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

[1] EPA, Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F, (March 2005).

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.

References:

Johnsrud, E.K., Koukouritaki, S.B., Divakaran, K., Brunengraber, L.L., Hines, R.N., and McCarver, D.G. (2003). Human hepatic CYP2E1 expression during development. J. Pharmacol. Exp. Ther. 307, 402-7.

Levine, E.G., and Bloomfield, C.D. (1992). Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin. Oncol. 19, 47-84.

Pyatt, D.W., Hays, S., and Cushing, C. (2005). Do Children Have Increased Susceptibility for Developing Secondary Acute Myelogenous Leukemia? Chemico-Biological Interactions 153-154, 230-229.

USEPA, (1997). Chemical and Radiation Leukemogenesis in Humans and Rodents and the Value of Rodent Models for Assessing Risks of Lymphohematopoietic Cancers. EPA/600/R-97/090.