening level the risk of 1×10^{-6} including exposure parameters is used . . . EPA Region 6 screening level 1,3-butadiene concentrations for air for Superfund sites is 0.04 ppb for residential exposure and 0.18 ppb for industrial exposure. . . .

Response: Regardless of the IUR used by TCEQ, there are differences between TCEQ and USEPA in how potential health risk is assessed and addressed at federal and state superfund sites. Screening level differences between agencies (e.g., TCEQ, USEPA, ATSDR) are common due to differences in the methodologies/equations contained in state and federal rules and guidance, target risk levels, and toxicity factors. Although USEPA uses a target risk of $1x10^{-6}$ to calculate screening values, it is TS's observation that action at federal superfund sites is typically taken based on a higher risk level. For example, USEPA may choose not to take action unless the risk from a given chemical in an environmental medium (e.g. soil) exceeds $1x10^{-4}$, or even higher, whereas action would be required under the TCEQ rule (Texas Risk Reduction Plan) for a chemical with a risk above $1x10^{-5}$.

3) Studies referenced in the DSD to support the higher carcinogenic ESL are flawed.

109. **Comment:** Page 8, Figure 1. The source of the data for the national average for urban/suburban areas in the Measured Ambient Concentration (ppb) block is not referenced . . .Furthermore, a more suitable metric for the DSD would be ambient concentrations for Texas with a separate measure for Harris County.

Response: The purpose of the DSD is not an exposure assessment for the Texas general population, but a toxicity assessment, which involves hazard identification and dose-response modeling, resulting in the development of toxicity factors. Figure 1 is not a necessary component of the DSD, but is provided for informational purposes. Figure 1. *BD Health Effects and Regulatory Levels* has been modified to include the references for the ambient concentrations. The BD air concentration ranges are from Section 2.6 of USEPA (2002) and include values for Texas. There are different databases, such as NATA, that provide modeled BD air concentrations or USEPA AirData (http://www.epa.gov/air/data/index.html) that provide measured BD air concentrations reported from monitors throughout the nation:

Range of Year 2007 Arithmetic Mean Concentrations (ppbv) of 1,3-Butadiene by Location Type
Source: USEPA AirData, http://www.epa.gov/air/data/index.html

Geographic Area	Location Type Assigned to Monitoring Site					
	Rural	Suburban	Urban & Center City	Unknown	Not Reported
USA	0.01 to 0.15	0.01 to 0.34	0.01 to 1.57	0.01 to 0.02	0.02 to 1.04
TX	0.01 to 0.02	0.01 to 0.33	0.02 to 1.57	no data	0.04 to 1.04
Harris County	no data	0.12 to 0.27	0.03 to 0.26	no data	0.24 to 1.04

Each of these databases provide values in the same ballpark, as noted in comments from the City of Houston. Separate values for individual counties will not be provided in the DSD, although the above ranges of mean BD concentration by location type indicate that Harris County does not have the highest measured BD values in Texas.

110. **Comment:** The caption in Figure 1 states "USEPAs current acceptable cancer risk range (is) based on an outdated epidemiology study." The SEER study published in 2001 analyzes data from 1973 to 1998 and is the latest report cited on EPA's IRIS website . . .

Response: This comment suggests a lack of understanding regarding what a SEER study represents. A SEER study (Surveillance Epidemiology and End Results) provides data on cancer statistics (i.e., incidence and mortality rates). It is not an epidemiology study and does not evaluate the association of specific chemicals (or exposure concentration estimates) with specific diseases. The SEER database does not provide the information needed to perform dose-response analyses for a specific chemical. The TCEQ obtained US mortality and incidence rates for 2000-2003 for all leukemia from the 2006 SEER database (see Appendix 4 from the DSD). Air concentrations were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988) and data from the 2006 SEER database.

111. **Comment:** The TCEQ uses re-analyses of the UAB study originally conducted on workers from 1943-1991 to update the USEPA 2002 assessment. If there are "no other epidemiology studies that would be appropriate to evaluate human cancer risk from BD exposure," is data collected only as late as 1991 sufficient to revise the ESL in 2008?

Response: USEPA (2002) used the original UAB epidemiology study (Delzell *et al.* 1995; 1996) to develop their IUR. Numerous epidemiology studies were reviewed, but USEPA (2002) concluded the UAB exposure estimates provided the best published set of data to evaluate human cancer risk from BD exposure. The original UAB epidemiology study was not just reanalyzed, additional information was added. The original UAB epidemiology study included workers through 1991, but the updated study provided seven more years of follow-up (through 1998), a larger number of decedents, and a total of 81 deaths with leukemia as the primary or contributing cause. In addition, exposure estimates were updated (Macaluso *et al.* 2004) and validated (Sathiakumar *et al.* 2007). Based on the validation study of Sathiakumar *et al.* (2007), the updated exposure estimates of Macaluso *et al.* (2004) have a higher confidence than original exposure estimates used by EPA. The TS believes the updated studies are superior to the original studies, and the external expert peer review panel agreed that the updated UAB epidemiology studies were the most appropriate studies to use to estimate the IUR for BD for the reasons stated in Section 4.2.2 *Epidemiological Studies and Exposure Estimates.* It takes a great deal of time to gather necessary information on workers, organize and analyze the data, perform statistical analyses, write up the results, submit results for publication, and get the results peer-reviewed.

Therefore, data collected only as late as 1998, which represents a current assessment, is sufficient to revise the ESL in 2008. The updated UAB epidemiological studies are high quality studies.

112. **Comment:** The City advocates lowering the ESL to the EPA recommended values and believes that revising the ESL to a higher concentration based on the re-analyses of this older data is a mistake.

Response: See response to Comment #104.

113. **Comment:** "Cheng *et al.* (2007) results support the presence of a relationship between high cumulative exposure and leukemia and high intensity of exposure and leukemia." A reanalysis of a worker mortality study is not an appropriate surrogate for risk to the community. . . These types of worker studies are limited in detecting incidence of leukemia due to the healthy worker effect.

Response: The uncertainty involved in using a worker mortality study to estimate risk to the community is discussed throughout the uncertainty section, but specifically in Section 4.2.5.1 *Estimating Risks for other Potentially Sensitive Subpopulations* and Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence.* Epidemiology mortality studies of workers have been used as a basis for risk assessments for the general public for several chemicals such as benzene, nickel, arsenic, silica, etc., despite the potential for healthy worker effect. There is less uncertainty in using well-conducted human epidemiological studies than using animal cancer studies to predict risks to humans. Conservative default assumptions were used to develop the BD IUR as discussed in the BD DSD and also in the bulleted items for response to comment #115).

114. **Comment:** Additionally, worker exposure is based on an 8-hour work day whereas residents are exposed for a much longer time period each day.

Response: Section 4.2.3.2 *Dosimetric Adjustments* provides the calculations that convert occupational concentrations to environmental concentrations protective for the general population following accepted guidelines, (i.e. USEPA (1994)). Worker concentration exposures for an 8-h day, based on a ventilation rate of 10 m^3/day, were converted to a 24-h concentration protective for the general population by the use of a ventilation rate of 20 m^3/day. In addition, the 5 days/week for an occupational exposure was converted to 7 days/week, which is protective of the general population. The carcinogenic ESL is protective and assumes a person is continuously exposed 24 h/day, 7 days/week for 70 years.

115. **Comment:** Workers who had contracted leukemia, diagnosed or not, would not be counted unless they had died. . . When determining an ESL, the outcome to be measured should be incidence of disease, not mortality. Therefore, if incidence had been measured in the Cheng or Delzell studies, the number of workers with leukemia would likely have been much higher.

Response: It is not necessarily true that using mortality data underestimates the excess risk of leukemia incidence. Refer to response to comment #8 and #9 (panel teleconference comments). Section 4.2.5.5 *Use of Mortality Rates to Predict Incidence* discusses the uncertainty in using mortality rates to predict incidence. The IUR may be biased by a factor of 1.8-fold less conservative. However, the IUR is considered to be sufficiently health-protective because the following conservative default procedures were followed in the calculation of the preferred IUR of 1.1E-03 per ppm:

- A linear default was used to extrapolate to lower concentrations instead of using the log-linear Cox regression model to calculate the 10^{-5}-risk air concentrations, approximately 1.2 fold more conservative (Table 17);
- The IUR (95% UCL) was used instead of the IUR (MLE), approximately 1.4 fold more conservative (Table 17). The confidence intervals are indicators of the variability, and to some extent the uncertainty, in the dose-response curve for mortality. The risk of incidence will be lowered since using the IUR (95% UCL) adds conservatism to the estimate;
- Data restricted to the lower 95% of the exposure range was used, ranging from 4-to 5-fold more conservative when compared to unrestricted data (Section 4.2.5.3);
- Model did not adjust for the exposure to number of high intensity tasks > 100 ppm that occur in occupational exposure but not in environmental exposures (Section 4.2.5.2). The IUR would be 1.1-fold less conservative if exposure to number of high intensity tasks > 100 ppm were included; and
- Model was based on the average BD concentration estimated by Macaluso *et al.* (2004) and did not incorporate the correction to the exposure estimates suggested by Sathiakumar *et al.* (2007) (Section 4.2.5.3 and Appendix 7).

Therefore, the total conservatism is much greater than the possible 1.8-fold bias that may have resulted from the use of mortality data.

116. **Comment:** Although TCEQ accounts for differences in a worker mortality study and risk to a general population through numerical adjustments and models, it is not clear that the data used to establish the models or adjustment factors is sufficient to capture the variables that can occur within a community.

Response: The workers in the UAB cohort were exposed to much higher BD concentrations than the general public and were exposed to even higher peak exposures of BD when they participated in high intensity tasks. Therefore, the likelihood of workers developing leukemia is much greater than the general population exposed to much lower concentrations. The IUR is considered to be sufficiently health-protective because conservative default procedures were followed in the calculation of the preferred IUR of 1.1E-03 per ppm. These conservative default procedures are discussed in the DSD and listed in the bulleted items in response to comment #115. Also, refer to bulleted items in response to comment #101 for a discussion of epidemiological studies that examine risk at lower BD concentrations than BD-exposed workers in the UAB cohort.

117. **Comment:** Therefore, the City suggests that the TCEQ develop an appropriate epidemiology study in the Houston-Galveston area to answer these questions.

Response: The weight of evidence from epidemiological studies indicate the risks from exposure to low concentrations of BD experienced by the general population are within the acceptable risk range. Refer to bulleted items in response to comment #101. When the more comprehensive UTSPH study funded by the NIH becomes available, the TS will review it. Hopefully, this study will be submitted for publication in a peer-reviewed journal. The BD DSD will be revisited if compelling new data become available.

118. **Comment:** Page 53. second paragraph. “Toxicokinetic and toxicodynamic evidence indicates children are not more susceptible to chemical leukemogenesis than adults for acute myeloid leukemia and acute nonlymphocytic leukemia . . . Inhalation studies should be used when

determining an air concentration limit. This statement may be true for toxicokinetic and toxicodynamic evidence where cancer patients contract leukemia from chemotherapy, but the DSD is addressing inhalation exposure, not oral or intravenous injections. Epidemiological studies would make the better comparison as in the UTSPH study above.

Response: Inhalation studies were used to determine the air concentration limit, and Section 4.2.4.1 *Evaluating Susceptibility from Early-Life Exposures* provides the results when applying age-dependent adjustment factors (ADAFs) to account for the potential increased susceptibility of children as suggested by USEPA (2005). The studies reporting evidence where children cancer patients undergoing chemotherapy are not more susceptible than adults for acute myeloid leukemia and acute nonlymphocytic leukemia are provided because these results should be considered in the overall weight-of-evidence analysis and to be informative and thorough. ADAFs were used to calculate air concentrations protective of children with life-table analyses using the BEIR IV approach (NRC 1988) and data from the 2006 SEER database.

119. **Comment:** Children are affected more than adults by 1,3-butadiene exposure and leukemia. The UTSPH study discussed in Section 1 above indicates a relationship with higher 1,3-butadiene levels (> 1.15 ppbV vs. < 0.266 ppbV) and acute lymphocytic leukemia, acute myeloid leukemia and all leukemias.

    Response: The UTSPH study discussed in Section 1 is an ecological study design that used group data rather than individual data and did not adjust for race/ethnicity differences in background cancer rates. The study is a preliminary epidemiological study and should be viewed as such. Therefore, the study does not demonstrate that children are more affected than adults by BD exposure as the study does not demonstrate a cause-and-effect relationship, only associations. Refer to bulleted items in response to comment #101 for other epidemiological studies.

120. **Comment:** In the UTSPH study, the same associations with 1,3-butadiene and leukemias in children were not found for adults. However, when distance from the Ship Channel was examined, a significant increasing trend of acute myeloid leukemia in males was detected with proximity to HSC. It is likely then, that if specific types of leukemias had been analyzed in the Delzell studies that associations at lower butadiene concentrations may have been detected.

    Response: The original Delzell studies (Delzell *et al.* 1995; 1996) did not examine specific types of leukemias. However, specific types of leukemias were studied in the updated epidemiologic studies. The association of BD exposure with leukemia, lymphoid neoplasms, and myeloid neoplasms was investigated by both Cheng *et al.* (2007) and Sielken *et al.* (2007). Lymphoid neoplasms in workers were associated with ppm-years and myeloid neoplasms in workers were associated with number of high intensity tasks > 100 ppm in models that controlled only for age, but not after adjusting for multiple covariates (age, year of birth, race, plant, years since hire and dimethyldithiocarbonate exposure). These potency estimates were not used by the TS because evidence of an association between BD and all lymphoid neoplasm or all myeloid neoplasms was not persuasive (Cheng *et al.* 2007; Sielken *et al.* 2007). That is, for myeloid neoplasms, the association with BD exposures disappeared after adjusting for the various covariates.

121. **Comment:** Page 55, 4.2.5.2 Estimating Risks for the General Population from Occupational Workers. “No reliable data” claim in Grant paper is an incorrect use of terminology. TCEQ bases their claim that “There are no reliable data linking BD exposures at low concentrations typical for the general population to increased mortality from any cause in Texas” on the TDSHS report referenced in the Grant *et al.* paper. However, there are problems with the

TDSHS report. . . .

