# 1,3-BUTADIENE REFERENCE EXPOSURE LEVELS (DRAFT)

Air, Community and Environmental Research Branch
Office of Environmental Health Hazard Assessment
October, 2012

# Authority

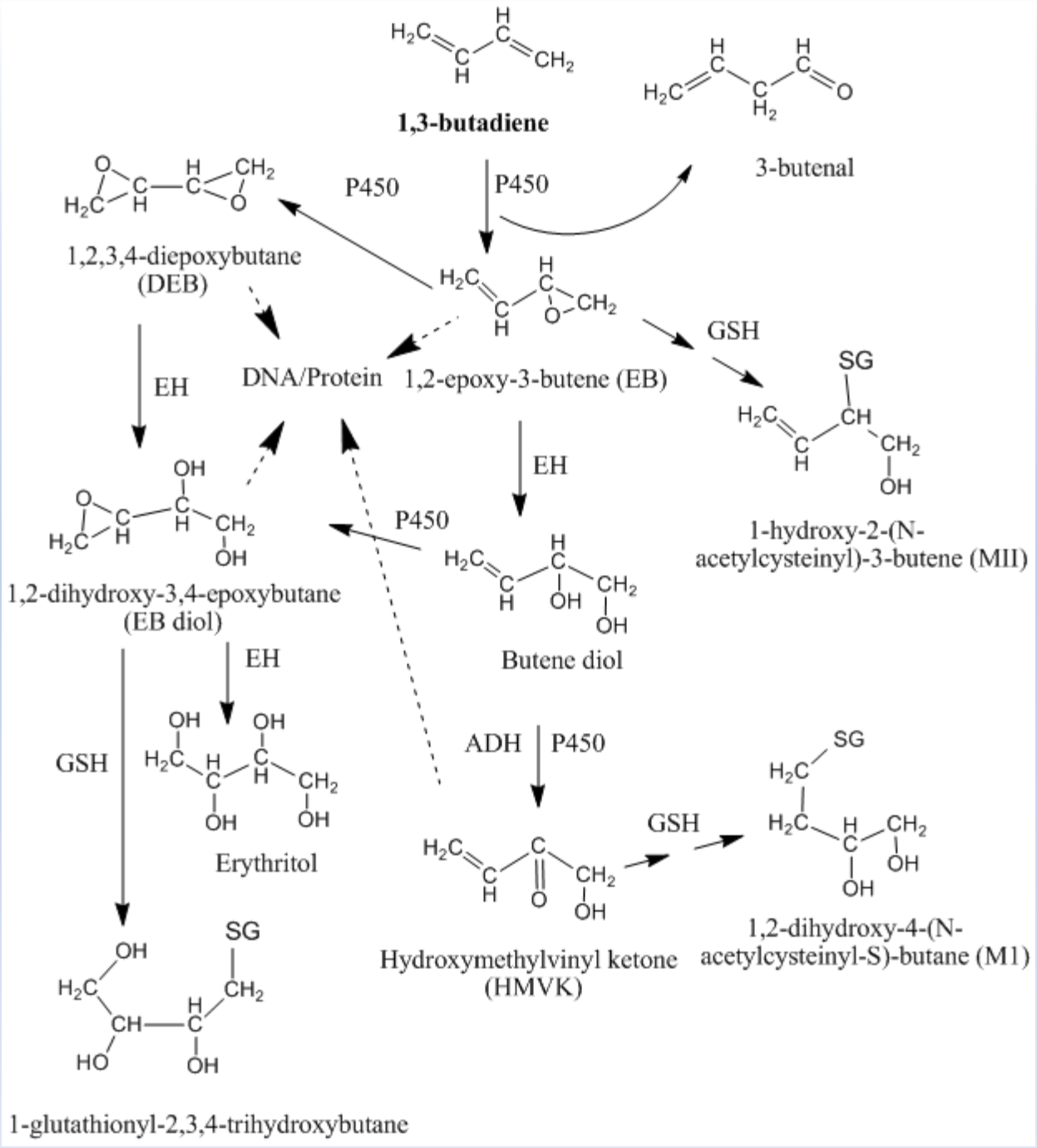
- **The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)).**
- **Consideration of possible differential effects on the health of infants, children and other sensitive subpopulations is mandated by the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, chapter 731, statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*).**

