

1,3-Butadiene

1,3-Butadiene is produced in very large amounts every year from the petroleum industry. It is used to make various types of rubber and plastics. The rubber produced from this compound is used mainly for car and truck tires. Some rubber and plastics may contain small amounts of 1,3-butadiene in them, although the levels are not high enough to cause health problems. 1,3-Butadiene may also be found in small amounts in gasoline, the exhausts of cars and trucks, gasoline vapours, cigarette smoke, and smoke from wood fires (ATSDR, 1992).

1. Physico-chemical Properties

Table 1. Physical and Chemical Properties of 1,3-Butadiene (Adapted from ATSDR 1992)

Property	Characteristic
Synonyms:	Butadiene; buta-1,3-diene; biethylene; bivinyl; vinylethylene; erythrene; 1,3-butadiene; trans-butadiene; divinyl; pyrrolylene
Chemical formula:	C ₄ H ₆
CAS number:	106-99-0
Molecular weight:	54.09
Colour:	Colourless
Physical state:	Gas
Melting point:	-108.9°C
Boiling point: at 1 atm at 5 atm at 10 atm	-4.4°C 47°C 76°C
Density: (liquid) at 20°C	0.6211g/mL
Odour:	Mildly aromatic
Odour Threshold: water air	0.0014 mg/L 2.21 – 3.54 mg/m ³ (recognition) 0.05525 mg/m ³ (detection)
Solubility: water at 25°C organic solvents	1624.35 mg/m ³ alcohol, ether, acetone, benzene, polar and nonpolar organic solvents
Partition coefficient: Log octanol/water Log K _{oc} (calculated from K _{ow})	1.99 2.46 2.59
Vapour pressure:	2100 mmHg

Property	Characteristic
Henry's law constant: 25°C (calculated)	$7.05 \times 10^{-2} \text{ atm}\cdot\text{m}^3/\text{mol}$
Autoignition temperature:	414°C
Flashpoint:	-76°C
Flammability limits: in air	Extremely flammable
Explosive limits:	2-11.5%
Conversion factors: ppm (v/v) to mg/m ³ in air (20°C) mg/m ³ to ppm (v/v) in air (20°C)	2.21 0.445
Bioconcentration factor: (calculated from K_{ow})	19

2. Environmental Fate

The environmental fate of 1,3-butadiene has been reviewed extensively by ATSDR (1992). It is important to note there have been no experimental data located on the partitioning of 1,3-butadiene in the environment and, partitioning can only be predicted based on the physical and chemical properties of 1,3-butadiene. A brief summary is provided here.

Due to the high volatility of 1,3-butadiene, it is expected to partition mainly to the atmosphere. It will likely not adsorb significantly to any particulate matter. Once in the atmosphere, 1,3-butadiene undergoes rapid reactions with electrophilic oxidants to form oxygenated species such as formaldehyde, depending on local conditions. The most rapid reaction is with photochemically produced hydroxyl radicals. The estimated half-life of 1,3-butadiene under natural sunlight is hours. In addition, the destruction of 1,3-butadiene by nitrate radicals is expected to be a significant night-time process in urban areas.

The estimated half-life of 1,3-butadiene for volatilization from a model river is hours. (Lyman *et al.* 1982) The experimental data on the degradation of 1,3-butadiene in aquatic systems are limited and are restricted to microbial degradation under aerobic conditions.

When inoculated with methane utilizing organisms, 1,3-butadiene was found to biodegrade to 1,3-butadiene monoepoxide (or epoxybutene). As a result, it is concluded that a biological sewage system should be able to degrade 1,3-butadiene, given suitable acclimation conditions.

Based on a calculated soil adsorption coefficient of 288, 1,3-butadiene is not expected to significantly adsorb to sediment and suspended organic matter. This compound is expected to biodegrade in soil, under aerobic conditions. Although it may be moderately mobile in soil, due to its high volatility and potential rapid degradation in soil, it is unlikely to leach into groundwater.

Based on a calculated bioconcentration factor (BCF) of 19, derived from its log octanol/water partition coefficient (K_{ow}), 1,3-butadiene will not significantly bioconcentrate in fish and aquatic organisms.

However, it is important to note that no experimental data are available to support these theoretical values.

3. Toxicokinetics

Humans and animals are exposed to 1,3-butadiene predominantly via inhalation. Therefore most experimental studies on disposition of the chemical have been derived from inhalation exposure studies. A brief summary of the toxicokinetics of 1,3-butadiene will be provided here, based on the detailed reviews by ATSDR (1992), USEPA (1998) and CEPA (1999).

The metabolism and pharmacokinetics of 1,3-butadiene display distinct quantitative species difference in the animal models studied, including mice, rats and monkeys. These differences may account for the observed differences in the toxic effects of 1,3-butadiene in these animal species.

