CHRONIC TOXICITY SUMMARY

1,3-BUTADIENE

(butadiene; buta-1,3-diene; biethylene; bivinyl; divinyl; vinylethylene)

CAS Registry Number: 106-99-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 µg/m^3** (8 ppb)
Critical effect(s)	Increased incidence of ovarian atrophy in mice
Hazard index target(s)	Female reproductive system

II. Physical and Chemical Properties Summary (HSDB, 2000; CRC, 1995)

Description	Colorless gas
Molecular formula	C_4H_6
Molecular weight	54.09 g/mol
Boiling point	–4.4^{o}C
Melting point	–108.9^{o}C
Vapor pressure	910 torr at 20^{o}C
Solubility	Very slightly soluble in water (735 mg/L); soluble in ethanol, ether, acetone, benzene and organic solvents
Conversion factor	1 ppm = 2.21 mg/m^3 at 25^{o}C

III. Major Uses and Sources

1,3-Butadiene is a major commodity product of the petrochemical industry, usually produced as a by-product of ethylene. The majority of 1,3-butadiene is used in the production of styrene-butadiene rubber copolymers (SBR). Other applications include use as a polymer component for polybutadiene, hexamethylene diamine, styrene-butadiene latex, acrylonitrile-butadiene-styrene (ABS) resins, chloroprene and nitrile rubbers. A variety of industrial syntheses use 1,3-butadiene resins (AB as a chemical intermediate, such as in the production of adiponitrile (a nylon precursor), captan and captofol fungicides, ethylidene norbornene and sulfolane, boron alkyls, and hexachlorobutadiene. Additionally, 1,3-butadiene is found in automobile exhaust, gasoline vapor, fossil fuel incineration products, and cigarette smoke (HSDB, 2000). In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of 1,3-butadiene was approximately 0.2 ppb (CARB, 1999). The South Coast Air Quality Management District (SCAQMD, 2000) detected ambient levels of 1,3-butadiene ranging from 0.1 to 0.8 ppb at 10 stationary monitors placed throughout the South Coast Air Basin. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 20,846 pounds of 1,3-butadiene (CARB, 2000).

IV. Effects of Human Exposure

An early occupational study reported complaints of irritation of eyes, nasal passages, throat, and lungs in rubber manufacturing workers following acute exposure to unknown levels of 1,3-butadiene (Wilson, 1944). Additional symptoms reported included coughing, fatigue, and drowsiness; however, all symptoms ceased on removal from the exposure.

Studies on the chronic effects of 1,3-butadiene have been centered in the styrene-butadiene rubber manufacturing industry, which uses large quantities of 1,3-butadiene, and in the 1,3-butadiene monomer industry. One retrospective epidemiological study reported an increase in overall mortality, emphysema, and cardiovascular diseases (chronic rheumatic and arteriosclerotic heart disease) among rubber workers (McMichael *et al.*, 1976). Two other occupational studies (Divine and Hartman, 1996; Matanoski *et al*., 1990) indicated that the standardized mortality ratio for deaths from arteriosclerotic heart disease was elevated (~1.4-1.8) among black workers in the 1,3-butadiene rubber industry. Other occupational studies have described the potential for adverse hematological effects due to butadiene exposure (Checkoway and Williams, 1982; McMichael *et al.*, 1975). A survey of workers at a styrene-butadiene rubber plant revealed slightly lower levels (but within normal range) of red blood cells, hemoglobin, platelets, and neutrophils in exposed (mean = 20 ppm) versus unexposed workers (Checkoway and Williams, 1982). And 1,3-butadiene has been implicated in hematopoietic malignancies among styrene-butadiene rubber workers at levels lower than 20 ppm (McMichael *et al.*, 1975). Since the workers in these studies were exposed to mixtures of chemicals, the specific contribution of butadiene to the adverse respiratory and hematopoietic effects remains unclear.

V. Effects of Animal Exposure

The few available chronic animal inhalation studies have focused on the potential carcinogenicity of 1,3-butadiene. The National Toxicology Program (NTP) has sponsored two chronic inhalation studies in $B6C3F_1$ mice (NTP, 1984; Melnick *et al.*, 1990; NTP, 1993), while Hazelton Laboratories Europe (HLE) Ltd. conducted a chronic inhalation study in Sprague-Dawley rats (HLE, 1981; Owen *et al.*, 1987; Owen and Glaister, 1990).