# Summary

- Butadiene is a major commodity product of the petroleum industry.
- Workers acutely exposed to butadiene experienced irritation of eyes and nasal passages, throat and lungs.
- Some workers experienced coughing, fatigue, and drowsiness.
- Inhalation of butadiene is mildly narcotic at low concentrations.
- Exposure to very high concentrations can result in narcosis, respiratory paralysis and death.
- Repeated exposures can damage human sperm cells and increase ovarian atrophy in mice.

| Table 1. 1,3-Butadiene Air Sampling in the San Francisco Bay Area (BAAQMD, 2008) | | | | |
|---|---|---|---|---|
| **Site** | Average, ppb | Maximum, ppb | Number of Samples | % Less than MDL |
| **Benecia** | 0.0275 | 0.1 | 30 | 96.7 |
| **Berkeley** | 0.0358 | 0.13 | 61 | 85.2 |
| **Concord** | 0.0287 | 0.070 | 31 | 90.3 |
| **Crockett** | 0.025 | NA | 31 | 100 |
| **Fremont** | 0.039 | 0.12 | 31 | 67.7 |
| **Livermore** | 0.031 | 0.090 | 31 | 90.3 |
| **Martinez** | 0.028 | 0.070 | 30 | 93.3 |
| **Napa** | 0.043 | 0.17 | 31 | 74.2 |
| **Oakland** | 0.0352 | 0.090 | 31 | 87.1 |
| **Redwood City** | 0.0453 | 0.15 | 31 | 80.6 |
| **Richmond** | 0.0261 | 0.060 | 31 | 96.8 |
| **San Francisco** | 0.0276 | 0.080 | 31 | 96.8 |
| **San Jose** | 0.0687 | 0.26 | 31 | 58.1 |
| **San Pablo** | 0.0261 | 0.060 | 31 | 96.8 |
| **San Rafael** | 0.0250 | NA | 31 | 100 |
| **Santa Rosa** | 0.0416 | 0.170 | 31 | 83.9 |
| **Sunnyvale** | 0.0259 | 0.050 | 28 | 100 |
| **Vallejo** | 0.0365 | 0.160 | 31 | 83.9 |

Note MDL = Minimum Detection Limit


1,3-butadiene
3-butenal
P450
P450
1,2,3,4-diepoxybutane
(DEB)
1,2-epoxy-3-butene (EB)
GSH
EH
DNA/Protein
SG
EH
1-hydroxy-2-(N-
acetylcysteinyl)-3-butene (MII)
P450
1,2-dihydroxy-3,4-epoxybutane
(EB diol)
Butene diol
EH
GSH
Erythritol
ADH
P450
GSH
SG
Hydroxymethylvinyl ketone
(HMVK)
1,2-dihydroxy-4-(N-
acetylcysteinyl-S)-butane (M1)
SG
1-glutathionyl-2,3,4-trihydroxybutane

# Acute Toxicity in Animals

- **Developmental toxicity in mice (Hackett et al. , 1987; original report).** 78 pregnant female mice exposed to 0, 40, 200, or 1000 ppm butadiene for 6hr/d on gestation days(gd) 6-15. Significant dose-dependent reduction of fetal body weight at all doses in males ($P<0.05$). LOAEL = 40 ppm. $BMCL_{05}$ = 13.4 ppm, HEC = 22.5 ppm, UF = 100, aREL = 225 ppb (0.5 mg/m3).

# Acute Toxicity in Animals (Cont.)

- **Developmental toxicity in mice (Hackett et al. , 1987; reanalyzed by Green, 2003).** Significant dose-dependent reduction of fetal body weight at 200 and 1000 ppm. NOAEL = 40 ppm, LOAEL = 200 ppm. $BMCL_{05}$ = 17.7 ppm, HEC = 29.7 ppm, UF = 100, aREL = 297 ppb (0.66 mg/m3).