Absorption

Various animal studies observed rapid absorption of 1,3-butadiene by the lungs. At exposure concentrations <1,000 ppm, 1,3-butadiene uptake exhibits first-order kinetics, but at higher concentrations, the process becomes saturated. At concentrations up to 1,800 ppm, the uptake of 1,3-butadiene in mice is approximately four-fold higher than in rats. Furthermore, the mice accumulate more 1,3-butadiene and/or its metabolites than equally exposed rats. Limited data on monkeys suggest that the metabolic uptake is lower than for both rats and mice.

Distribution

The distribution of 1,3-butadiene was studied in rats and mice. After inhalation exposure both species showed high concentration of 1,3-butadiene and its metabolites in their body tissues. The highest concentration was observed in the fat with lower levels in the blood, heart, lung, liver, bone marrow, thymus and kidney. However, the levels were consistently higher in the target tissues of mice than rats.

Metabolism

Several *in vitro* and *in vivo* studies have elucidated the metabolic pathway of 1,3-butadiene. Available data indicate that metabolism is qualitatively similar among the various species (including humans) studied, although there may be quantitative differences in the metabolic rates and the proportion of metabolites generated. These differences appear to agree with variation in sensitivity observed among the various rodent species tested today towards butadiene-induced toxic effects.

The major metabolic pathway involves initial oxidation of 1,3-butadiene via cytochrome P-450 enzymes (predominantly P-450 2E1, although other isozymes may also be involved) to the reactive metabolite, 1,3-butadiene monoxide (or epoxybutene). Epoxybutene can be further activated via cytochrome P-450 mediated transformation to another active metabolite 1,2,3,4-diepoxide (or diepoxybutane). The

epoxybutene and diepoxybutane can be detoxified by hydrolysis or glutathione conjugation and is mediated by epoxide hydrolase and glutathione S-transferase. A minor pathway may involve chloroperoxidase-dependent oxidation of 1,3-butadiene to 3-butanal, which tautomerizes readily to crotonaldehyde. These reactions occur at different rates in different organ tissues studied, including liver, kidney and lung. Metabolism of 1,3-butadiene and subsequent conversion of epoxybutene to diepoxybutane may also take place to a limited degree in the bone marrow, mediated by other enzyme systems, such as myeloperoxidase.

Epoxybutene, diepoxybutane and crotonaldehyde are all DNA-reactive and known mutagens. They are believed to be responsible for the toxic effects of butadiene. Both epoxybutene and diepoxybutane can form haemoglobin and DNA adducts. However, crotonaldehyde has not been studied as extensively because crotonaldehyde was only recently identified as a butadiene metabolite.

Extensive data indicate that the active epoxide metabolites (including diepoxide) are formed to a greater degree in mice than in rats exposed similarly to 1,3-butadiene. A comparison of butadiene epoxide levels in target tissues (blood, bone marrow, lung, heart, fat, spleen and thymus) of rats and mice following low level exposure to 1,3-butadiene showed consistently higher epoxide levels in mouse than in rat tissues. The greater susceptibility of mice to the toxic effects of 1,3-butadiene may be related to the higher rate of formation of epoxybutene and limited detoxification, resulting in greater accumulation of the active metabolites in this species. Limited data from non-human primates showed that the steady-state tissue levels of reactive butadiene metabolites are lower in monkeys than in rats or mice.

Although data are limited, humans appear to metabolize butadiene to the mono- and diepoxide metabolites to a much lesser extent than mice. However, based on the observed variability in the formation of haemoglobin adducts with butadiene metabolites in occupationally exposed individuals, there appears to be interindividual variation in humans.

Excretion

1,3-butadiene is excreted via the respiratory tract, urine or faeces. The rate of excretion by rats and mice appears to be unaffected by the exposure concentration. Elimination of radioactivity from the blood and tissues of rats and mice after inhalation exposure to ¹⁴C-1,3-butadiene was biphasic, with a half-life of hours for initial removal and 5-60 days for slower elimination. Half-lives for urinary excretion of radioactivity were similar for rats and mice (5.6 and 4.6 h, respectively), but fecal excretion was greater in rats (22 h) than in mice (8.6 h). A portion of the inhaled dose was exhaled in the form of carbon dioxide and epoxide metabolites in rodents and monkeys exposed to 1,3-butadiene. In monkeys, carbon dioxide was the major exhalation product at low exposure levels, and at high exposure levels, the proportion of carbon dioxide decreased whereas epoxy-metabolites increased.

Mice, rats, hamsters, and monkeys predominantly produced two urinary metabolites, the glutathione conjugate of epoxybutene (M-II), and the glutathione conjugate of the hydrolysis product of diepoxybutane (M-I). M-I but not M-II was also found in the urine of workers exposed to low levels of 1,3-butadiene.

4. Human Health Effects

A brief summary of the human health effects of 1,3-butadiene, based on the reviews in ATSDR (1992), USEPA (1998) and CEPA (2000) will be provided.