The two $B6C3F_1$ mice inhalation studies sponsored by NTP (Huff *et al.*, 1985; Melnick *et al.*, 1990; NTP, 1984; NTP, 1993), although focused on carcinogenicity, identified other adverse chronic effects. The earlier NTP (1984) study in mice administered 0, 625 or 1250 ppm 1,3-butadiene for 6 hours/day, 5 days/week for up to 61 weeks. Nonneoplastic changes observed were elevated testicular and ovarian atrophy at both doses (625 and 1250 ppm); liver necrosis in male mice at both doses and in female mice at 1250 ppm; and nonneoplastic lesions in the nasal cavity at 1250 ppm. At the highest dose, adverse changes in the nasal cavity included chronic inflammation, fibrosis, cartilaginous metaplasia, osseous metaplasia, and atrophy of the sensory epithelium. No nasal or respiratory lesions were seen in the controls. This study identified a chronic LOAEL of 625 ppm for gonadal atrophy in both sexes.

The later NTP study (Melnick *et al.*, 1990; NTP, 1993) used lower exposure concentrations of 1,3-butadiene (0, 6.25, 20, 62.5, 200 or 625 ppm) administered 6 hours/day, 5 days/week for up

to 2 years. Two-year survival was significantly decreased in mice exposed to 20 ppm and greater, primarily due to chemical-related malignant neoplasms. Increased incidences of non-neoplastic lesions in exposed mice included bone marrow atrophy, gonadal atrophy (testicular, ovarian and uterine), angiectasis, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and cardiac endothelial hyperplasia. Gonadal atrophy was observed at 200 ppm and 625 ppm for males and at 6.25 ppm and higher for females. Bone marrow toxicity (regenerative anemia) was seen at 62.5 ppm and higher. This study identified a chronic LOAEL of 6.25 ppm for reproductive toxicity, and a NOAEL of 200 ppm and a LOAEL of 625 for non-neoplastic hematotoxic effects.

Table 1. Reproductive system atrophy and 2 year survival (NTP, 1993)

	Butadiene (ppm)	*Female survival*	*Atrophy of ovary*	*Atrophy of uterus*	*Male survival*	*Atrophy of testicle*
	0	37/50	4/49	1/50	35/50	1/50
	6.25	33/50	19/49	0/49	39/50	3/50
	20	24/50	32/48	1/50	24/50	4/50
	62.5	11/50	42/50	1/49	22/50	2/48
	200	0/50	43/50	8/50	4/50	6/49
	625	0/80	69/79	41/78	0/70	53/72

The U.S. EPA (1985) reviewed data from a 2-year chronic inhalation toxicity study sponsored by the International Institute of Synthetic Rubber Producers (IISRP) at Hazelton Laboratories Europe, Ltd (1981) on Sprague-Dawley rats exposed to 0, 1000 or 8000 ppm 1,3-butadiene. Results from the study were also reported later by Owen *et al.* (1987; 1990). Minor clinical effects, including excessive eye and nose secretions plus slight ataxia, were observed between 2 and 5 months in rats exposed to 8000 ppm 1,3-butadiene. Alterations in organ weight were also observed in this high exposure group. A dose-related increase in liver weights was observed at both the 52-week interim kill and at study termination. Absolute and relative kidney weight was also significantly increased and associated with nephrosis. No reproductive organ atrophy was reported in this rat study; however, tumors were found in reproductive tissues (Owen *et al.*, 1987).

Penn and Snyder (1996a,b) exposed cockerels (young male chickens) to 0 or 20 ppm 1,3-butadiene 6 hr/day, 5 days/week for 16 weeks to study arteriosclerotic plaque development. The cockerel is a sensitive animal model for studying the effects of environmental arteriosclerotic plaque-promoting agents. Plaque frequency and location were not affected. However, plaque sizes were significantly larger in 1,3-butadiene-treated cockerels than in controls.