# Acute REL

- Study: Hackett et al. (1987). Developmental toxicity
- Exposure: 0, 40, 200, 1000 ppm butadiene 6hr/d gd 6-15
- NOAEL = 40 ppm
- $BMDL_{05}$ = 17.7 ppm
- HEC = 29.7 ppm (17.7 x 1.68 DAF)
- Interspecies TK UF = 1
- Interspecies TD UF = √10 (default)
- Intraspecies TK UF = 10
- Intraspecies TD UF = √10 (default)
- Cumulative UF = 100
- aREL = 29.7/100 = 297 ppb (0.66 mg/m3)

## Table 2. Body Weight and Fetal and Placental Measures after 1,3-Butadiene Exposure (Hackett et al. 1987)

| Observation | 1,3 Butadiene Concentration (ppm) | | | |
|---|---|---|---|---|
| | 0 | 40 | 200 | 1000 |
| **Number examined** | | | | |
| **Mothers** | 18 | 19 | 21 | 20 |
| **Litters** | 18 | 19 | 21 | 20 |
| **Fetuses** | 211 | 237 | 259 | 244 |
| **Maternal weight gain (g)[a] (11-16 gd)** | 13.3 ± 0.6[b] | 12.7 ± 0.4[b,c] | 11.4 ± 0.5[c,d] | 10.6 ± 0.4[d] |
| **Pup body weight (g)[a]** | | | | |
| **Females** | 1.30 ± 0.02[b] | 1.25 ± 0.01[b] | 1.10 ± 0.02[c] | 1.02 ± 0.03[d] |
| **Males** | 1.38 ± 0.03[b] | 1.31 ± 0.02[c] | 1.13 ± 0.02[d] | 1.06 ± 0.02[e] |
| **Sex ratio (% male)** | 51.6 ± 3.91 | 49.8 ± 3.06 | 51.5 ± 3.68 | 51.8 ± 3.29 |
| **Placental weight (mg)[a]** | | | | |
| **Females** | 83.1 ± 3.03[b] | 80.9 ± 2.46[b] | 74.7 ± 3.52[b,c] | 70.1 ± 2.33[c] |
| **Males** | 89.3 ± 3.05[b] | 89.5 ± 2.27[b] | 80.1 ± 2.35[c] | 74.5 ± 1.81[c] |

[a]Mean ± standard error; [b-e] Values that do not share a common superscript letter are significantly different ($p \leq 0.05$) from one another.

## Table 2. Body Weight and Fetal and Placental Measures after 1,3-Butadiene Exposure (Re-analysis of Green, 2003)

| Observation | 1,3 Butadiene Concentration (ppm) | | | |
|---|---|---|---|---|
| | 0 | 40 | 200 | 1000 |
| **Number examined** | | | | |
| **Mothers** | 18 | 19 | 21 | 20 |
| **Litters** | 18 | 19 | 21 | 20 |
| **Fetuses** | 211 | 237 | 259 | 244 |
| **Maternal weight gain (g)[a] (11-16 gd)** | 13.3 ± 0.6 | 12.7 ± 0.4 | 11.4 ± 0.5 | 10.6 ± 0.4 |
| **Pup body weight (g)[a]** | | | | |
| **Females** | 1.309 ± 0.028 | 1.253 ± 0.012 | 1.100 ± 0.022* | 1.015 ± 0.026* |
| **Males** | 1.382 ± 0.033 | 1.307 ± 0.016 | 1.132 ± 0.016* | 1.060 ± 0.024* |
| **Sex ratio (% male)** | 51.55 ± 3.866 | 48.66 ± 2.947 | 51.44 ± 3.667 | 51.80 ± 3.310 |
| **Placental weight (mg)[a]** | | | | |
| **Females** | 83.15 ± 3.023 | 80.89 ± 2.474 | 74.33 ± 3.540 | 70.84 ± 2.284* |
| **Males** | 89.58 ± 2.995 | 89.71 ± 2.263 | 80.27 ± 2.324 | 74.64 ± 1.785* |

[a]Mean ± standard error; * values are significantly different ($p \leq 0.05$) from control.