Response: The potential problems with the TDSHS report are discussed in Grant *et al.* (2007). However, the Grant *et al.* (2007) paper does not rely only on the TDSHS report but also discusses the Donelson (1980) study evaluating the association of exposure in female graduates of the Port Neches-Grove High School located downwind of a styrene-BD manufacturing facility and the more comprehensive Loughlin *et al.* (1999) study that extended the Donelson study to include men and students for the school years 1963-64 to 1992-93 for a cohort of 15,403 students. Neither study found evidence of an excess of lymphatic and haematopoietic cancer due to an environmental effect:

- R.K. Donelson, Female Mortality from Lymphatic and Hematopoietic Neoplasm in a High School near Industrial Plants Producing Styrene Butadiene Rubber, 1964-1978, Department of Health, Austin, July 8, 1980;
- J.E. Loughlin, K.J. Rothman, N.A. Dreyer, Lymphatic and haematopoietic cancer mortality in a population attending school adjacent to styrene-butadiene facilities, 1963-1993, J. Epidemiol. Community Health 53 (1999) 283-287.

122. **Comment:** Therefore, a more accurate statement would be that there is insufficient data, not "no reliable data," linking BD to mortality from "any cause" in Texas.

Response: The original sentence has been revised from:

"There are no reliable data linking BD exposures at low concentrations typical for the general population to increased mortality from any cause in Texas (Grant *et al.* 2007)."

To:

Epidemiological studies in Texas at sites downwind of facilities that produce styrene-butadiene rubber that investigated BD exposures and increased mortality from any cause at low concentrations typical for the general population have not found a significant association between mortality from leukemia and potential BD exposure, although there are only a few epidemiology studies that have been conducted (reviewed by Grant *et al.* 2007).

123. **Comment:** Cumulative risk from other carcinogenic air toxics prevalent in Houston is not considered in ESL development.

Response: Toxicity factors are developed based on scientifically-defensible and accepted practices. However, cumulative risk from air toxics is discussed in RG-442 ESL Guidelines (TCEQ 2006). Please refer to Section 1.2 *Consideration of Cumulative Risk*, Section 1.3 *General Risk Management Objectives*, and Section 1.4 *Specific Risk Management Objectives (No Significant Risk Levels)* in the ESL Guidelines (TCEQ 2006). Specifically, in Section 1.4 the following information is provided:

> In consideration of cumulative and aggregate exposure, the Toxicology Section (TS) uses an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with a nonlinear dose-response assessment. The TS uses a risk management goal of 1×10^{-5} to calculate long-term ESLs for individual chemicals with a linear dose-response assessment. Further adjustment of this no significant risk level is not necessary since few chemicals with a linear dose-response assessment are routinely permitted in Texas. These risk management goals were approved by the Commissioners and

Executive Director of the TCEQ and are consistent with other TCEQ programs. ESLs developed in accordance with these no significant risk levels are intended to prevent adverse effects potentially associated with cumulative and aggregate exposures as defined in Section 1.2.

124. **Comment:** Use and purpose of the ESL is not consistent with the risk level used to develop the ESL.

Response: This comment does not relate to the development of toxicity factors, but refers to policy decisions and uses of ESLs, as outlined in the RG-442 ESL Guidelines (TCEQ 2006), which underwent two public comment periods and an external scientific peer-review process.

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APPENDIX A: TCC Comments August 28, 2007

TEXAS CHEMICAL COUNCIL
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August 28, 2007

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re:

Texas Chemical Council Comments Regarding the 1,3-Butadiene Effects Screening Level Development Support Document

TCEQ Toxicology Section:

The Texas Chemical Council (TCC) submits these comments in response to the Texas Commission on Environmental Quality's (TCEQ) request for public comments on its Effects Screening Level (ESL) Development Support Document concerning 1,3-Butadiene.

The Texas Chemical Council is a statewide trade association representing approximately 85 chemical manufacturers at over 200 Texas facilities. Our industry has invested more than $50 billion in physical assets in the State and pays over $1 billion annually in state and local taxes. TCC's members provide approximately 70,000 direct jobs and over 400,000 indirect jobs to Texans across the State.

TCC appreciates the opportunity to comment on the ESL values for 1,3-Butadiene. TCC understands the importance of ESLs in providing the TCEQ with guidance to protect human health and welfare regarding its authority for air permitting and air monitoring. Air quality is also important to the regulated community, particularly to members of TCC.

In general, TCC believes the Draft Development Support Document for 1,3-Butadiene is scientifically sound and demonstrates the diligence of the TCEQ to recommend supportable values. However, we do believe that TCEQ was overly conservative on a few key scientific issues which affect the chronic ReV, the URF and ultimately the chronic ESL value. The attached comments briefly discuss these risk assessment issues that would impact the chronic ESL value. By offering the following comments, TCC hopes to provide perspectives to enhance the scientific basis of the ESL values for 1,3-Butadiene.

Again, TCC appreciates the opportunity to comment on this important document and looks forward to future discussions with the TCEQ.

Sincerely,

Gregory S. Merrell

Gregory S. Merrell
Texas Chemical Council
Director of Regulatory Affairs

Texas Chemical Council (TCC)

Comments Regarding the TCEQ Development Support Document for 1,3-Butadiene ESL Values

1.0 The statement (page 16) that some humans might be as sensitive as mice is not supported by the current literature, which is quite extensive.

The Development Support Document correctly discusses the importance of metabolism to the toxicity of 1,3-Butadiene, and summarized the very significant species differences in metabolism, particularly differences between mice and humans. The Development Support Document also reviews some available data pertaining to human polymorphisms with respect to enzymes important for metabolism of 1,3-Butadiene. While polymorphisms are important and have been characterized, the Development Support Document overstates the nature of human variability by concluding *'activation rates in humans exhibit a high degree of variability and appear to span the range of activation rates between mice and rats, so humans might be as sensitive as mice.'* The suggestion that some humans might be as sensitive as mice is clearly not supported by the extensive scientific information that is available. Attached is a review of the literature on species differences, and polymorphisms in humans, with regard to butadiene and importantly the impact on biologically important genotoxicity endpoints. This review was prepared by Dr. Richard Albertini. Dr. Albertini concluded that the difference in metabolism due to polymorphisms is, at most, a factor of 2 or 3. Most studies have failed to find genetic effects of butadiene exposure in human populations and the few studies where such effects are reported, have shown only a 2 to 3.5 fold difference with polymorphisms. These differences are covered by the intraspecies uncertainty factor of 10 used by TCEQ.

"Albertini - POLYMORPHISMS IN

2.0 The Chronic ReV and ESL based on ovarian atrophy in mice includes an interspecies uncertainty factor of 1. While this is directionally correct with respect to the use of a data based alternative to default uncertainty factors, in this instance a factor of less than one would be supported by available literature.

As indicated in the Development Support Document as well as in the report by Dr. Albertini discussed above, the mouse makes significantly more of the diepoxide metabolite of 1,3-Butadiene than rats or humans. TCEQ cites a difference of 78 fold between mice and humans based on the hemoglobin adduct data. Dr. Albertini's review notes that mice are at least 10 times more sensitive than humans with regard to metabolite production. Because the diepoxide is the recognized metabolite of importance to ovarian atrophy, and production of the diepoxide in mice is documented to be more than 10 fold higher than in humans, an uncertainty factor of less one should be used.

3.0 The available evidence would not support the inclusion of an early life correction factor for 1,3-Butadiene.

The Development Support Document concluded that 1,3-Butadiene is a chemical which is acting though a mutagenic mode of action for carcinogenesis, and therefore included a correction for children. This might be consistent with the TCEQ Guideline as well as with the EPA's guidance regarding early-life exposures

to carcinogens[1] as a default position, but in the case of 1,3-Butadiene this is not justified.

Although the cancer risk is derived from data for adult workers, their application to childhood exposures is expected to be adequately protective, even without adjustment. There is both toxicokinetic and toxicodynamic support for this view. With respect to toxicokinetics, the ontogenesis of CYP2E1 in developing humans has been well studied. Activity is generally absent in fetal liver during the first trimester, but is seen at low levels during the second and third trimesters (Johnsrud *et al.*, 2003). Levels increase after birth, but generally remain low (compared to levels in adults) during the neonatal period. CYP2E1 levels show a clear trend gradually increasing with age such that the fetus (0.35 – 6.7 pmol/mg protein) < nonate < older infants (8.8 pmol/mg protein) < children (23.8 pmol/mg protein) < young adults (41.4 pmol/mg protein). Because butadiene must be activated by CYP2E1 to the genotoxic form, and is not genotoxic itself, children would be expected to produce less metabolites than adults. Thus, basing the risk assessment for children on studies of adults is adequately protective, without the need for an additional factor. Regarding the toxicodynamics, data for human leukemia indicate that, with respect to early-life susceptibility, younger children appear to be less susceptible to leukemia of unknown origin than older children, who in turn are less susceptible than adults (Levine and Bloomfield, 1992; USEPA, 1997). More recently, Pyatt et at., (2005) reported that children do not appear to be at increased risk of AML following exposure to alkylating agents or topoisomerase-reactive drugs. Thus, TCC believes there is strong scientific basis for concluding that children are not likely to be at greater risk than adults for leukemia following exposure to butadiene and thus an adjustment for childhood susceptibility is not needed in the butadiene risk assessment to adequately protect children.

4.0 The Development Support Document overstates cancer risk by using the upper confidence level instead of the most likely estimate.

Historically, EPA has used the MLE (maximum likelihood estimate) when deriving unit risk factors (URFs) from human data, and the new cancer risk assessment guidelines do not offer any scientific rationale for changing that policy, nor is it even clear from the new cancer risk assessment guidelines that this issue was addressed during the external peer review of the new cancer risk assessment guidelines. TCC believes that use of the MLE is scientifically appropriate in most cases for URFs derived from human data, and that the upper confidence limit (UCL) should be used with human data only where substance-specific justification is presented.
In this case, in particular, given the strength of the underlying study, TCC believes use of the MLE is scientifically appropriate and protective of human health. If the UCL is used, then TCC believes the final document should recognize the element of conservatism inherent in that approach. Further, if the UCL is used, then that decision would represent another reason why an adjustment factor for childhood exposure would not be scientifically necessary. Specifically, given that the scientific evidence (described above) demonstrates that children are likely to be less susceptible than adults, rather than more, there is no scientific rationale for believing that use of the UCL derived from exposed workers would not be fully protective of children.

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Polymorphisms in Metabolic Genes: Relevance for Human Susceptibility to Butadiene

Richard J. Albertini
August 24, 2007

Introduction

The Texas Commission on Environmental Quality (TCEQ) Risk Assessment correctly states that:

> *"Human genetic polymorphisms are likely to affect individual susceptibility to butadiene (BD) and its metabolites. Activation rates in humans exhibit a high degree of variability and appear to span the range of activation rates between mice and rats, ----------" (p.16, lns 22 - 24).*

However, the assessment then goes on to speculate on the effects of these polymorphisms:

> *" ------ so humans may be as sensitive as mice (p.16, ln 24).*

This speculation appears to be based solely on the range of variability of the various enzyme activities, *as measured by in vitro analyses of enzyme kinetics*, and does not take account of the abundant literature that deals with the metabolic and genotoxic consequences of these polymorphisms, as measured in human cells *in vitro* and metabolic and genotoxic biomarkers determined *in vivo.* The relevant literature is reviewed here.

In order to compare humans to mice, and to speculate as to whether any humans can be as sensitive as mice to the gentoxic (and therefore, carcinogenic) effects of BD, it is first important to identify the magnitude of the differences between these species for the metabolic and genotoxic (presumably reflecting carcinogenic) consequences of BD exposures.

Mouse-Human Inter-Species Comparisons

Metabolic endpoints will be considered first, followed by genotoxic consequences.

Metabolism

As regards oxidative metabolism of BD to its most genotoxic metabolites (mediated by P450 enzymes, especially CYP2E1), mice greatly predominate over humans, as measured by the accumulation of 2-hydroxy-3-butanyl-valine (HBVal; 1,2-epoxy3-butene [EB] derived) and N,N-(2,3-dihydroxy-1,4-butadyl)-valine (*pyr*-Val; 1,2:3,4-diepoxybutane [DEB] derived) hemoglobin adducts in the two species. Comparing mice exposed to 1.0 ppm BD by inhalation for four weeks to humans exposed to an average of 0.8 ppm BD by inhalation for several years showed a *pyr*-Val adduct concentration of between 20 to 30 pmol/g globin (males versus females) in the mice while, for humans, this DEB specific adduct was NOT QUANTIFIABLE (Boysen *et al.* 2007, Albertini *et al.* 2007). Therefore, for this most genotoxic of BD metabolites, the metabolic difference between mice and humans is infinity, using this particular *pyr*-Val assay. Assuming some insensitivity in this assay, an upper bound of the fold-difference between these

species for DEB production can be estimated to be greater than 10.

EB production, as determined by HBVal adduct concentrations, was not estimated in the mice exposed to 1.0 ppm BD, but an earlier study exposing mice to 3.0 ppm showed that HBVal adduct concentrations were approximately the same as the *pyr*Val adduct concentrations (Boysen *et al.* 2004). The humans exposed to 0.8 ppm BD showed a HBVal adduct concentration of 2.2 pmol/g globin (Albertini *et al.* 2001, 2003). Therefore, using the *pyr-Val* concentration as a surrogate for the HBVal concentration in mice exposed to 1.0 ppm (estimating ~ 25 pmol/g globin HBVal), the fold-difference in EB production for mice compared to humans can be estimated as also being somewhat greater than 10.

Detoxification of BD metabolites (as opposed to oxidative metabolism) is measured *in vivo* by conjugation and hydrolysis products. The urinary metabolites 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 2-hydroxy-1-(N-acetylcysteinyl)-3-butene (collectively known as M2 metabolite) are indicators of the percentage of detoxification that occurs using the Glutathione-S-transferase (GST) mediated conjugation pathway. In mice, approximately 77% of BD detoxification occurs via this route (Bechtold *et al.,* 1994). By contrast, in humans, only 1 to 3% of detoxification utilizes this conjugation pathway (Albertini *et al.* 2001, 2003, 2007). Hydrolysis, however, which is mediated by epoxide hydrolase (EH), is greatly enhanced in humans compared to mice. Approximately 97-99% of detoxification occurs by this pathway, as judged by urinary 1,2-dihydroxy-4-(N-acetylcysteinly)-butane (M1 metabolite) concentrations (Albertini *et al.,* 2001, 2003, 2007). In mice, this pathway accounts for approximately 23% of the detoxification (Bechtold *et al.,* 1994). The concentration of the 1,2,3-trihydroxybutyl-valine (THBVal) hemoglobin adduct, which is derived from 1,2-dihydroxy-3,4-epoxybutane (EBD), also reflects hydrolytic detoxification of BD metabolites, and is higher in humans than mice at the various levels of BD exposure (Boysen *et al., 2004,* Albertini *et al.,*2001, 2003).