The U.S. EPA (1985) described another secondary report, that of Miller (1978), which reviewed a group of Russian studies of subchronic 1,3-butadiene exposure in rats. One study (reported by Ripp in 1967) continuously exposed rats to relatively lower concentrations of 0.45, 1.4 or 13.5 ppm. At 13.5 ppm, blood cholinesterase was elevated, blood pressure was lowered, and motor activity was decreased. Histopathological changes reported at 0.45 ppm were congestion in the spleen and hyperemia and leukocyte infiltration of cardiac tissue. Alterations in lung tissue

noted at 1.4 and 13.5 ppm included atelectasis, interstitial pneumonia, and emphysema. No other studies used such low exposure levels or measured such endpoints. Unfortunately, the specific research methods and results for this study are unavailable for direct review and comparison.

A series of reproductive and developmental toxicity studies undertaken by U.S. EPA was summarized by Morrissey *et al*. (1990). In developmental toxicity studies, pregnant female rats and mice were exposed to 0, 40, 200, or 1000 ppm 1,3-butadiene for 6 hrs/day on days 6-15 of gestation. In rats, maternal body weight gain and extra-gestational body weight gain was reduced at the highest exposure. However, no evidence of developmental toxicity was observed. In mice, maternal body weight gain and extra-gestational body weight gain were reduced at 200 and 1000 ppm. Gravid uterine weight was reduced at 1000 ppm. Fetal and placental weights were reduced in an exposure-dependent manner with reduced male fetal body weight reaching statistical significance at 40 ppm and above. In the sperm head morphology assay and the dominant lethality study, groups of male mice were exposed to 200, 1000, and 5000 ppm 1,3-butadiene for 5 consecutive days. Concentration-related small increases in the percentages of abnormal sperm heads were observed, but were statistically significant only at the two highest exposures. Dominant lethal effects were observed only in the first two weeks following exposure. At week 1, the percentage of dead implants/total implants was increased only at 1000 ppm, and the percentage of females with $\geq$ 2 dead implants was increased at 200 and 1000 ppm. The number of dead implants/pregnancy was increased beginning at 1000 ppm at week 1, and 200 and 1000 ppm at week 2. While not strongly concentration dependent, the dominant lethality results are consistent with an adverse effect of 1,3-butadiene on more mature cells (spermatozoa and spermatids).

An acute and subchronic (10 week) study identified male-mediated F_1 effects in mice exposed to 12.5 or 1250 ppm 1,3-butadiene for 6 hours/day, 5 days/week (Anderson *et al.*, 1996). An additional group of mice were also exposed to 6250 ppm 1,3-butadiene in the acute study. Meaningful toxic effects were not observed in the acute study and no reproductive parameters were affected in either study. In the 10-week study, 1250 ppm (2762.4 mg/m^3) resulted in a statistically significant reduction in the number of implantations, an induction of dominant lethal mutations, an increased incidence of early and late deaths, and an increase in abnormalities. The lower level of 12.5 ppm (27.63 mg/m^3) resulted in an increase of late deaths and fetal abnormalities.

A follow-up of the Anderson *et al.* (1996) dominant lethality study exposed male mice to 12.5 or 125 ppm 1,3-butadiene under the same subchronic exposure conditions (Brinkworth *et al*., 1998). A statistically significant increase in early deaths was observed at 125 ppm. The incidences of late deaths, dead fetuses, and abnormalities were elevated at 125 ppm but were not statistically significant. Testicular DNA damage, as detected by the Comet assay, was observed at 125 ppm.

Further dominant lethality studies in rodents by the same research group exposed male mice to 12.5, 65, and 130 ppm 1,3-butadiene 6 hr/day, 5 days/week for four weeks (Anderson *et al*., 1998). Groups of male rats were also exposed to 65, 400, and 1250 ppm 1,3-butadiene 6 hr/day, 5 days/week for 10 weeks. In mice, a statistically significant increase in early deaths was observed at 65 and 130 ppm but was not dose-related. Male-mediated effects in rats were not observed at any exposure level.

