

Responses to Comments on the Draft Technical Support Document for Proposed Reference Exposure Levels (RELs) for 1, 3-Butadiene:

1. Comments from the American Chemistry Council (7/16/12)

Comment 1. Occurrence and Exposure p.2.

The OEHHA document states “Most environmental releases of butadiene are associated with fugitive or accidental emission during manufacture, use, transport, storage, or disposal.” This sentence is misleading because the primary source of butadiene environment releases is via emissions from gasoline and diesel-powered vehicles and equipment, not via industrial manufacture. According to the U.S. Environmental Protection Agency, 1.6% of environmental emissions of butadiene are from industrial production and use, 78.8% from mobile sources, and 19.9% from other miscellaneous combustion sources (EPA, 2002⁴). The document should be revised to accurately state the major source contributors for butadiene exposure.

Response to Comment 1.

The text refers to “point sources” which are the primary focus of the hot spots program. The sentence will be revised to clearly distinguish contributions of point and non-point or mobile sources of butadiene emissions.

Comment 2. p.10 and 11, Asthma.

*This section notes the study conducted by Delfino et al., 2003, in which the authors interpreted the results as suggestive of an increased risk of asthma symptoms associated with butadiene exposure. As the document clearly states, this study had several limitations including study size and the results were strongly influenced by one subject. The document would be improved to also include further detail provided by Delfino et al. on the low reporting of positive symptoms by the study participants. The study size, low reporting and influence of one subject could have skewed the results. Additionally, the sentence on page 11 that states “Misclassification of VOC exposures may have occurred for some chemicals such as formaldehyde with important indoor sources but data from other studies support the view that motor vehicle emissions strongly influence the exposures to other VOCs such as benzene, ethylbenzene, toluene, xylenes and **probably butadiene** (bolded for emphasis).” There is nothing in the text that warrants the inclusion of butadiene in this sentence and thus the reference to butadiene should be removed.*

Response to Comment 2.

OEHHA believes the sentence in question is a reasonable extension to related volatile compounds included in the study. In their discussion (p.652), the authors clearly state,

“Although CIs were wider, ORs were positive for symptom scores >1 in relation to lag 1 concentrations of the same VOCs **as well as 1,3-butadiene**” (bolded for emphasis).

Comment 3. DART Rat Study (Section 6).

“This section discusses several studies that were conducted in mice that have shown some toxicity but it fails to include a discussion of a rat study which was previously provided to OEHHA by the Panel. On October 1, 2003...”

Response to Comment 3.

We have added a description of the Hackett et al. (1987b) rat developmental toxicity inhalation study. This study is largely negative and appears to be the companion to the mouse developmental study we have used in the derivation of the acute REL.

Comment 4. Hackett et al. (1987) Study and Green (2003) Re-analysis.

“As well, this section discusses at length the findings from the Hackett et al., 1987⁶ study and notes toxicity effects on male fetal body weight as a critical effect which was ultimately used as the basis for the REL. However, previously the Panel provided extensive comments to OEHHA in 2003 that dispute the apparent finding of reduced fetal body weights in male mice from the Hackett et al. study. The Panel noted in those comments that this finding was based on an inappropriate statistical analysis and provided additional documentation in support of this point. The Panel’s comments also consisted of the Green statistical re-analysis⁷ of the mouse data reported by Hackett et al. which confirmed that a reduction in male fetal body weight is not seen at 40 ppm when proper statistical methods are applied. The Panel has included an additional copy of this statistical re-analysis in the attachment.”

Response to Comment 4.

We have reviewed the Green 2003 re-analysis of the Hackett et al. (1987) data and agree that the low dose in the study now appears to be a NOAEL rather than a LOAEL. However, as reported in our draft document, our proposed acute REL is not based on a NOAEL/LOAEL approach but rather on a benchmark dose method which uses the entire dose response to derive an alternative to the NOAEL, namely the BMCL₀₅, or the 95% lower bound on the 5% response level. In our draft analysis this value was 13.4 ppm. We have now repeated this analysis using the Green revised values (Table 1, p.15 in the Green report) and find a BMCL₀₅ of 17 ppm based on this latter analysis (Hill model, exact fit). This new analysis and a revised acute REL are included in the revised draft.

Comment 5. Derivation of the REL Values.