## Table 5. Benchmark Dose Analysis of Male Mouse Fetal Weight Data of Hackett et al. (1987) and Green (2003).

| Dose Metric | N, male fetuses | Model | $BMC_{05}$ | $BMCL_{05}$ | $BMCL_{05}$ ppm BD equivalent | Human ppm equivalent 1.68 DAF |
|---|---|---|---|---|---|---|
| **Applied BD ppm 6 hr/d** | | | | | | |
| **0** | 109 | Hill | 28.5** | 13.4 ** | 13.4** | 22.5 |
| **40** | 118 | Polynomial | 448.8 | 41.1 | 41.1 | 69.0 |
| **200** | 133 | Power | 261.0 | 225.0 | 225.0 | 378 |
| **1000** | 126 | Hill (Green) | 37.2** | 17.7** | 17.7** | 29.7 |
| **PBPK AUC Maternal BMO µMhr/d** | | | | | | |
| **0** | 109 | Hill | 134.0** | 70.1** | 66.5** | 27.7 |
| **166.4** | 118 | Polynomial | 100.0 | 69.2 | 14.9 | 25.0 |
| **371.9** | 133 | Power | 106.0 | 90.7 | 19.8 | 33.3 |
| **493.8** | 126 | | | | | |
| **PBPK AUC Fetal BMO µMhr/d[a]** | | | | | | |
| **0** | 109 | Hill | 10.9** | 5.1** | 13.4** | 22.5 |
| **15.2** | 118 | | | | | |
| **74.3** | 133 | | | | | |
| **356.7** | 126 | | | | | |

** indicates exact model fit by graph and tabular output, P values were not applicable for exact fits of the Hill model to the continuous data sets or given as P <0.0001 for the other models despite obvious high degrees of fit visually and by tabular output of observed and predicted values;

[a] based on average fetal BMO AUC during gestation days 9-18.

# 8-Hour REL

- Study:  NTP (1993) supported by Doerr et al. (1996).
- Study Population: Female B6C3F1 mice
- Exposure: Inhalation of 1,3-butadiene at 0, 6.25, 20, 62.5, 200, or 625 ppm , 6hr/d, 5d/week for various periods up to 103 weeks.
- Effect: Dose-dependent increases in ovarian atrophy
- $BMDL_{05}$ = 1.01 ppm
- Time adjustment  =  758 ppb (1.01 x 6/8 hr/d)
- Human Equivalent Concentration = 1.27 ppm (0.758 x 1.68 DAF)
- Interspecies UF = √10
- Intraspecies UF = 30 (10 PD x √10 PK)
- Cumulative UF = 100
- 8-Hr REL = 1.27/100 = 12.7 ppb (28 µg/m3)

**Table 3.Ovarian Atrophy in Female Mice in 2-Year Inhalation Study of 1, 3-Butadiene (NTP, 1993).**

| Exposure Period | Model | $X^2$ | P | $BMC_{05}$ ppm | $BMCL_{05}$ ppm | $BMCL_{05}$ continuous, ppm | Comments |
|---|---|---|---|---|---|---|---|
| 9 months | Multistage | 2.47 | 0.78* | 35.0 | 19.25 | 3.44 | Full data set, N = 58 |
| 15 months | Log probit | 10.74 | 0.030 | 11.2 | 3.66 | 0.654 | Full data set, N = 52 |
| | Log probit | 10.64 | 0.014 | 11.1 | 3.45 | 0.616 | Without top dose, N = 50 |
| 24 months | Log probit | 6.47 | 0.091 | 0.056 | 0.0034 | 0.00054 | Full data set, N = 325 |
| | Log probit | 2.80 | 0.42* | 0.254 | 0.031 | 0.0055 | Without top dose, N = 246 |
| 9-24 mo time adjusted ** | Log probit | 1.7 | 0.64* | 2.04 | 1.01 | 0.18 | Full data, N = 435 |
| 9-24 mo time adjusted** | Log logistic | 1.13 | 0.89* | 2.03 | 1.58 | 0.28 | Full data, N = 435 |