Pacchierotti *et al*. (1998) investigated 1,3-butadiene-induced toxic effects on spermatogenic cell stages and first-cleavage embryos. Exposure of male mice to 130, 500, and 1300 ppm 1,3-butadiene 6 hr/day for 5 days did not result in an increase of unfertilized oocytes after pairing with untreated females. However, statistically significant increases of cytogenetic aberrations in first-cleavage embryos were observed in the first mating week in mice exposed to 500 and 1300 ppm, and in the second mating week in mice treated with 1300 ppm. Treatment-related effects on differentiating spematogonia were shown by a concentration-dependent decrease of round spermatids occurring 21 days after exposure, and confirmed 7 days later by a similar decrease of elongated spermatids. Testis weight was significantly reduced at all doses tested, 21 days after the end of exposure. A dose-dependent increase of variant sperm with single-stranded DNA content was observed 28 days after exposure, and attained statistical significance at 1300 ppm.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP (1993)
Study population	$B6C3F_1$ mice (70/sex/group)
Exposure method	Discontinuous inhalation (0, 6.25, 20, 62.5, 200, 625 ppm) over 2 years
Critical effects	Increased incidence of ovarian atrophy
LOAEL	6.25 ppm
NOAEL	Not observed
BMC_{05}	1.40 ppm
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	103 weeks
Average experimental exposure	0.25 ppm for BMC_{05} (1.40 ppm x 6/24 hr/day x 5/7 days/week)
Human equivalent concentration	0.25 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	8 ppb (0.008 ppm; 0.02 mg/m^3; 20 $\mu g/m^3$)

The chronic REL for butadiene is based on an increased incidence of ovarian atrophy in mice. Characteristically, affected females had no evidence of oocytes, follicles, or corpora lutea. Significant reproductive toxicity was observed in both sexes of mice at the interim 9-month, interim 15-month, and 2-year study termination as gonadal atrophy (NTP, 1993). Testicular atrophy was induced in male B6C3F1 mice at 625 ppm or above in this principal study and in a previous study (NTP, 1984). In female mice exposed for 9-months, ovarian atrophy was observed at 200 and 625 ppm (442 or 1381 mg/m^3, respectively). After 15 months, ovarian atrophy was observed at exposure levels of 20 ppm (44.2 mg/m^3) and above. In mice exposed

for up to 2 years (103 weeks), the incidence of ovarian atrophy increased at all exposure concentrations relative to controls, which establishes a chronic LOAEL of 6.25 ppm (13.81 mg/m^3) for reproductive toxicity.

Presentation of the ovarian atrophy data in quantal form (see Table 1) allows the use of the benchmark concentration (BMC) approach to determine the REL. A log-normal probit analysis (U.S. EPA, National Center for Environmental Assessment, benchmark dose software, version 1.20) using only the control group and the log-dose of the three lowest butadiene exposure groups provided the lowest chi-square value (i.e., the best line fit to the data points). The proportion of mice developing ovarian atrophy in the two highest exposure groups did not increase appreciably with increasing exposure concentration, and therefore, deviated from the log-normal probit plot. The significantly shortened survival rate in these two groups may be one reason for this deviation. Another possible cause is that a relatively resistant subgroup of mice (to ovarian atrophy) is revealed at the two highest doses following 2-year exposure to 1,3-butadiene. Thus, it may be biologically plausible to remove these resistant subgroups when using a BMC approach. The maximum likelihood estimate (MLE) for a 5% response was 1.53 ppm. The resulting 95% lower confidence limit at the MLE provided a BMC_{05} of 1.40 ppm. A BMC_{05} is considered to be similar to a NOAEL in estimating a concentration associated with a low level of risk.

The mouse ovary is more sensitive to butadiene's epoxide metabolites than the rat ovary. Doerr *et al*. (1996) administered butadiene monoepoxide (BMO) or butadiene diepoxide (BDE) intraperitoneally to female B6C3F1 mice and Sprague-Dawley rats for 30 days and found that BMO and BDE exhibited a greater ovotoxic potential in the mice compared to the rats. Dahl *et al*. (1991) reported that, for equivalent inhalation exposures, the concentrations of total butadiene metabolites in blood were 5-50 times lower in the monkeys than in the mice and 4-14 times lower than in the rats. People may be more like the monkey than the mouse or the rat in their formation of epoxides from butadiene. In vitro metabolism studies with human liver tissue present conflicting results regarding whether humans would be more like rats or mice in forming epoxide metabolites (Bond *et al*., 1996; Duescher and Elfarra, 1994). The considerable degree of interindividual variability in human samples was a reason given for the inconsistencies. Several pharmacokinetic models (Sweeney *et al*., 1997; reviewed by Himmelstein *et al*., 1997) have been developed to adjust for species differences in pharmacokinetics. However, an interspecies pharmacodynamic adjustment for this ovarian atrophy endpoint with butadiene is still needed. Therefore OEHHA staff use an interspecies uncertainty factor of 3 to account for pharmacodynamic differences between mice and women.