Mutation Induction

Important inter-species comparisons between mice and humans are those for irreversible genotoxic effects, i.e. gene and chromosome level mutations. Mice show statistically significant increases in *Hprt* gene mutations at an exposure level as low as 1.0 ppm BD for four weeks (where the *pyr*-Val adduct concentrations were also measured, see above) (Meng *et al,* 2007). By contrast, with the exception of a single laboratory studying Texas BD facilities (Legator *et al.* 1993, Ward *et al.,* 1994, 1996, 1997, 2001, Ma *et al.,*2001, Ammenheuser *et al.* 2001, Abdel-Rahman *et al.* 2001, 2003, 2005), several large multi-institution studies involving many laboratories to study facilities at different locations have failed to find increases in *HPRT* gene mutations at any level of BD exposure (Tates *et al,* 1996, Hayes *et al,*1996, 2000, 2001, Zhang *et al,* 2004, Albertini *et al,* 2001, 2003, 2007).

Reasons for the discordant results between the Texas laboratory and all of the others are not known. The Texas group has employed a variant of the *HPRT* assay (autoradiography) while the others have used a more conventional cloning assay. Results of the two assays, however, while possibly measuring events in different cell sub-populations, should be in the same direction. Furthermore, the Texas laboratory was a collaborator in one of the comprehensive Czech studies (see below), where they too failed to show increases in *HPRT* mutations in exposed workers using autoradiography. Close inspection of the Texas data (different aspects reported in the several references given above) suggest some potential for confounding, as indicated by differences in group mean mutant frequencies in different worker groups having different mean BD exposure levels that were not reflected by within group associations of mutant frequencies with individual exposure levels. Nonetheless, the differences between the Texas results and the others remain to be explained.

An NIH study in China, in which the highest individual BD exposure levels have been reported, not only

failed to find an increase in *HPRT* mutations, it failed also to find an increase in Glycophorin A gene mutations (Hayes, 2001, 2003, Zhang *et al.* 2004). As noted, this study was multi-institutional, with the different mutation assays being conducted independently of each other. The two Czech studies were also multi-institutional, and also involved several different laboratories, each conducting its assays independently (Albertini *et al.* 2002, 2003, 2007). Both Czech studies employed extensive external exposure assessments, involving 8 to 10 individual 8 h worker measurements using personal monitors, occurring over a two to four month period prior to the collection of biological samples (to accommodate the time-lag requirements of the different biomarker assays). These studies included rigorous blinding, with the laboratories conducting the assays not knowing sample identities until after they had submitted their complete data sets to the data management facility, which was in a different location managed by different personnel disinterested in the study outcome. As noted above, the autoradiographic assay for *HPRT* mutations was included in the 1st Czech study to help resolve the conflict between the discordant results just described. There were no increases in *HPRT* mutation frequencies related to BD exposure in any of these studies.

Chromosome level mutations (aberrations and or micronuclei) have been found whenever looked for in BD exposed mice (Himmelstein *et al.,* 1997). Similar to the findings for *HPRT* gene mutations, these genotoxic lesions have not been found in humans. A single study that originally reported an increase in mean aberration frequencies (Tates *et al.* 1996, with definitive report by Sram *et al.* 1998), subsequently found the aberration frequencies did not correlate with BD exposure levels, as measured by DNA adduct levels, and therefore were influenced by other factors (Zhao *et al,* 2001). Numerous other studies have failed to find significantly elevated mean levels of chromosome aberrations in groups of BD exposed humans (Au *et al.,* 1995, Hallberg *et al.,* 1997, Sorsa *et al,* 1994, 1996, Zhao *et al.,* 2001, Hayes *et al.,* 1996, 2000, 2001, Warholm *et al.* 2003, Fustinoni *et al.,* 2004, Albertini *et al.,* 2001, 2003, 2007), although the Sorsa *et al.*1996 paper did report differences according to GST genotypes (see below) and a single poster report did indicate a significant correlation among workers between chromosome aberrations and BD exposure levels, as assessed by surrogate urine metabolite and hemoglobin adduct measurements (Warholm *et al.* 2003). [It is noteworthy that this poster report was not cited by one of the authors, who subsequently reviewed the several chromosome studies in her report of a negative study (Fustinoni *et al.* 2004)]. Increases in chromosome level mutations relative to BD exposure levels were not found in any of the large, multi-institutional studies.

Comparisons of the magnitudes of the differences in *sensitivity* to BD exposure between mice and humans, therefore, range from a factor in excess of 10, for metabolic endpoints, to nearly qualitative differences (magnitude near infinity), for the different genotoxic endpoints. The greatest differences have been observed for production of the DEB metabolite, as assessed by *pyr*-Val hemoglobin adduct concentrations, and for the biomarkers of irreversible genotoxic effects such as gene mutations and chromosome aberrations. It is these latter that most likely serve as indicators of the kinds of genotoxicity that underlies carcinogenesis. These mouse-human inter-species comparisons provide a context for assessing the magnitude of intra-species differences in BD *sensitivity*, as assessed in humans of different metabolic genotypes, as determined by a variety of biomarker responses in several studies.

Human Intra-Species Differences by Genotypes

The several studies of human intra-species differences by genotype have examined one of several of the following metabolic genetic polymorphisms in BD exposed humans:

- CYP2E1: Several genetic polymorphisms for this phase I activating enzyme have been identified in the various studies. The *RsaI* polymorphism encodes for alleles c1/c2 (c2 = high activity). The $G_{-35} \rightarrow T$ polymorphism encodes for a G wild-type and T variant allele, with the latter suggested to be associated with higher transcriptional activity. A 96 bp 5' flanking region repeat

polymorphism, and an A→T intron 6 polymorphism have also been studied, both of uncertain biological significance.

- Glutathione-S-transferases (GST): These are phase II enzymes that detoxify by conjugation. Polymorphisms of several GST genes have been studied. These include the wild-type and null alleles for the GST M1 and GST T1 genes, and the Ile→Val exon 5 substitution at residue 104 and the Ala→Val exon 6 substitution at residue 113 for the GST P1 gene. For GST M1 and T1, the null alleles are deficiency alleles: the biological significance of the GST P1 polymorphisms are uncertain. GST phenotypes (activity determined irrespective of genotype) are determined by various functional tests, such as the administration of chlorzoxazone and analysis of urinary metabolites.
- Microsomal epoxide hydrolysase (EH): This is a phase II enzyme that detoxifies by hydrolysis. Several polymorphisms have been studied. These include 5' flanking region polymorphisms: the -200 linkage group (200 C/T, -259 C/T, -290 T/G), the -600 linkage group (-362 A/G, -613 T/C, -699 T/C), and the independent -399 T/C. These flanking region variants may be associated with increases in gene transcription. The most frequent EH polymorphisms studied are the tyr→his exon 3 substitution at residue 113 and the his→arg exon 4 substitution at residue 139. The 113 his substitution results in a 40% decline in enzyme activity, while the 139 arg substitution produces approximately a 25% increase in activity. These polymorphisms can be combined to give combinations that result in fast, intermediate and low hydroxylation, which constitutes a phenotypic designation for the individual. These combinations are:
    - Fast hydroxylation: tyr/tyr (113) arg/arg (139, tyr/tyr (113); arg.his (139) and try/his (113), arg/arg (139).
    - Intermediate hydroxylation: tyr/tyr (113), his/his (139) and tyr/his (113), arg/his (139)
    - Slow hydroxylation: tyr/his (113), his/his (139); his/his (113), arg/his (139) and his/his (113) and his/his (139).
- Alcohol dehydrogenases (ADH): The ADHs constitute a family of genes that catalyze the oxidation of alcohols and ketones. The ADH 1 gene is not polymorphic; the ADH 2 and 3 genes are. Polymorphisms of both have been identified in BD studies. These are the arg → his substitution at residue 47 in ADH 2 and the Ile → val substitution at residue 349 in ADH3. Both substitutions result in lower enzyme activities compared to wild-type.

Metabolism

A study designed to measure dietary and genetic factors affecting human metabolism of BD in 133 normal human subjects (different races, sexes) exposed to 2.0 ppm BD by inhalation for 20 minutes (administered dose ~ 0.6 ppm h) measured BD uptake and calculated metabolic rates (K_{met}; oxidation) by use of PBPK modeling (Smith *et al.* 2001). CYP2E1 *RsaI* genotypes were determined by DNA analyses and CYP2E1 phenotypes determined by chlorzoxane administration and urine metabolite studies. No significant associations were found between either BD uptake or K_{met} and CYP2E1 genotypes or phenotypes.

Fustinoni *et al.* (2002) examined the relationship between several genetic polymorphisms and both urine M1 metabolite concentrations and THBVal hemoglobin adduct levels in 30 workers exposed to BD at very low levels (range = 0.002 to 0.09 ppm). CYP2E1 *RsaI*, G_{-35}→T and 96 bp repeat polymorphisms, EH113 and 139 polymorphisms, EH hydroxylation phenotypes, GST M1, T1 and P1 (104 and 113) polymorphisms and the ADH3 polymorphism were determined for all subjects. Individuals with either the GST M1 or T1 homozygous null genotype showed significantly higher THBVal adduct concentrations than did individuals not possessing this genotype, but the differences were small (< 10%). Workers with either the CYP2E1 GT_{-35} or the $T_{-35}T_{-35}$ genotypes had non-significantly lower concentrations of THBVal adducts (<20%) than did workers of the GG genotype. It is of interest that an examination of the influence

of hydroxylation phenotypes as indicated by combinations of EH polymorphisms (fast, intermediate, slow hydroxylation) did not show statistically the significant differences in THBVal adduct adduct that might have been predicted from the respective enzyme kinetics conferred by these different genotypes. However, there was only a single individual in the fast hydroxylation category, and the THBVal adduct concentration of that worker was approximately twice the median values for workers in the other two hydroxylation categories (intermediate and slow). Even if this single value is a valid approximation of the median for a group of fast hydroxylators, this would indicate an increase in hydroxylation (detoxification) by only a factor of two in such individuals. The only polymorphism that showed a suggested influence on urinary M1 concentrations was the GST P1 arg→ val substitution at residue 113, where the median urinary concentration of M1 was 73% higher than in workers with the other genotypes at this locus. The difference was not statistically significant, however. Combined analyses that included the GST M1 and T1 genotypes as well as the CYP2E1 G_{-35}→T showed that the THBVal adduct concentrations increased as a function of the number of these polymorphic genotypes that individually increase these adduct concentrations. However, even here, the greatest difference among individual workers with different combined genotypes was a factor of approximately two.

Two relatively small studies examined the influence of GST M1 and T1 polymorphisms on hydrolysis leading to EBD in BD exposed humans. In the study reporting negative results, the THBVal adduct concentrations in 17 BD workers, exposed to a median level of 0.2 ppm BD (range up to ~ 8.0 ppm), showed no relationship with GST M1 or T1 genotype (Begemann *et al.* 2001). In the other, reporting positive findings, N-1-(2,3,4-trihydroxybutyl) adenine (THB A) DNA adduct concentrations and GST M1 and T1 genotypes were analyzed in 15 BD exposed workers (range 0.05 – 8.0 ppm) (Zhao *et al.* 2000, 2001). The mean adduct level was significantly higher in the exposed workers than in a control, unexposed group, and in workers of the M1- (null genotype) compared to the M1+ (non-null genotypes). Fold-differences due to genotypes cannot be determined from these reports, however, because adduct concentrations relative to genotypes are given without corrections for BD exposures levels. (For example, although there is a > 25-fold higher THB A concentration in an individual with the M1-/T1- genotype compared with individuals with the M1+/T1+ genotype, there is only a single worker in the former group, and this worker is an outlier as regards BD exposure, having the highest measured external BD exposure level (8.0 ppm) (Zhao *et al.* 2000). Multiple linear regressions that accounted for BD exposure levels (and other factors) indicated that it was only the M1 genotype that was a significant factor determining adduct concentrations after accounting for BD exposures. It is of note, however, that THB A adduct levels were not positively correlated with chromosome aberration frequencies in this analysis (Zhao *et al.* 2001)

BD metabolic products measured in urine or as hemoglobin adducts have also been measured in three large, multi-institution molecular epidemiological studies, in which metabolic genotypes were also determined. In an NCI study in China, M1 urine metabolite concentrations and THBVal hemoglobin levels were measured in 41 workers exposed to a median BD concentration of 2.0 ppm (6 h TWA), ranging in the extreme to > 1000 ppm (Hayes *et al.,* 1996, 2000, 2001). Female as well as male workers were included in this study. GST M1 and T1 genotypes were also determined and were reported as having no effect on the metabolic endpoints. There were also no reported differences between the female and male workers.

Two comprehensive molecular epidemiological studies have been conducted in BD exposed workers in The Czech Republic. In the first, including 24 monomer production and 34 polymerization workers, extensive external exposure measurements indicated mean BD exposure levels (8 h TWA) of ~ 0.3 ppm and 0.8 ppms in the monomer and polymerization workers, respectively, with wide ranges in both groups (Albertini *et al.* 2001, 2003). Urinary M1 and M2 metabolites and HBVal and THBVal hemoglobin adducts, as well as CYP2E1 *SaI* and A→T intron 6, EH 113 and 139, GST M1 and T1 and ADH2 and ADH3 genotypes were determined. Genotypes were found to have some significant, but small, influences on the metabolic parameters. Conjugation detoxification, as indicated by the M2/ (M1 + M2) ratio of

urinary metabolites, decreased from 0.0143 to 0.009 in workers of the GST M1 null genotype (-/-) compared with workers of the other two genotypes (i.e. +/+ and +/-), a statistically significant difference. A similar decrease in this ratio was seen in workers of the GST T1 null genotype compared to workers with the other two genotypes (from 0.0134 to 0.006), but this difference failed to achieve statistical significance. The M2/(M1 + M2) ratio differences as a function of BD exposure level were seen at all levels of BD exposure. Of note, M2 levels in urine as a function of BD exposure concentrations were also greater in individuals heterozygous for the CYP2E1 intron 6 polymorphism than in individuals homozygous for the wild-type allele, a difference reflected in M2/(M1+M2) ratios as a function of exposure. In these same workers, hemoglobin adducts also showed significant but small, and sometimes inconsistent, associations with polymorphisms of the EH gene. Workers homozygous for the arg139 genotype (high activity allele) had lower HBVal (EB derived) hemoglobin adduct concentrations as a function of BD exposure levels than did individuals of the other two genotypes. However, workers homozygous for the his 139 genotype (low activity allele) also had lower HBVal adduct concentrations, relative to BD exposure levels, than did the heterozygotes (arg139/his139). An unpredicted finding was that workers homozygous for the arg 139 genotype also had significantly lower TBHVal adduct (EBD derived) concentrations as a function of BD exposure levels compared to the other two genotypes, while individuals homozygous his 139 genotype also had lower concentrations of this adduct relative to exposure than did heterozygous workers (arg 139/his 139). Analyses of EH phenotypes (fast, intermediate and slow hydroxylation) based on genotype combinations, as described above, however, showed no influence of hydroxylation status on concentrations of either of the urine metabolites or hemoglobin adducts.