# Doerr et al. (1996)Supporting Study

- Butadiene monoxide (BMO,0.005-1.43 mmol/kg bw_d i.p. x 30d, n = 10 female mice/dose)
- Butadiene diepoxide (DEB, 0.002-0.29 mmol/kg bw_d i.p. x 30 d , n = 10 female mice /dose)
- Decrease in ovarian weight w/ BMO & DEB (0.0425-0.02; 0.0375-0.015)
- Decrease in uterine weight w/ BMO & DEB (0.27-0.10; 0.34-0.03)
- Internal dosimetry by PBPK model: AUC BMO in blood, AUC DEB in blood, Hb adducts w/i.p. simulated doses
- Best fit metric for ovarian atrophy: AUC DEB µM hr/d from BMO i.p.; Polynomial model (P = 0.92), $BMDL_{05}$ = 20.5 µM hr/d, $BMDL_{05}$ 6 hr mouse BD equivalent = 1.8 ppm

# Chronic REL

- Study: NTP 1993 supported by Doerr et al. (1996)
- Study Population: Female B6C3F1 mice
- Exposure:  6hr/d, 5 d/wk, 9-24 months, increased ovarian atrophy
- $BMCL_{05}$ = 1.01 ppm
- Time adjustment = 180 ppb (1.01 x 6/24 hr x 5/7 d)
- HEC = 302 ppb (180 x 1.68 DAF)
- Interspecies UF = √10
- Intraspecies UF =  10 x √10
- Cumulative UF = 100
- cREL = 302 ppb/100 = 3.0 ppb (6.7 µg/m3)

# Overall RELs Summary

- Acute REL = 0.66 mg Butadiene/$m^3$ Development
- 8-Hr REL = 28 µg Butadiene/$m^3$ Development
- Chronic REL = 7 µg Butadiene/$m^3$ Development

# Comments Received

- Comment 1: Hackett et al. (1987) used inadequate statistics to identify a 40ppm LOAEL for male fetal weight. The Green (2003) re-analysis shows 40 ppm is a NOAEL.
- Response 1. OEHHA agrees that the Green (2003) re-analysis of the Hackett data shows that 40 ppm is a NOAEL. However our aREL derivation is not based on a NOAEL approach but rather a benchmark dose method that uses the entire dose response to derive an alternative to the NOAEL namely the $BMCL_{05}$. In our draft this value was 13.4 ppm and with the Green re-analyzed data the $BMCL_{05}$ is 17.7 ppm, about 30% higher. This would increase the proposed aREL to 297 ppb from 225 ppb.

# Comments Continued

- Comment 2:The draft states that most environmental releases of butadiene are associated with fugitive or accidental emission during manufacture, use, transport, storage, or disposal. The U.S. Environmental Protection Agency reports 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, 2002).
- Response 2:The text refers to “point  sources” 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.

# Comments Continued

- Comment 3: The Draft 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 3. 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).

# Comments Continued

- Comment 4: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 4:*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's difficult to extrapolate toxic effects between rodent species much less 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.

# Comments Continued

- Comment 5: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 5:The use of a UF of 10 for intraspecies uncertainty in toxicokinetics is based on OEHHA's guidance developed in response to the California Children's Environmental Health Act of 1999 (OEHHA, 2001). Unless we have adequate information on all segments of the exposed population we must acknowledge that uncertainty and apply a larger $UF_{TK}$. 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.

# Comments Continued

- Comment 6: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 interspecies uncertainty factor related to interspecies differences pertaining to ovarian atrophy and argues strongly that this value should be **less** than 1.
- *Response 6:* We have reduced our usual uncertainty subfactor for toxicokinetics from √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. Human data on this point are relatively limited and at this time OEHHA does not favor the use of fractional UFs. As 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.