Christian (1996) has postulated that it may be inappropriate to develop health-protective values for 1,3-butadiene based on 2-year ovarian atrophy in mice because the mice are beyond their normal reproductive age. It was suggested that the 15-month evaluation of ovarian atrophy conducted by the NTP (1993) would be a better indicator of reproductive risk. However, OEHHA staff believes that butadiene-induced ovarian atrophy represents a toxic manifestation in an organ system. The fact that it occurs in a reproductive organ is immaterial for the development of a chronic REL. Nonetheless, a comparison REL based on the 15-month interim evaluation for ovarian atrophy can be estimated. Quantal data at the 15-month interim evaluation shows that no mice developed ovarian atrophy (0/10) in the control group or at the

lowest exposure. Ovarian atrophy was observed in 1/10, 9/10, 7/10, and 2/2 mice at the 20, 62.5, 200, and 625 ppm exposure groups, respectively. A log-normal probit analysis (U.S. EPA, National Center for Environmental Assessment, benchmark dose software draft, beta version 1.1b) based on the 15-month ovarian atrophy data provided an MLE of 8.12 ppm and a BMC_{05} of 3.08 ppm. Following adjustment for exposure continuity (6/24 hr/day, 5/7 days/wk) to 0.55 ppm and dividing by a total UF of 30 (3 for interspecies variability and 10 for intraspecies variability), a REL of 20 ppb (40 $\mu g/m^3$) was attained.

Another comparison to the proposed REL can be made using the dominant lethality study of Anderson *et al*. (1998). Early fetal deaths were observed at 65 and 125 ppm, but not 12.5 ppm. An earlier dominant lethality study (Anderson *et al*., 1996) indicated that early deaths may occur at 12.5 ppm but the toxicological effect could not be repeated at this concentration in subsequent studies. The average exposure duration at the NOAEL is 3.125 ppm (12.5 ppm x 6 hr/24 hr). Use of an RGDR of 1 and a cumulative uncertainty factor of 30 (3 for interspecies and 10 for intraspecies) resulted in a REL of 0.1 ppm (0.2 mg/m^3). Since the endpoint is a function of exposure during sperm maturation, no subchronic UF was used. The U.S. EPA had observed developmental toxicity in fetal rats (reduced male fetal body weight) at 40 ppm (Morrissey *et al*., 1990). However, unlike the Anderson *et al*. (1998) study, a NOAEL was not determined.

Recent studies have implicated 1,3-butadiene in accelerating arteriosclerotic plaque development in cockerels (Penn and Snyder, 1996a,b), although no animal studies in mammals have implicated 1,3-butadiene in this disease. The worker study by McMichael *et al*. (1976) observed a slight increase in mortality from arteriosclerosis among all rubber workers. But more recent mortality studies in the rubber industry found no association or found an actual mortality decrement from arteriosclerosis and other circulatory diseases when compared to a reference population, suggesting a 'healthy worker' effect (Divine and Hartman, 1996; Matanoski *et al*., 1990; Sathiakumar *et al*., 1998).

When mortality among rubber workers was adjusted for race, two studies found that black rubber workers had a small, although statistically significant, increased mortality from arteriosclerosis compared to the black male U.S. population (Divine and Hartman, 1996; Matanoski *et al*., 1990). But a larger study of black workers in the rubber industry found no association between circulatory diseases, which includes arteriosclerosis, and mortality (Sathiakumar *et al*., 1998). Weaknesses in these worker analyses include relatively small cohort sizes, the bias of having racial information on all deaths and not on all living workers, the lack of racial data on some workers (up to 15% of cohort), and the lack of complete or specific work histories of the subjects. Also, black men of certain age groups are known to have an increased standardized mortality ratio for arteriosclerotic (ischemic) heart disease compared to white men (CDC, 2000). Limited data, conflicting worker mortality results, and lack of underlying mechanisms of action prevent the use of these findings in 1,3-butadiene REL development. However, there clearly is a need for further animal and epidemiological studies to determine if there is a true association between 1,3-butadiene exposure and arteriosclerotic diseases.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the 1,3-butadiene REL is the observation of a dose-response effect in a well-conducted lifetime inhalation exposure study. The major weaknesses are the lack of adequate human health effects and metabolism data and the lack of a NOAEL observation in the key study.

VIII. References

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