The second Czech molecular epidemiological study included 23 BD exposed female and 30 BD exposed male workers, with some repeats for males that had been included in the first study (Albertini *et al.* 2007). Again, the external exposure assessments were extensive, revealing mean 8 h TWA BD concentrations of 0.180 and 0.370 ppm for the females and males, respectively. As in the first study, there were wide ranges in the exposure levels. The urinary metabolites and hemoglobin adducts measured in the first study were measured also the second study, with the addition of *pyr*-Val adduct (DEB derived) levels. The same genotypes as assessed in the first study were also measured in the second study. As in the first study, workers with either or both of the GST M1 and T1 null genotypes (-/-) showed lower rates of rise of the urinary M2 metabolite as a function of BD exposure levels. However, in the newer study, it is only the GST T1 null genotype for which this difference is statistically significant. (It was the GST M1 genotype that was significant in the first study). Unlike in the first study, analysis of EH effects using combined genotypes (the different combinations of EH 113 and 139) specifying fast, intermediate and slow hydroxylation, now showed that the rate of rise of urinary M2 production as a function BD exposure was significantly higher in the combinations specifying slow hydroxylation than in the other two combinations, females and males combined. Analyses of HBVal and THBVal hemoglobin adduct concentrations are incomplete for this study at this time, but the important *pyr*-Val adducts were not quantifiable in any of the exposed workers, as indicated above, indicating very low levels of production. This finding was not influenced by any of the metabolic genotypes. Of note, in this study it was found that the females apparently absorbed less BD per unit of exposure than did males, as reflected by lower urinary concentrations of both the M1 and M2 metabolite. However, the M2/(M1+M2) ratio was the same in males and females, reflecting the same relative utilization of the conjugation (producing M2) and hydrolysis (producing M1) detoxification pathways in the two sexes. Conjugation constituted approximately 2 to 4% of detoxification metabolism in this second study, compared to ~ 1% in the first study.

Results of these genotype-metabolism association studies, taken *in toto*, suggest that metabolic genotypes do have some effects on BD metabolism, as reflected by the production of the different metabolites. However, findings of differences related to genotypes are inconsistent. When differences have been shown, they have usually but not always been in the directions predicted by enzyme activities.

Furthermore, the differences between genotypes for specific metabolic endpoints have generally been small. Where they could be measured with some confidence, the difference has been by a factor of approximately two – certainly not of the magnitude of the inter-species differences that are seen between mouse and human.

Mutation Induction

The suggestion of metabolic polymorphisms modifying BD's genotoxicity originated from *in vitro* studies. Although such studies are unsatisfactory from a quantitative perspective, as specific metabolites and their exposure concentrations are determined by the experimenter and not the genotype, they can suggest qualitative *susceptibility* differences among individuals. The experimental design used in all of the studies involved incubation of peripheral blood lymphocytes from donors of different genotypes with one of the BD metabolites (EB, EBD or DEB) for a specified time in culture. The most common end-point measured was the sister-chromatid exchange (SCE), which is not a mutational event *per se*, as it does not change genetic information content. None-the-less, SCEs often reflect the kinds of genotoxic lesions that can result in true mutations at the gene or chromosome level and are, therefore, valid surrogates for such lesions in these studies. Obviously, it is only variability in phase II detoxification metabolism that is assessed by *in* vitro studies as phase I activation metabolism is being bypassed.

Early studies indicated that lymphocytes from human donors homozygous for the GST M1 null allele showed significantly higher percentages of SCEs following short term EB treatments *in vitro* (Uuskula *et al.* 1995). The difference was a 31% increase in SCE's in cells from the null donors. Perhaps because EB is a poor inducer of SCEs *in vitro* (Kligerman *et al.* 2007), most of the *in vitro* studies of BD susceptibility have assessed SCE induction in cells incubated with DEB (Wiencke *et al.* 1995, Pelin *et al.,* 1996, Landi *et al.* 1998, Kligerman *et al,* 1999, 2007). It is of interest that "sensitivity", as reflected by an increase in SCE induction as a function of DEB dose, was associated with the GST T1 genotype; neither the GST M1 (nor GST P1) having an effect. This is in contrast to the findings with EB, noted above. The fold-increase in DEB sensitivity, when it could be determined, ranged from "slight" to a factor of ~2 in GST T1 null cells compared to cells of the other genotypes. The specificity of this sensitivity for DEB, however, might be somewhat open to question as the GST T1 null genotype cells in these studies usually had higher frequencies of *baseline* SCEs, suggesting possibly some mechanisms predisposing to this genotoxic event. GST M1 and T1 polymorphisms were also tested for their ability to confer sensitivity to SCE induction by EBD (Bernardini *et al.* 1996). Neither genotype had an effect.

There are only a few reports of *in vivo* human studies that have suggested genetic sensitivity to mutation induction. Sorsa *et al.* (1996) reanalyzed cytogenetic data from a study of BD exposed workers originally reported as negative (1994, see above), and reported an increase in chromosome aberration and micronuclei frequencies in workers of the GST T1 null, but not the GST M1 genotype. Although statistically significant, the increases were less than a factor of two. There were no genotype effects on SCE induction. Kelsey *et al.* (1995) had earlier reported no differences in SCE induction in workers of the GST T1 genotype exposed to < 2.0 ppm compared to exposed workers of the other two GST T1 genotypes. In a study reported only as a poster, chromosome aberration frequencies were reported to be higher in individuals of the GST M1 and GST T1 null genotypes, and that GST P1 and ADH 3 polymorphisms also had an effect, although there was no increase in frequencies in the overall worker population exposed to BD up to 0.40 ppm (see above) (Warholm *et al.*2003). The fold-increase in the null –individuals was ~ 2.5 or less, where stated.

No other human *in vivo* study has found metabolic genotypes to influence chromosome level mutations in BD exposed workers (references given above). [A study from the Slovak Republic identified a variety of metabolic and DNA-repair polymorphisms and found associations between some and chromosome

aberration frequency increases in tire plant workers (Vodika *et al.,* 2004). That study is not considered here because the workers were exposed to a variety of potentially genotoxic xenobiotics in addition to BD]. In fact, the study reported by Zhao *et al.* (2001) actually reported a negative correlation between chromosome aberration frequencies and the GST null genotype in BD exposed workers. These several negative studies for chromosome aberrations include the large, multi-institution studies (Hayes *et al,* 1996, 2000, 2001, Zhang *et al.* 2004, Albertini *et al.* 2001, 2003, 2007). Among these, the NCI China study assessed aneuploidy as well as structural chromosome aberrations (Hayes *et al.,* 1996, 2000, 2001, Zhang *et al.* 2004). In the Czech studies (Albertini *et al.* 2001, 2003, 2007), in addition to analyses of all genotypes singly, chromosome aberration frequencies relative to BD exposure levels were analyzed as a function of EH fast, intermediate or slow hydroxylation phenotypes. No associations were found (manuscript in preparation).

As for chromosome aberrations, most laboratories have not found associations between genotypes and *HPRT* mutations. The exception again is the Texas group, who reported increases in *HPRT* mutant frequencies associated with BD exposures that correlated with EH genotypes. Three reports describe the associations of different EH polymorphisms, or combinations of polymorphisms, in the same worker cohort, in which the autoradiographic assay had previously assessed mutations (references given above) (Abdel-Rahman *et al.,* 2001, 2003, 2005). In the first analysis, workers who possessed at least one polymorphic EH his 113 allele (genotype his/his, tyr/his) exposed to BD levels of 0.15 ppm or greater, showed an approximately 3-fold in increase mutant frequencies over workers of the tyr/typ genotype (Abdel-Rahman *et al.* 2001). This finding is somewhat unusual in that it suggests that a deficiency allele (his 113) is functioning as a co-dominant, unless some gene dosage effect is operative. There were no effects of GST T1 or M1 polymorphisms, although workers of either the GST T1 or M1 null genotypes, combined with at least a single EH his 113 alleles, showed slightly higher mutant frequencies than did those with his 113 and GST T1 and M1 non-null genotypes. No genotypic effects were observed at BD exposure levels < 0.15 ppm. Somewhat anomalously, however, some controls (without BD exposures), had individual mutant frequency values as high as the "susceptible" BD exposed workers, raising the question of specificity of these findings relative to BD. In the second study, EH exon 4 as well as exon 3 polymorphisms were determined for this same worker group, and mutant frequencies were correlated with EH phenotypes of fast, intermediate and slow (Abdel-Rahman *et al,* 2003). Again, it was found that workers exposed to BD at levels of 0.15 ppm or greater showed mean mutant frequencies that were 3-fold higher for the slow compared to the fast hydroxylators and 2-fold higher for the slow compared to the intermediate hydroxylators. The mutant frequencies by EH hydroxylation status for non-BD exposed individuals are not given in this report. The third study of this series examined the effects of the 5' flanking polymorphisms of EH, again in the same worker cohort (Abdel-Rahman *et al.* 2005). Workers exposed to 0.150 ppm or greater BD and homozygous or heterozygous for the -600 flanking polymorphic variant allele reportedly showed an *HPRT* mutant frequency approximately 3-fold higher than did exposed workers without this variant allele, which was a significant difference. Of interest, workers of these "sensitivity" genotypes not exposed to BD also showed an almost 2-fold increase over the non-exposed worker background mutant frequencies. Workers similarly exposed to BD but homozygous or heterozygous for the -200 flanking polymorphic variant allele showed a similar increase in mutant frequency than did the -600 flanking region variant workers, although, in this case, the increase over workers not possessing this variant allele was not significant. Mutant frequencies were actually decreased in workers homozygous or heterozygous for EH -399 flanking polymorphism.

In contrast to the findings just described, none of the genotypes, or genotypic combinations, have been found to influence gene mutations frequencies at either the *HPRT* or *GPA* locus in the large multi-institutional studies described above. *HPRT* mutations were assessed by both the conventional cloning assay and by the autoradiographic assay in the 1st Czech study, and EH genotypic effects have been analyzed both by studying gene effects singly and by combining EH genotypes into fast, intermediate and slow hydroxylation status. Including controls, each of these large studies included more subjects than

were in the Texas cohort just described. A total of 266 workers have been included in the China and Czech studies, combined, with some repeats between Czech 1 and 2. Multi-racial groups have been investigated. It seems most probable that, if metabolic genotypes really influenced BD induced gene mutations, some evidence would have been found.

Genotypic effects on BD induced true mutations at either the chromosome or gene level have been inconsistently shown, at best, in humans. Most studies have failed to find such effects. Those that have, taken at face value, have reported either chromosome aberrations or gene mutations increased in the range of 2- to 3.5-fold, or frequently less. Again, the *in vivo* gene mutation effects have been reported from a single laboratory, and have not been replicated. However, for estimating a "worst-case scenario", this fold-increase in genotoxic sensitivity might be taken as an upper limit. This can be compared with the upper-limit of a 2-fold increase in sensitivity for sensitive genotypes for metabolic endpoints, as described above. Neither of these, of course, approaches the inter-species differences in sensitivity that have been demonstrated between mice and humans.

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APPENDIX B: ISP Elastomers Comments August 29, 2007

ISP ELASTOMERS
1615 Main Street • PO Box 667 • Port Neches, TX 77651 • Tel: 409-722-8321

August 29, 2007

TCEQ Toxicology Section
MC-168, P.O. Box 13087
Austin, Texas 78711-3087

Re: Proposed 1,3-Butadiene Development Support Document

To Whom It May Concern:

Pursuant to the information and materials presented in TCEQ's August 22, 2007 public information session, ISP Elastomers, L.P. (ISP) is pleased to provide comments on TCEQ's Proposed August 2007 1,3-Butadiene Development Support Document (DSD). ISP commends TCEQ's continued efforts to refine its approach to the development and application of ESLs and ReVs, especially with regards to its outreach to the public and the regulated community.

ISP owns and operates two manufacturing facilities in Texas that operate under authority of various New Source Review (NSR) air quality permits. The 1,3-Butadiene ESLs and ReVs routinely play an important role in the NSR permitting for these sites in that they are tools used by TCEQ to ensure that ISP's plants are operated in a manner that is protective of human health and the environment. Accordingly, ISP has kept abreast of TCEQ's efforts in this regard, and in June 2006 provided comments to TCEQ on its draft "Guidelines to Develop ESLs, ReVs and URFs".

ISP's additional comments at this point in time are limited to stating our general support of the methodology employed by TCEQ in developing the Proposed 1,3-Butadiene DSD, and of the overall format and content of the DSD document. As mentioned in our earlier June 2006 comments, ISP supports the use of ESLs as a conservative screening tool in the permitting process but believes clearer documentation on the basis used to develop ESLs and ReVs, and the roles each of these values play in TCEQ's air quality control program would be useful, especially when dealing with air pollutant watch list (APWL) areas. Based on our initial review of the proposed DSD, and TCEQ's presentation on August 22nd, we believe TCEQ has indeed provided much clearer documentation on these matters. In particular, the proposed DSD provides extensive narrative of TCEQ's analytical approach, references for key data and assumptions, and provides clear and useful summary tables of the proposed ESLs and ReVs. In short, we believe the documentation and rationale provided in the proposed DSD provides a strong and supportable scientific basis for the proposed ESLs and ReVs contained in the report.

ISP appreciates TCEQ providing the opportunity to comment on this important initiative and we look forward to providing additional comments after the peer review group has issued their report later this year.