As well, OEHHA selected ovarian atrophy in mice as the key non-cancer health effect for butadiene to derive the 8-hr and chronic REL. While the Owen et al., 1987

publication indicated only that gonads were examined, the original study report shows ovarian atrophy was observed in 2 of 46 control rats and 1 of 24 rats in the 8000 ppm exposure group (Table 24, Page B55 of the report). Thus, it appears that ovarian atrophy is an effect specific to the mouse and likely a consequence of the mouse's high rate of butadiene metabolism compared to other species. Given available knowledge of interspecies differences in metabolism, the selected endpoint is of questionable human relevance.

Response to Comment 5.

The ovarian atrophy in female mice in the NTP study was the most sensitive non-neoplastic effect noted among several organ weight effects (lung, liver, and kidney) and uterine, testicular and nasal olfactory epithelial atrophies. It is difficult to extrapolate toxic effects between rodent species, let alone between rodents and humans. OEHHA does not accept the notion that studies in mice are not relevant to human risk assessment or that rats are necessarily “more human” than mice. Duescher and Elfarra (1994) reported that: “Butadiene monoxide formation rates in human liver microsomes were similar, or higher, than the rate obtained in mouse liver microsomes, whereas 1,3-butadiene oxidation rates in human and mouse liver microsomes were higher than the rate obtained in rat liver microsomes. These results provide direct evidence that 1,3-butadiene is a substrate for multiple P450 enzymes and suggest that humans may be at higher risk of expressing 1,3-butadiene toxicity compared to mice or rats. In addition, these results suggest that the mouse may be the more appropriate animal model to assess human risk.”

Comment 6. Intraspecies Uncertainty Factor.

Finally, the REL for chronic exposure to butadiene includes an intraspecies uncertainty factor of 30, which included an uncertainty factor of 10 for toxicokinetics however OEHHA provides minimal justification for the selection of this value. The document should be updated to include greater justification for the selection of this uncertainty factor based on the available database.

Response to Comment 6.

The use of a UF of 10 for intraspecies uncertainty in toxicokinetics is based on OEHHA's non-cancer risk assessment guidance (OEHHA, 2008), which was developed in response to the California Children's Environmental Health Act of 1999. Unless we have adequate information on all segments of the exposed population we must acknowledge that uncertainty and apply a larger UF_{HK}. As noted in the draft, the human metabolism of butadiene is based on studies in relatively few (deceased) adults (e.g., Duescher and Elfarra, 1994) and in our view is insufficient to encompass the possible range of metabolism and toxicokinetics, particularly in young children.

Comment 7. Interspecies Uncertainty Factor.

OEHHA is also encouraged to refer to the recent analysis described in the TCEQ DSD for Butadiene regarding the chronic REL and the reliance on the ovarian atrophy effect

*in mice and only mice. The TCEQ assessment and the assessment conducted by the US EPA (Health Assessment of 1, 3 Butadiene, EPA/600/P-98/001F October 2002) both provide several references in the literature regarding the essential role of the diepoxide metabolite of butadiene as the metabolite critical to the occurrence of ovarian atrophy in mice (including references pertaining to observations of ovarian atrophy in rats when exposed directly to the diepoxide metabolite). Critically, significant evidence is provided that this diepoxide metabolite is produced in the mouse in far greater quantities than any other species, including and especially humans, with limited conclusive evidence that humans can produce this metabolite at all. This information should inform OEHHA regarding the magnitude of specific uncertainty factor related to interspecies differences pertaining to ovarian atrophy and argues strongly that this value should be **less than 1**.*

Response to Comment 7.

We have cited a published summary of the TCEQ butadiene assessment in the draft (Grant et al., 2010) and have reduced our usual interspecies uncertainty subfactor for toxicokinetics from $\sqrt{10}$ to 1 based on the published evidence of greater metabolism of butadiene to epoxide metabolites in the mouse compared to results with other species. As noted in the responses above, human data on this point are relatively limited and at this time OEHHA does not favor the use of fractional UFs. As also noted above the ovarian atrophy endpoint was the most sensitive observed in the experimental animals. Our assessment does not assume that this is the exact effect that will occur in exposed humans. Butadiene exposure caused many other toxic effects that may be more relevant to humans. This is part of the uncertainty.