Sincerely,

ISP SYNTHETIC ELASTOMERS LP

Matt Tokheim
Environmental Manager
PO Box 667
Port Neches, TX 77651

Appendix C: TCC Comments March 10, 2008

TEXAS CHEMICAL COUNCIL
1402 Nueces Street • Austin, Texas 78701-1586 • (512) 646-6400 • Fax (512)646-6420

March 10, 2008

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re: Texas Chemical Council Comments Regarding the document entitled "Peer Review of 1,3-Butadiene Development Support document and Report of Follow up Conference Call," dated December 21, 2007

TCEQ Toxicology Section:

The Texas Chemical Council (TCC) submits these comments in response to the Texas Commission on Environmental Quality's (TCEQ) request for public comments on the peer review of its Effects Screening Level (ESL) Development Support Document concerning 1,3-butadiene.

The Texas Chemical Council is a statewide trade association representing approximately 85 chemical manufacturers at over 200 Texas facilities. Our industry has invested more than $50 billion in physical assets in the State and pays over $1 billion annually in state and local taxes. TCC's members provide approximately 70,000 direct jobs and over 500,000 indirect jobs to Texans across the State.

TCC appreciates the opportunity to comment on the peer review of the ESL development document for 1,3-butadiene. TCC understands the importance of ESLs in providing TCEQ with guidance to protect human health and welfare regarding its authority for air permitting and air monitoring. Air quality is also important to the regulated community, particularly to members of TCC.

In general, TCC believes TCEQ Draft Development Support Document for 1,3-butadiene is scientifically sound and demonstrates the diligence of TCEQ in developing supportable values. As discussed in the attached comments, TCC disagrees with some of the scientific issues raised in the peer review report. By offering the following comments on the peer review report, TCC hopes to provide scientific perspectives to assist TCEQ in enhancing the scientific basis of the ESL values for 1,3-butadiene.

Again, TCC appreciates the opportunity to comment on this important document and looks forward to future discussions with TCEQ.

Sincerely,

Michael McMullen
Texas Chemical Council
Director of Regulatory Affairs

Texas Chemical Council (TCC)

Comments Regarding the Document Entitled "Peer Review of 1,3-Butadiene Development Support Document and Report of Follow up Conference Call," Dated December 21, 2007

TCC Supports TCEQ's Decision to Adjust the Risk Assessment to Account for the Effects of High Intensity Tasks (HITS).

The purpose of the Effects Screening Level (ESL) is to provide guidance for exposure to the general population. In developing the ESL for 1,3-butadiene, TCC believes that TCEQ appropriately used the most recent available epidemiology study (Sathiakumar *et al.*, 2005; Graff *et al.*, 2005; HEI, 2006). This study population was a worker population, not the general public, and certain tasks within this worker population involved some short-term, high intensity exposures, termed HITS. The general population exposure will not include similar short-term high intensity exposures, such as those possible in workplaces, and thus, any risk related to these short-term exposures is not relevant to the general population. TCC believes that TCEQ's decision to make an adjustment for the effects of HITS was appropriate.

When reviewing the Integrated Risk Information System (IRIS) risk assessment on 1,3-butadiene, the EPA Science Advisory Board (SAB) recommended that the risk assessment be adjusted for the role of HITS (which they referred to as "peaks"), stating, "Since butadiene exposures to the public will almost never approach the peak exposure range, a more appropriate model for risk would factor out the peak-exposure component." (SAB, 1998).

The definition of HITS is related to individual short-term exposures of 100 ppm or more for any duration of time (Macaluso *et al.*, 2004). These types of exposures were associated with certain tasks, such as opening lines to take samples. Moreover, analyses based on the most recent University of Alabama at Birmingham epidemiology study show that the addition of cumulative number of butadiene HITS to the model results in a statistically significant improvement in the model's ability to predict leukemia mortality (with age and cumulative butadiene ppm-years also in the model) (Sielken *et al.*, 2007). Finally, short-term exposures of 100 ppm are highly unlikely to occur outside a facility that manufactures or uses butadiene. Under the current OSHA standard for butadiene (29CFR1910.1051), short-term, high intensity exposures are also very unlikely in the workplace.

TCC believes that TCEQ's decision on whether to use the adjustment for HITS in the butadiene assessment should be based on a careful analysis of the issues involved and scientific judgment as to the most appropriate approach for adapting a workplace study to an environmental exposure situation, and not just selection of the approach that results in the highest estimate of risk.

TCC Believes that the Excess Risk Calculations Were Appropriately Based on Leukemia Mortality

The leukemia potency estimate was based on a mortality study, and thus the calculation of excess risk is appropriately based on mortality as well. While TCC recognizes the public health goal of reducing cancer incidence as well as cancer mortality, TCC believes it is inappropriate to estimate incidence from a mortality study and that doing so introduces errors in the calculation.

To make an adjustment for incidence, TCEQ would have to assume that leukemia incidence and mortality have the same (cumulative) exposure-response relationship for 1,3-butadiene. There is no evidence to support this assumption. Moreover, using incidence data would be comparing apples to oranges, because the cancer potency value is still derived from mortality data in the epidemiology study. In addition, as Teta *et al.* (2004) have shown, substitution of background incidence rates for background mortality rates does not necessarily improve the estimation of excess lifetime risk, even for diseases with relatively high survival rates.

TCC believes that TCEQ's decision on whether to base the calculation of excess risk on incidence or mortality should be based on a careful analysis of the issues involved and judgment as to the most scientifically appropriate approach. TCEQ's decision should not be based solely on the calculation that provides the greatest estimate of risk.

TCEQ Should Use the Maximum Likelihood Estimate Rather Than the Upper Confidence Level in Its ESL Support Document

As stated in previous comments, TCEQ should use the maximum likelihood estimate rather than the upper confidence limit in its calculations. The decision whether to use the maximum likelihood estimate (MLE) or the upper confidence limit (UCL) should be based on the quality and statistical power of the underlying epidemiology data. For butadiene, the UAB study selected (Sathiakumar *et al.*, 2005; Graff *et al.*, 2005; HEI, 2006) is a state-of-the-art, large, high quality epidemiologic investigation in which exposure to1,3-butadiene and other agents (styrene and dimethyldithiocarbamate) were estimated for each individual in the cohort. Additionally, historical exposure estimates for 1,3-butadiene were validated in a comprehensive comparison of estimated versus measured exposures (Sathiakumar *et al.*, 2007). Regarding the study's size, the analyses of lymphohematopoietic cancer mortality risk by Graff *et al.* (2005) are based on 16,579 men who worked at 6 styrene-butadiene rubber (SBR) plants, with mortality observations covering a 55-year period (1948 to 1998). Over 4,000 observed deaths and approximately half a million person-years of observation were included in the study. Notably, the study period encompassed World War II and the post-war expansion period when workplace exposures were much higher than they are today. Finally, medical records were used (where available) to confirm death certificate diagnoses for all subjects whose death certificate mentioned any form of lymphohematopoietic cancer. There were a total of 81 leukemia deaths in the cohort.

The peer reviewers who supported the use of the UCL appear to base that recommendation on EPA's use of the UCL in some cancer risk assessments. Historically, EPA has used the MLE when deriving unit risk factors (URFs) from human data. More recently, EPA has used the UCL for some cancer risk assessments. However, the decision by EPA to use the UCL rather than the MLE was arbitrary. The new cancer risk assessment guidelines do not offer any scientific rationale for using the UCL, and the issue of using the MLE or UCL does not appear to have been addressed during the external peer review of the new cancer risk assessment guidelines. TCC believes that use of the MLE is scientifically appropriate in most cases for URFs derived from human data, and that the upper confidence limit (UCL) is appropriate for deriving URFs from human data only where substance-specific justification is presented.

In this case, in particular, given the strength of the underlying study, TCC believes use of the MLE is scientifically appropriate and protective of human health. If the UCL is used, then TCC believes the final document should recognize the element of conservatism inherent in that approach and provide scientific rationale supporting that decision.

TCEQ Should Base Its Choice of UCL or MLE and Incidence or Mortality on Its Analysis of Issues and Uncertainties

The peer review report appears to recommend additional calculations and presentation of the analysis using the MLE, the UCL, mortality, and incidence. If this recommendation is accepted, TCEQ should pay particular attention to the further acknowledgment of the peer reviewers that the choice should be made based on issues and uncertainties noted in the two analyses and not based on the final number. TCC agrees these selections should not be a matter of picking the lowest value, but should be based on a more thoughtful approach. As stated above, TCC believes it is not scientifically correct to mix incidence and mortality in the calculations. In addition, if the UCL is used, the final document should recognize the element of conservatism inherent in that approach and provide scientific rationale to support it.

TCEQ Should Base the Acute ESL on Maternal Body Weight

The peer review document suggests that TCEQ consider additional benchmark modeling of fetal and maternal endpoints for acute ESL development. If TCEQ performs these calculations, they should again avoid the simplistic approach of choosing the lowest number. Thoughtful qualitative assumptions remain important. In particular, TCC supports the language in the draft Development Support Document for 1,3-Butadiene pertaining to the relevance of maternal weight to fetal weight effects. Specifically, TCEQ states: "Therefore, if a point of departure (POD) for maternal toxicity is determined using the endpoints of 'extragestational weight gain' and 'weight gain at GD 11-16,' then potential effects on the developing fetus (i.e., reduction in fetal weight, minor skeletal abnormalities) would be prevented . . . . Reduction in maternal body weight gain was an effect that was consistently observed in studies in rats, although at much higher concentration . . ." (TCEQ, 2007, page 14).

TCC agrees with the opinion expressed in the peer review report that it is important to adjust for litter size. "For effects on fetal weight, one should adjust for litter size because the size of the litter affects the weight of the fetuses." (TERA, 2007, page 12).

The Chronic ReV and ESL Based on Ovarian Atrophy In Mice Includes an Interspecies Uncertainty Factor of 1. An Interspecies Uncertainty Factor of Less Than 1 Is Supported by Available Literature.

TCC commented previously on this issue and reiterates here that there is sufficient data to support an interspecies uncertainty factor of less than 1 for the Chronic ReV and ESL based on ovarian atrophy in mice (see TCC comments dated August 28, 2007 and attached document by Dr. Richard Albertini). Dr. Albertini notes that the mouse makes significantly more of the diepoxide metabolite of 1,3-butadiene than rats or humans. TCEQ cites a difference of 78-fold between mice and humans based on the hemoglobin adduct data. Dr. Albertini's review notes that mice are at least 10-times more sensitive than humans because they produce at least 10-times more diepoxide metabolite. Because the diepoxide is the recognized metabolite of importance to ovarian atrophy, and production of the diepoxide in mice is documented to be more than 10-fold higher than in humans, an uncertainty factor of less than one is supported by the existing data.

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Appendix D: ISP Elastomers Comments March 5, 2008

ISP ELASTOMERS
1615 Main Street • PO Box 667 • Port Neches, TX 77651 • Tel: 409-722-8321

March 5, 2008

TCEQ Toxicology Section
MC-168, P.O. Box 13087
Austin, Texas 78711-3087

Re: Proposed 1,3-Butadiene Development Support Document

To Whom It May Concern:

Pursuant to the information and materials referenced in TCEQ's January 23, 2008 email, ISP Synthetic Elastomers LP (ISP) is pleased to provide comments on TCEQ's proposed 1,3-Butadiene Development Support Document (DSD) and the associated final TERA Peer Review Report dated December 21, 2007. ISP commends TCEQ on its continued efforts to employ sound scientific principles in refining its approach for the development and application of ESLs and ReVs, and on its outreach to the public and the regulated community to solicit input on these matters.

ISP owns and operates two manufacturing facilities in Texas that operate under authority of various New Source Review (NSR) air quality permits. The 1,3-Butadiene ESLs and ReVs routinely play an important role in the NSR permitting for these sites in that they are tools used by TCEQ to ensure that ISP's plants are operated in a manner that is protective of human health and the environment. Accordingly, ISP has kept abreast of TCEQ's efforts in this regard, and provided comments to TCEQ in June 2006 on its draft "Guidelines to Develop ESLs, ReVs and URFs", and in August 2007 on its proposed 1,3-Butadiene DSD.

At this point in time, ISP would like to simply reiterate our general support of the methodology employed by TCEQ in developing the Proposed 1,3-Butadiene DSD, including its decision to solicit the input of a qualified independent peer-review panel. As mentioned in our earlier comments, ISP supports the use of ESLs as a conservative screening tool in the permitting process but believes clearer documentation on the basis used to develop ESLs and ReVs, and the roles each of these values play in TCEQ's air quality control program would be useful, especially when dealing with air pollutant watch list (APWL) areas. Based on our review to date of materials related to the proposed DSD, we believe TCEQ has indeed provided much clearer documentation on these matters. In particular, the proposed DSD provides extensive narrative of TCEQ's analytical approach, references for key data and assumptions, and provides clear and useful summary tables of the proposed ESLs and ReVs. In short, we believe the documentation and rationale provided in the proposed DSD provides a strong and supportable scientific basis for the proposed ESLs and ReVs contained in the report.

ISP appreciates TCEQ providing the opportunity to comment on this important initiative and we look forward to further updates concerning finalization of the 1,3-Butadiene DSD.

Sincerely,

ISP Synthetic Elastomers LP

Matt Tokheim

Matt Tokheim
Environmental Manager
PO Box 667
Port Neches TX 77651

APPENDIX E: IISRP Comments March 10, 2008

Via email: tox@tceq.state.tx.us 10 March 2008

Toxicology Section, MC168
Texas Commission on Environmental Quality
121 Park 35 Circle, Bldg. F
Austin, Tx 78753

Attention: Dr. Michael Honeycutt

Re: IISRP Comments Regarding the document entitled "Peer Review of 1,3-Butadiene Development Support Document and Report of Follow up Conference Call," dated December 21, 2007

Dear Dr. Honeycutt:

Thank you for the opportunity to submit comments on behalf of members of the International Institute of Synthetic Rubber Producers, Inc. (IISRP) We are an international trade association representing the interests of more than 40 corporations engaged in the production of synthetic rubber, three of which are located in Texas. Each of these is a significant consumer of 1,3-butadiene, and we therefore have a major interest in any modification to the Effects Screening Level.

The IISRP has conducted significant scientific research, especially the extensive epidemiology on the health effects of 1,3-butadiene since 1975 and have sponsored publication of many of the scientific references cited in the Development Support Document. We, along with our research partners at the American Chemistry Council's Olefin Panel, have also presented this research at scientific symposia.

We have had the opportunity to review the comments submitted by the Texas Chemical Council (TCC) and support them as presented. We believe in general the TCEQ's draft DSL to be a very good work product; however we share the TCC's concerns for some scientific issues .

Again we thank you for having the opportunity to provide our comments.

Sincerely,
James L. McGraw

Managing Director & CEO

APPENDIX F: Written Comments on the Health-Based Acute ReV and ^{acute}ESL (June 2008 version)

(TCEQ Contract 582-7-80167-03)

Reviewer #1 Review of Revised 1,3-Butadiene Risk Assessment
July 3, 2008

As requested, I have restricted my review to giving my overall impression of section 3 of the revised review. Overall, I believe that the appropriate critical effect was chosen, and that the right point of departure was selected. My main criticism with the revision is with its organization. It is organized around the statistics, rather than around the biological effects and risk assessment. The dose-response modeling should be viewed as a tool to assist the selection of the appropriate critical effect, not as an end in itself. Organizing the text according to the results of different dose-response models leaves the impression that this was a statistical exercise instead of a risk assessment.

First, I agree that decreased fetal weight was the appropriate endpoint to select as the critical effect. There is general consensus in the developmental toxicology discipline that significantly decreased fetal weight is an adverse effect. This effect was produced at the lowest concentration of butadiene that was adverse in the principal study. It occurred at the same concentration as an increase in supernumerary ribs. I agree with the decision not to use extra ribs as the critical effect. There is disagreement in the field as to whether these are really adverse or are non-adverse variations of the norm and/or non-specific manifestations of generalized toxicity. Using decreased fetal weight as the critical effect would protect against other effects, including extra ribs, produced at the same or higher dose levels.

Even though the dose-response models did not provide a good fit for the fetal weight data, the best models did in fact produce a BMDL that was consistent with the empirical NOAEL. This provides some assurance that the point of departure is not inordinately low.

As for the organization of the section describing BMD calculations, I recommend that it be organized by effect, not dose-response model. After all, the purpose of this report is to assess the risk of butadiene, and should focus on the toxic effects and their dose-response relationships, not the methods by which those relationships are calculated. On p. 26, I disagree with the use of the section title of "Preferred Modeling Results" because different models might be preferable for any given endpoint. Likewise, the first sentence under this section is misleading because it suggests that the power model is best regardless of which endpoint.

Some additional editorial points:
P. 9, the last sentence (and carrying over to p. 10): I would delete this sentence. You can (and do) deal with the subject of differential sensitivity of different species later in the document. It is confusing to try to introduce it in the first sentence of a section on Human Studies.

P. 19, last sentence: I think this should be worded differently. One would want to select a critical effect because it is adverse, biologically plausible (e.g., consistent with the proposed MOA, dose-responsive), and is among the effects occurring at the lowest levels of exposure. This will probably still be the lowest POD, but the rationale is much more palatable and correctly reflects the thought you have put into this assessment.

P. 21, the long paragraph after the bullet points: This seems more like a discourse on benchmark dose methods than anything having to do specifically with butadiene. I found it out of place and I recommend deleting it.

Reviewer #2 Comments on Revised DSD for 1,3-Butadiene, June 5, 2008 Draft

The TCEQ authors clearly spent substantial effort in conducting the additional modeling and documenting the results. In particular, the tables in the appendices are noteworthy, documenting all key results in a compact manner and largely removing the need for pages of output.
I agree with the final conclusions of TCEQ from the modeling. My comments are generally minor, and (with the exception of the first comment) perhaps more in the tone of "ideas for future assessments," rather than things that are critical for the butadiene assessment.

1. I agree that it is reasonable to choose the NOAEL for fetal body weight as the basis for the acute ReV, but found the documentation for that choice not fully transparent. The discussion of the linear model in Section 3.1.4.2.2 gives the impression that the linear model for fetal body weight with 3 doses gives an adequate fit to the data. The visual fit is fine, and the g-o-f p value is acceptable, although not ideal. No other issues are noted with this modeling, and Section 3.1.4.2.4 gives the impression that the linear model for fetal body weight is not chosen for the point of departure only because the power model is preferred overall. However, based on the data in Table 2D of Appendix 2, it appears that the linear model was rejected based on the results of test 3, but that was not stated explicitly. What was the reason for rejecting the linear model? I would not expect that choosing the power model for other endpoints would be sufficient reason to reject the results of the linear model for fetal body weight. On the other hand, failing test 3 may not require that the model be rejected, if the variance is fit adequately in the range of the BMR. It was also noted that test 3 failed for the power model for placental weight, but the power model results were reported in the main text for this endpoint.

   The statement on p. 26 that "since it was not possible to model fetal body weight with the unrestricted power model, the POD for this endpoint is the study NOAEL of 40 ppm" implies that only results for the power model were considered for the fetal body weight endpoint. The statement can also be confusing since it is followed by the presentation of the BMCLs for reduced fetal body weight using the 3-dose linear model. The statement that supernumerary ribs was *another* (emphasis added) endpoint that could not be modeled also implies that fetal body weight could not be modeled. Despite these points, as the authors note, the choice of the BMCL from the linear model vs. using the NOAEL has a small impact on the POD.

2. While it is not necessary to rework the butadiene document, I found it a bit confusing to organize the modeling results by model, rather than by endpoint. Organizing the results by model also made it harder to compare the different models for each endpoint and determine the most appropriate model (if any) for each endpoint prior to comparing the results for each endpoint. Organizing the results by endpoint could also help to reduce the confusion noted above, some of which appears to be related to considering the best model overall, rather than the best model for each endpoint.

3. The text regarding the hybrid model looks as though it may have been added in response to a reviewer question. I'm not sure that the text is really needed, since the text that appears to have prompted the reviewer comment/question has been changed/clarified. If this or similar text is included in this or other DSD's, a few comments: First, the hybrid model (at least in the forms I

have used it) does not require dichotomizing the data, and I'm not sure whether it really needs individual animal data. The point of the model is to be able to use the full information in the continuous results, but have the results in a form that is more interpretable. Furthermore, given the current reporting and standard BMR definitions for BMDS, results equivalent to running the hybrid model are available. The one standard deviation definition of the BMR for continuous endpoints is based on the determination using a hybrid model approach that, for a normal distribution, and 1% background adverse response, 1 SD corresponds to an increased risk of being adversely affected of about 10%.

Reviewer #3 General Comments on Revised TCEQ Analysis of Butadiene

I have focused attention on section 3 and the response to comments associated with that section (as well as Appendix 2, which gives the details of the modeling results discussed in that section). In general, I think the revision does a better job of reflecting the dose-response characterization of the data, and does address the comments that the reviewers offered. However, there are a few things that I think could still be improved and I list those here, in no particular order.

1. In the responses to comments, Comment 3, the response ends with this statement:

"Mean fetal body weight could not be modeled with the unrestricted power model, which is the preferred model used by the TS for BD (Section 3.1.4.2.4 *Preferred Modeling Results* and Appendix 2 *Benchmark Modeling Results Using the Power Model (11/19/07 Email from Bruce Allen*)), so it is important to identify the correct study NOAEL."

I think that there is still too much strict reliance on and maybe misinterpretation of the results of the tests reported by BMDS. Appendix 2 shows that the modeled variance does not adequately characterize the variation when the linear model is fit to the 3-dose data. There are ways around that (especially if you are going to use the 1-sd definition for the BMDL) that involve adding a constant to the means until a good characterization of the variation is found. If that is the only reason for saying that the modeling is not adequate for the fetal weight endpoint, this is not very satisfying. In general, here and in other of my comments, you will see that I much prefer any option that allows dose-response modeling rather than reliance on NOAELs. In fact, I would do my utmost to use PODs that do not depend on NOAELs. Even if some adjustment of the means does not get around the problem of the variances not being modeled all that well, don't worry about it. As long as the control group variance looks about right and the dose-response for the means is good (Test 4 suggests that it is fine), then the BMD can be used without untoward concern.

In fact, I suspect that a major reason the document concludes that the fetal weight response could not be adequately modeled by the power model (based on the results of Test 4 from BMDS) relates to the handling of the variance and not to the dose-response for the means. I may be wrong (i.e., perhaps the means cannot be adjusted so that the variance can be related to those means in the way that BMDS does it) but I think it is worth investigating.

2. The response to Comment 8 includes the sentence, "It was not possible to exclude the highest concentration for the unrestricted power model since the power model requires four exposure

concentrations to model data with 95% confidence." I would not agree with this. It is certainly possible to fit the power model with all three parameters estimated to data sets with 3 dose groups. You can get valid BMDs and BMDLs from such exercises. What you cannot get is a statistical test of fit since there are not degrees of freedom. I do not worry about that too much in cases where this is necessary (and I think there may be such cases here). I am quite happy to rely on visual fit and scaled residual values to decide if the model is doing an adequate job. In many situations the fit may be exact, and that is ok. In others (especially some of those in the BD analyses where there are nonmonotonicities in the data) the fit will not be exact, but it is still generally good – and, most importantly, better than what you would get if you restrict the power to be a fixed value (e.g., 1, which give the linear model). I definitely think there are some situations where you have rejected the linear model fit to the 3-dose data that would benefit from fitting the power model even though the statistical evaluation of the fit would not be possible. The cases I am thinking of are the non-monotonic cases like reduced ossification and supernumerary ribs. In those cases, the linear model is not going to fit that well because it is going to have to split the difference between the first two doses to get the linear trend that hits the response at the high (3^{rd}) dose. The power model can have a flatter low-dose shape that might better approximate what is going on at the low dose and still curve up to hit the response rate for the 3^{rd} dose. This is what you want and will give a better value of a BMD and BMDL.

3. The response to Comment 17 says, "…the CES of one standard deviation was most predictive for the unrestricted power model." I do not know what "predictive means here. The definition of the CES is just a choice, it is not predicting anything specific to a model. If you are saying that it is a better choice for that model (because it gets out of the steep-slope region) then just say that. But really, I think there are other good reasons – the fact that it corresponds to EPA guidance which in turn are based on studies that show that that choice corresponds to assumptions about the background level of adverse response and the implied increase in that level of response at the BMD associated with it. (That, by the way, is not true for the relative change CES defintions).

4. In the revised document, in the discussion of the hybrid approach (p. 21, paragraph below the bullet items), it says, "Another major disadvantage is that it is difficult to define a cutoff that is considered adverse for each endpoint." When you are using any definition of the BMD, you are at least implicitly defining a cutoff, even using the continuous models and BMR choices in BMDS. For example, with the 1-sd definition, you are basically assuming that there are about 5% of individuals who, absent exposure, would have an adverse level of the continuous endpoint (when the increase in response is about 10% for the BMD). That gets translated into a specific cutoff depending on the model-predicted mean and sd for the control group. I would not cite this as a reason to avoid the hybrid approach – you are doing it anyway and perhaps making it more explicit and needing supporting toxicological justification may be a good thing.

5. In the revised document, p. 22, right below the bullet items, it says, "However, the variance for these data sets was not nonhomogeneous either, as defined by the BMD software (i.e., in BMDS 1.4.1c, the nonhomogeneous variance model assumes that the variance in each dose group is proportional to the magnitude of the mean raised to a power)." It cannot be right to say that the variances and not homogeneous and not nonhomogeneous! Just say that using the unadjusted means, the nonhomogeneous variance could not be adequately modeled as it is done in BMDS. As I mentioned in an earlier response, there are ways around that and they should be explored before NOAELs are relied on.

6. The beginning of section 3.1.4.2.2 (p.22) does not sit right. I know this is just for the linear model results, but it really leaves the impression that modeling was not very useful for your analysis. One thing I would suggest is that rather than organizing your report by linear model vs. power model, why not just show the modeling for each endpoint, starting by fitting the power model and resorting to linear (or dropping the high dose) as needed, i.e., work through the process for picking a model for each endpoint.

Moreover, I disagree with the statement in that first paragraph of section 3.1.4.2.2 that says the visual fits of the linear model to the two data sets called out were not very good. They look perfectly fine to me.

Bottom line: I think not enough has been done to get modeling results that can be used. Table 8 in particular is bothersome as it shows so few model-based results and so many NOAELs. I would not exclude from analysis the endpoints with no trend – your statistical analyses have shown there to be trends (NOAELs less than the highest dose), so go ahead and model them – they will give BMDLs that are way high and can be ignored. Don't worry if BMDS says no trend – you have done other analyses that lead you to want to consider them and the test reported by BMDS (Test 1) has no bearing on the ability of the models to fit and describe a dose-response relationship (even if it appears to be very flat).

I suspect that there are perfectly adequate ways to model the supernumerary ribs and fetal weight endpoints that give you the lowest NOAELs that drive your calculations, and, I strongly suspect, that the BMDLs for those endpoints will end up being greater than 40 ppm. So this will definitely change the final number (but not by much since it cannot go up above about 51 ppm (from the Table 8 result for extragestational weight gain).

APPENDIX G: Comments from the City of Houston Texas (June 2008 version)

BILL WHITE
MAYOR

OFFICE OF THE MAYOR
CITY OF HOUSTON
TEXAS

July 11, 2008

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Re: City of Houston Comments on DSD for 1,3-Butadiene

Dear Michael,

The City of Houston is grateful for the invitation to comment on the TCEQ Development Support Document (DSD) for 1,3-Butadiene. Dangerous levels of 1,3-butadiene measured at Milby Park in Houston have the City very concerned about the impact of exposure to these elevated concentrations on its citizens and the surrounding community.

The TCEQ proposes a carcinogenic Effects Screening Level (ESL) of 9.1 ppb and a noncarcinogenic ESL of 4.5 ppb for 1,3-butadiene, the lower of which (4.5 ppb) is proposed to be the working level. The TCEQ's proposed level decreases the current ESL of 5.0 ppb by 0.5 ppb. This is much less of a decrease than the City expected. The City is opposed to TCEQ's proposed 1,3-butadiene ESL of 4.5 ppb and in favor of lowering the ESL to the EPA recommended level of **0.15 ppb at $1x10^{-5}$ risk level**, for several reasons:

1) Important local research indicates 1,3-butadiene is posing an unacceptable cancer risk in Houston,
2) EPA advocates the use of a lower more health protective value and use of a different level introduces inconsistency within the state,
3) Studies referenced in the DSD to support the higher carcinogenic ESL are flawed,
4) Cumulative risk from other carcinogenic air toxics prevalent in Houston is not considered in ESL development, and
5) Use and purpose of the ESL is not consistent with the risk level used to develop the ESL.

These reasons are discussed below.

1) **Important local research indicates 1,3-butadiene is posing an unacceptable cancer risk in Houston**

The most important reason that the City advocates a lower, more conservative ESL consistent with the EPA is that recent epidemiological data indicate that the high concentrations found in the Houston Ship Channel (HSC) area are strongly correlated with increased incidence of certain childhood leukemias. A University of Texas School of Public Health (UTSPH) study reported that higher 1,3-butadiene levels (≥1.15 ppbV vs. <0.266 ppbV) were associated with acute lymphocytic leukemia, acute myeloid leukemia, and all leukemias in children.[1]. The trend of increasing 1,3-butadiene concentrations and increasing leukemia rates was statistically significant for children for the cancers listed in Table 1.

Table 1. Cancers having statistically significant associations with 1,3-butadiene in the UTSPH study

Cancer Type	Houston 1,3-Butadiene Level*	Rate Ratio of Increased Incidence	p-value	p-value for trend
Hodgkin's Disease	1	1.00		0.099
	2	1.53	0.171	
	3	1.67	0.152	
	4	1.80	0.071	
All Leukemia	1	1.00		0.017
	2	1.10	0.530	
	3	1.19	0.292	
	4	1.40	0.024	
Acute Lymphocytic Leukemia	1	1.00		0.041
	2	1.09	0.629	
	3	1.11	0.528	
	4	1.38	0.051	
Acute Myeloid Leukemia	1	1.00		0.026
	2	1.50	0.359	
	3	1.79	0.217	
	4	2.53	0.033	

* level 1 = <0.266 ppbV; level 2 = 0.266 – 0.381 ppbV; level 3 = 0.382 – 1.14 ppbV; level 4 = ≥ 1.15 ppbV

[1] Walker KM, Coker AL, Symanski E, Lupo PJ. (2006) **A preliminary investigation of the association between hazardous air pollutants and lymphohematopoietic cancer risk among residents of Harris County Texas.** University of Texas Health Science at Houston, School of Public Health http://www.houstontx.gov/health/UT-main.html

These data approximately translate into the following concentration and incidence rates per 1 million people shown in Table 2.

Table 2. Leukemia incidence in children from UTSPH study

Concentration*	Approximate Leukemia Incidence in HSC Area per Million People (Children age <20 yrs)		
1,3 BD ppbV	all leukemia	acute lymphocytic leukemia	acute myeloid leukemia
0	45.1	34.6	4.7
0.266	47.7	36.7	6.3
0.382	52.1	38.1	7.8
1.15	60.2	46.6	10

* BD concentrations presented on low end of range in UTSPH study

If the baseline level is assumed to correspond to the incidence numbers associated with 0 1,3-butadiene concentrations, the *increased* incidence is found by subtracting the baseline from the other levels (Table 3):

Table 3. Increased leukemia incidence in children from UTSPH study

Concentration	Approximate *Increased* Leukemia Incidence in HSC Area per Million People (Children age<20 yrs)		
1,3 bd ppbV	all leukemia	acute lymphocytic leukemia	acute myeloid leukemia
0	0	0	0
0.266	2.6	2.1	1.6
0.382	7	3.5	3.1
1.15	15.1	12	5.3

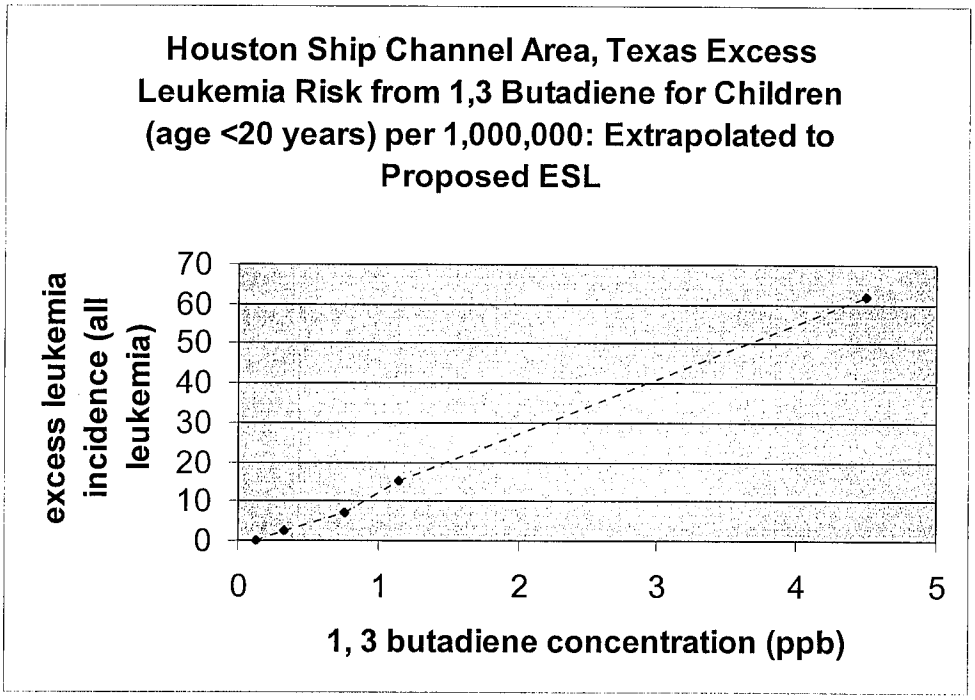
From these estimates, concentrations above 1.15 ppbv result in an increased incidence of **15 cases per million children, or risk of $15x10^{-6}$ (1.5×10^{-5} / ($\mu g/m^3$)) from 1,3-butadiene alone**. This estimated cancer incidence risk exceeds the TCEQ level of $1x10^{-5}$ and the EPA risk goal of $1x10^{-6}$. This area also has high concentration of other air toxics (see comment 4). The EPA recommended range is $1x10^{-6}$ to $1x10^{-4}$ with a goal of $1x10^{-6}$ as found in the Clean Air Act.[2]

In a simple extrapolation of the UTSPH data regressed for all leukemia cases as related to 1,3-butadiene, it is possible that 1,3-butadiene concentrations at 4.5 ppb would result in over 60 excess leukemia cases in children (age < 20 years) in a million people, if the incidence remained linear (Figure 1). **This would result in 60 $x10^{-6}$ risk or $6x10^{-5}$ risk.** Although this extrapolation is based on limited data and some key assumptions, the

[2] US Federal Register, 54CFR Volume 38, Part 44. 1989

results indicate that a more conservative health protective standard (as recommended by EPA) is the best course of action while further in depth studies in the HSC area are conducted.

Figure 1. Excess leukemia risk from 1,3-butadiene for children in HSC area



The UTSPH report was not referenced by the TCEQ in the DSD. Although the findings are on a pilot study level, a more comprehensive UTSPH study funded by the National Institutes of Health (NIH) and supported by the City of Houston is currently being conducted (Symanski personal communication, June 2008). Unlike the adult male worker study referenced in the DSD, the UTSPH pilot study findings apply to the general population and most directly to the Houston community. The City of Houston feels that the pilot study findings indicate that the proposed 1,3- butadiene ESL is not protective and should be lowered to the EPA recommended concentration level.

The City believes that the UTSPH pilot study findings will likely be verified with the more in depth current UTSPH findings because:

- The National Institutes of Health granted funding for the current study. This is an indication that the pilot findings were found to be credible and of significant interest.
- Results from the exposure to a child receptor represent the simplest category of human exposure because issues with confounding factors associated with travel to work, occupation, smoking or previous exposure are not relevant.

2) **EPA advocates the use of a lower more health protective value and use of a different level introduces inconsistency within the state**

The state is proposing to use a different 1,3-butadiene air standard than that used and advocated by the EPA. The state's value is:

- less conservative than the EPA's,
- not based on local cancer incidence and
- will result in inconsistent regulation within Texas.

The inhalation unit risk (IUR) value in EPA Integrated Risk Information System (IRIS) remains $3x10^{-5}/(\mu g/m^3)$. The Office of Air Quality Planning & Standards (OAQPS) also recommends this toxicity value. Neither EPA IRIS nor EPA OAQPS has plans to change the 1,3-butadiene IUR values and there are no ongoing EPA reassessments for 1,3-butadiene (personal communication by email with Roy L. Smith, Ph.D. Office of Air Quality Planning & Standards, June 23, 2007).

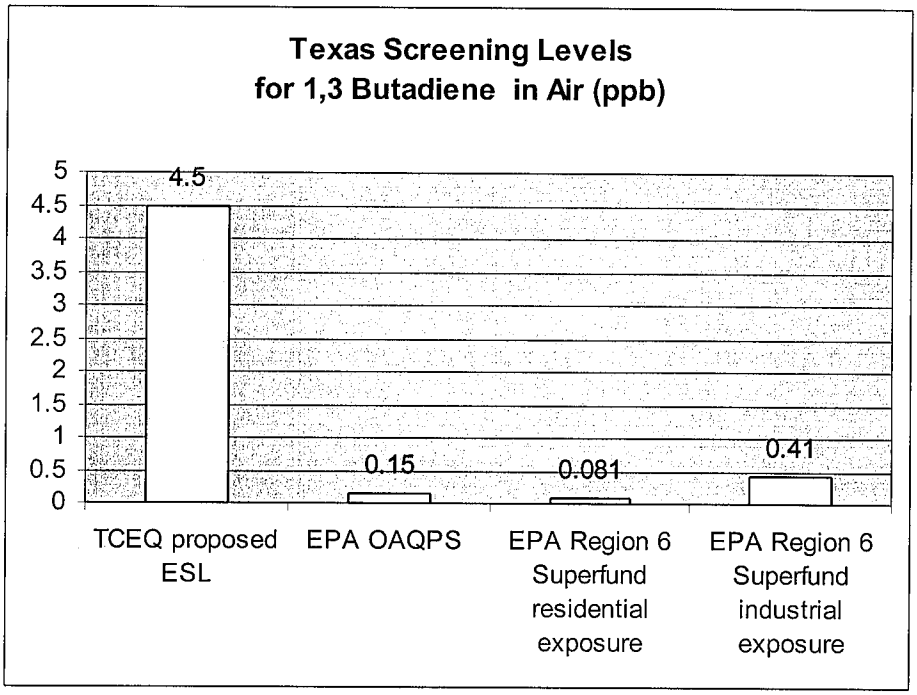
The 1,3-butadiene concentration corresponding to the EPA IUR is, for risk level of

$1x10^{-5}$, is 0.15 ppb and the TCEQ proposes to use 4.5 ppb at the same risk level. The proposed TCEQ number is 30x less conservative than what EPA advocates. Within the state of Texas, according to EPA OAQPS, EPA regulated sites will be assessed using 0.15 ppb value at $1x10^{-5}$ risk level, based on unit risk, while the rest of the state will be assessed using the 4.5 ppb value at $1x10^{-5}$ risk level.

In addition, EPA Superfund sites within the state will be assessed using the IUR from EPA IRIS and OAQPS of $3x10^{-5}$ b/$(\mu g/m^3)$ but at the screening level the risk of $1x10^{-6}$ including exposure parameters is used (http://epa-prgs.ornl.gov/chemicals/index.shtml). EPA Region 6 uses air inhalation risk screening levels set at $1x10^{-6}$, in part to account for exposures from multiple chemicals. The Houston area also has exposures from multiple chemicals and therefore, the lower risk value of $1x10^{-6}$ should be used in Houston (see comment 4).

EPA Region 6 screening level 1,3-butadiene concentrations for air for Superfund sites is 0.04 ppb for residential exposure and 0.18 ppb for industrial exposure. Other EPA region sites using OAQPS standards will use a screening concentration of 0.15 ppb if they screen at $1x10^{-5}$ risk or 0.015 if they screen at $1x10^{-6}$ risk, while TCEQ proposes a screening level concentration of 4.5 ppb (Figure 2).

Figure 2. Comparison of existing with proposed screening levels for 1,3-butadiene in Texas



3) Studies referenced in the DSD to support the higher carcinogenic ESL are flawed

Several reasons given for a higher carcinogenic ESL in the DSD require further clarification or correction. The page number where the inconsistency is located and our comments are listed below.

Page 8, Figure 1.

The source of the data for the national average for urban/suburban areas in the Measured Ambient Concentrations (ppb) block is not referenced.

Data on the NATA website (http://www.epa.gov/ttn/atw/nata1999/tables.html) for 1999 county average for all sources from the county level emission summaries is given in micrograms per cubic meter and converts to 0.05 ppb for rural areas and 0.37 ppb for urban areas. Although in the same ballpark, these are not the same numbers as in the block in Figure 1 and repeats the question, "Where is this data from?" Furthermore, a more suitable metric for the DSD would be ambient concentrations for Texas with a separate measure for Harris County.

The caption in Figure 1 states that "USEPAs current acceptable cancer risk range (is) based on an outdated epidemiology study."

The SEER study published in 2001 analyzes data from 1973 to 1998 and is the latest report cited on EPA's IRIS website (http://www.epa.gov/NCEA/iris/subst/0139.htm#carc). The TCEQ uses re-analyses of the UAB study originally conducted on workers from 1943 -1991 to update the USEPA 2002 assessment. If there are "no other epidemiology

studies that would be appropriate to evaluate human cancer risk from BD exposure," is data collected only as late as 1991 sufficient to revise the ESL in 2008? The City advocates lowering the ESL to the EPA recommended values and believes that revising the ESL to a higher concentration based on the re-analyses of this older data is a mistake.

Page 45, last sentence
"Cheng et al. (2007) results support the presence of a relationship between high cumulative exposure and leukemia and high intensity of exposure and leukemia."

A reanalysis of a worker mortality study is not an appropriate surrogate for risk to the community.
Cheng et al. conducted a reanalysis of 1,3-butadiene exposure data collected by Delzell on synthetic rubber industry workers who died of leukemia. These types of worker studies are limited in detecting incidence of leukemia due to the healthy worker effect. Workers who had contracted leukemia, diagnosed or not, would not be counted unless they had died. Additionally, worker exposure is based on an 8-hour work day whereas residents are exposed for a much longer time period each day.

When determining an ESL, the outcome to be measured should be incidence of disease, not mortality. Therefore, if incidence had been measured in the Cheng or Delzell studies, the number of workers with leukemia would likely have been much higher. That would lower butadiene exposure estimates and show a relationship at a lower concentration.

Although TCEQ accounts for differences in a worker mortality study and risks to a general population through numerical adjustments and models, it is not clear that the data used to establish the models or adjustment factors is sufficient to capture the variables that can occur within a community. Therefore, the City suggests that the TCEQ develop an appropriate epidemiology study in the Houston-Galveston area to answer these questions.

Page 53. second paragraph.
"Toxicokinetic and toxicodynamic evidence indicates children are not more susceptible to chemical leukemogenesis than adults for acute myeloid leukemia and acute nonlymphocytic leukemia…

Inhalation studies should be used when determining an air concentration limit.
This statement may be true for toxicokinetic and toxicodynamic evidence where cancer patients contract leukemia from chemotherapy, but the DSD is addressing inhalation exposures, not oral or intravenous injections. Epidemiological studies would make the better comparison as in the UTSPH study above.

Children are affected more than adults by 1,3-butadiene exposure and leukemia.
The UTSPH study discussed in Section 1 above indicates a relationship with higher 1,3-butadiene levels ($\geq$1.15 ppbV vs. <0.266 ppbV) and acute lymphocytic leukemia, acute

myeloid leukemia, and all leukemias. It is possible that this association was not found in the studies referenced by the TCEQ because:

- The relationship found by UTSPH was in children while the cornerstone study on which TCEQ bases the 9.1 ppb 1,3-butadiene carcinogenic level (Delzell *et al.* 1995; 1996) addressed exposure in adult male workers only.
- The statistical trend is stronger for adults (lower p-values) when specific cancers and leukemias are tracked as opposed to combining all cancers into a larger group as has been done in previous studies.

In the UTSPH study, the same associations with 1,3-butadiene and leukemias in children were not found for adults. However, when distance from the Ship Channel was examined, a significant increasing trend of acute myeloid leukemia in males was detected with proximity to HSC. It is likely then, that if specific types of leukemias had been analyzed in the Delzell studies that associations at lower butadiene concentrations may have been detected.

Page 55
4.2.5.2 Estimating Risks for the General Population from Occupational Workers

"No reliable data" claim in Grant paper is an incorrect use of terminology.
TCEQ bases their claim that "There are no reliable data linking BD exposures at low concentrations typical for the general population to increased mortality from any cause in Texas" on the TDSHS report referenced in the Grant et al. paper. However, there are problems with the TDSHS report.

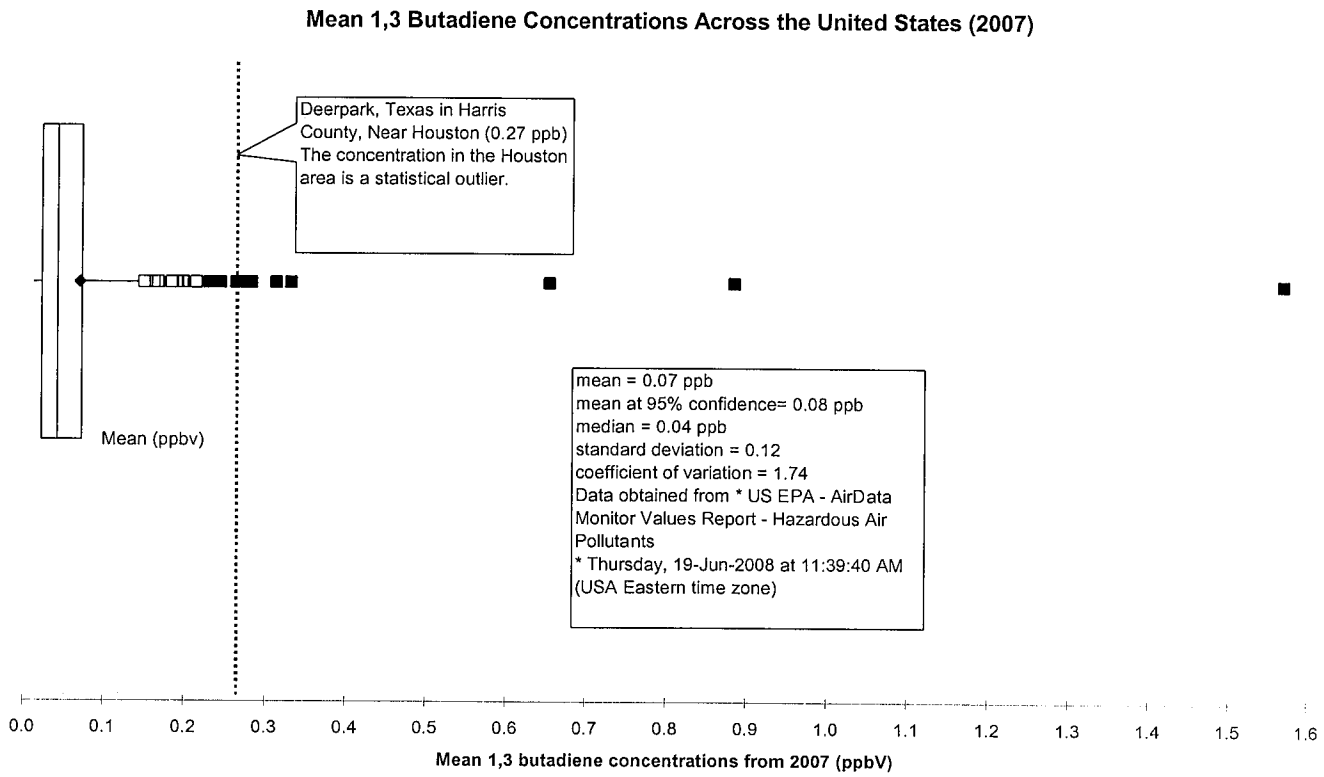
When calculating the standard mortality ratio (SMR) and standard incidence ratio (SIR), TDSHS uses Texas statistics instead of local information. The communities selected for this analysis are located close to industry and are generally more minority-populated and younger than the rest of Texas and would be expected to have different morbidity and mortality statistics.

Secondly, there are several limitations pointed out in the report: non-specific death certificate information, people moving in and out of the community, long latency period, lack of recent data, and limited power.

Therefore, a more accurate statement would be that there is insufficient data, not "no reliable data," linking BD to mortality from "any cause" in Texas. There is a key difference in the meaning of these statements.

The importance of looking at data from the Houston-Galveston area in developing a statewide ESL is further illustrated in the boxplot below. Although the national 2007 mean 1,3-butadiene concentration is 0.07 ppb, the mean concentration for the Deer Park monitor in the Houston-Galveston area is 0.27 ppb, a statistical outlier. If canister data were available for the Houston Milby Park monitor it would also be an outlier based on 2007 auto GC data.

Figure 3. Boxplot of mean 1,3-butadiene canister concentrations in the U.S. with outliers



4) Cumulative risk from other carcinogenic air toxics prevalent in Houston is not considered in ESL development

Citizens of the City of Houston and surrounding community are exposed to several criteria pollutants and air toxics simultaneously. Regulation of a single pollutant without consideration of exposure from others is ineffective in protecting human health. For example, when the risk from two main air toxics of concern in Houston are combined, the cumulative risk exceeds the $1x10^{-5}$ risk level for all but two locations. There are 7 pollutants posing a definite risk in Houston and the surrounding area as identified by experts on the Mayor's Task Force on the Health Effects of Air Pollution.[3] (Institute for Health Policy, 2006), therefore the risk will be even higher than those shown below.

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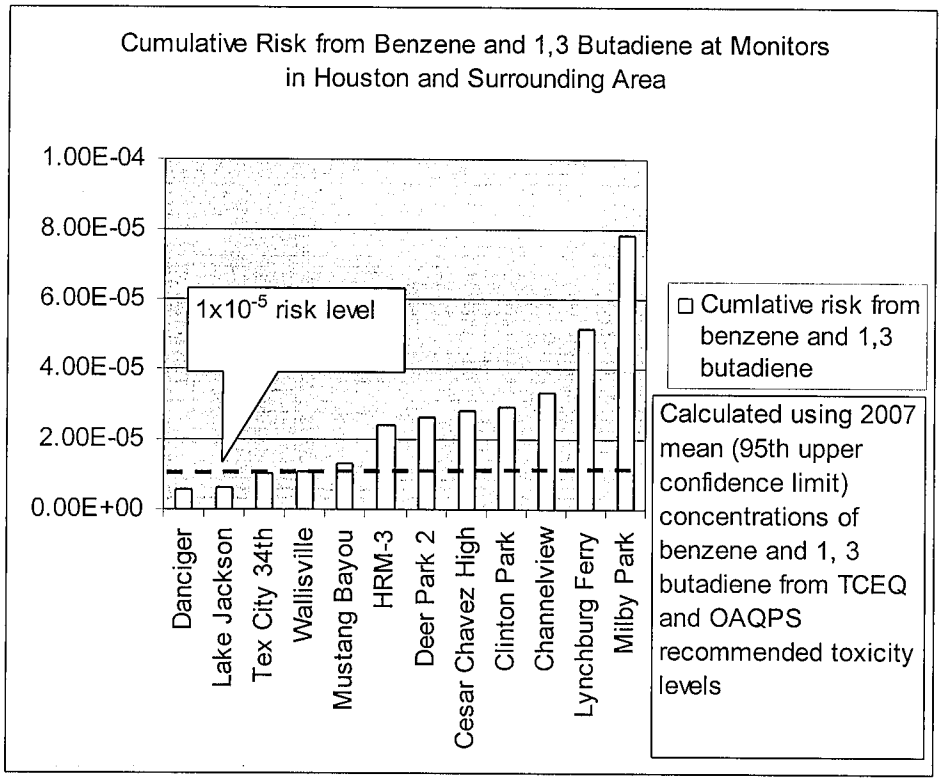
[3] Institute for Health Policy. University of Texas School of Public Health. 2006. A Closer Look at Air Pollution in Houston: Identifying Priority Health Risks
http://www.greenhoustontx.gov/reports/UTreport.pdf

Figure 4. Cumulative risk for benzene and 1,3-butadiene at Houston area monitors



5) Use and purpose of the ESL is not consistent with the risk level used to develop the ESL

The City of Houston understands the purpose of the Effects Screening Level for an air constituent to be

a) the limit at which industrial air permits cannot be exceeded at a specified downwind receptor location
b) an air monitor annual average ambient limit, above which the area is placed on the Air Pollutant Watch List. Permits in the watch list area are more stringently reviewed.

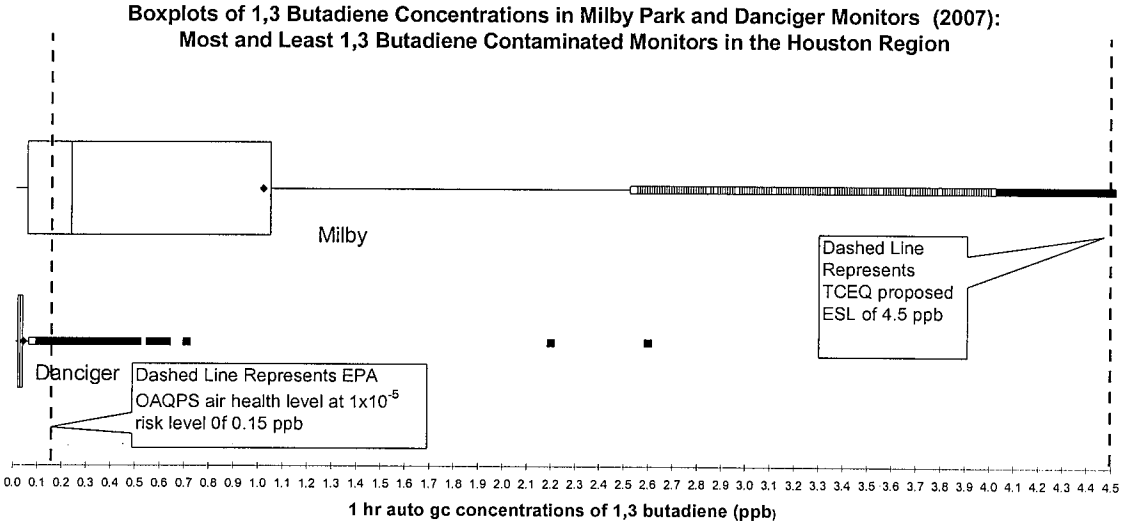
As the City of Houston outlined in comments on MERA earlier this year, there are many problems with the application of the ESL in the permit process (e.g., no model validation or verification, no measured receptor concentrations, no consideration for neighboring emission points etc.) in a) above.

A main point of departure, however, between the TCEQ and the City is in the fundamental understanding of the interpretation of the ESL in b) above. The City is in agreement with the state that the risk limit of $1x10^{-5}$ used to set the ESL is used to identify serious areas of concern, i.e., hot spot areas that are anomalies. We agree that extra resources in manpower and mobile monitors, should be allocated to remedy these anomalous areas expeditiously.

The problem arises when the TCEQ will not acknowledge that anything below this level is in need of improvement. In effect, the TCEQ does not use the ESL in b) above except as a bright line ambient standard.

The TCEQ repeatedly stands in the path of cleaner air in Houston when the city government initiates measures to make improvements in air quality. The City and multiple air experts, as documented in the Rice University report[4], feel that a health protective risk level of $1x10^{-6}$ should be our goal, especially in light of the additive risk of our several air pollutants. The figure below shows the Milby Park 1,3-butadiene concentrations from 2007 in a boxplot with the ESL and the OAQPS limits marked. The ESL set at $1x10^{-5}$ is so high that only a minority of sites and hours in a year exceed it, yet Milby Park has some of the highest 1,3-butadiene concentrations in the United States.

Figure 5. Boxplot of mean 1,3-butadiene auto GC concentrations at two Houston area monitors



It appears that the TCEQ would like the public to believe that everything below the ESL is acceptable even though the vast majority of observations at this monitor fall between EPA's health level and TCEQ's hotspot level. The City of Houston would like support from the TCEQ in improving our air quality. As in the case of the MCL in drinking water, the TCEQ should consider an MCLG for air, with a goal set to be more health protective (e.g, $5x10^{-6}$ or $1x10^{-6}$).

[4] Rice University 2006. The Control of Air Toxics: Toxicology Motivation and Houston Implications http://www.greenhoustontx.gov/reports/controlofairtoxics.pdf

Again, I appreciate the opportunity to comment and am happy to discuss this matter with you further.

Sincerely,

Loren Raun

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City of Houston
Mayor's Office