The predominant human health effects from exposure to 1,3-butadiene are effects on the heart, blood and lung, reproductive and developmental effects and cancer. Animal studies report an anaesthetic effect leading to death following acute inhalation exposure to 1,3-butadiene at high levels, although there is no evidence to support these findings in human data. At lower levels, respiratory effects, including irritation of respiratory passages, were observed in animals and humans. These effects may become more serious on prolonged chronic exposure. Following industrial accidents, in which there may have been a significant leak of 1,3-butadiene, the first signs of human exposure to this compound are nausea, dryness of the mouth and nose, headache, decreased blood pressure and decreased pulse rate.

Heart Effects

Epidemiological studies of occupationally exposed workers report excessive deaths from heart disease (arteriosclerotic and chronic rheumatic heart disease) after inhalation exposure to 1,3-butadiene when compared to controlled populations (McMichael *et al.* 1974). Animal studies involving mice report endothelial hyperplasia of the heart after chronic inhalation exposure (Melnick *et al.* 1990). Although human epidemiological data are limited, available data support the hematopoietic system being a critical target for butadiene-induced toxicity.

Blood Effects

Available data observed blood effects in workers in the rubber industry who were likely to have higher levels of exposure to 1,3-butadiene as opposed to other workers (Checkoway and Williams, 1982). Animal data, involving mice, support these findings. Treatment-related blood disorders in mice included decrease in red blood cell counts and total haemoglobin, due to reduced ability of the bone marrow to regenerate red blood cells. In contrast to mice, rats did not show blood effects on exposure to 1,3-butadiene.

Reproductive and Developmental Effects

Available data indicate that 1,3-butadiene induces reproductive and developmental effects in rodents. Reproductive toxicity is manifested as atrophy of the ovary and uterus in the females, atrophy of the testis and sperm abnormality in the males (NTP, 1984, 1993; Hackett *et al.* 1988, Anderson *et al.* 1993; Adler *et al.* 1994). The females are more sensitive to the effect of 1,3-butadiene than the males. Developmental effects observed after pregnant rodents were exposed during gestation to 1,3-butadiene consisted primarily of reduced foetal body weight and minor skeletal defects such as abnormal ribs (IISRP, 1982; Hackett *et al.* 1987a, b; Anderson *et al.* 1993). Developmental effects can be mediated by exposing male mice to 1,3-butadiene prior to mating (Anderson *et al.* 1993, 1995). Like other toxicological effects

induced by 1,3-butadiene, mice are more sensitive than rats to the induction of reproductive and developmental effects.

Although there has not been evidence for reproductive and developmental effects in humans, the animal data show that 1,3-butadiene is a potential reproductive hazard to humans, with women more sensitive than men. The animal data also show that there is a potential for developmental effects in human upon in utero exposure to 1,3-butadiene, and the effects may occur at concentrations below those causing maternal effects.

Cancer

1,3-Butadiene has been shown to be both genotoxic and carcinogenic in animals and humans. Epidemiological studies show increased death due to lymphohaematopoietic system cancer (leukemia, lymphosarcoma) among styrene-butadiene rubber (SBR) and butadiene monomer workers (McMichael *et al.* 1974, 1976; Meinhardt *et al.* 1982; Divine, 1990; Divine *et al.* 1993; Divine and Hartman, 1996; Delzell *et al.* 1996; Macaluso *et al.* 1996; Matanoski *et al.* 1989, 1993; Santos-Burgoa *et al.* 1992). Data in animals, particularly in mice, show that butadiene is a multisite carcinogen (lungs, heart, haematopoietic system, mammary gland, liver, forestomach, Harderian gland, ovary) even at the lowest dose of 6.26 ppm tested (NTP, 1993). However, it is important to note that interspecies differences between mice and primates, and the higher susceptibility of mice to the toxicity of 1,3-butadiene, may affect the applicability of these animal studies to humans.

United States Environmental Protection Agency (USEPA, 1992) and World Health Organization (WHO, 1992) have classified 1,3-butadiene as a probable human carcinogen in the past. Review of the recent evidence has moved United States Environmental Protection Agency (USEPA, 1998) to consider classifying 1,3-butadiene as a known human carcinogen. Similarly, Health Canada (CEPA, 2000) considers 1,3-butadiene highly likely to be carcinogenic in humans. Evaluation of human carcinogenicity for 1,3-butadiene, however, hinges on evidence of leukaemia risk from one large well-conducted study and two smaller studies. Since the body of evidence does not allow assessment of the consistency of results from two or more studies of adequate statistical power, World Health Organization (WHO, 1999) has retained the classification of 1,3-butadiene as a probable human carcinogen.

5. Potency Estimates

Inhalation-Cancer

USEPA (1998) calculated the cancer potency for 1,3-butadiene based on the Delzell *et al.* (1995) analyses of the retrospective cohort study they conducted on 15,000 male styrene-butadiene rubber production workers in 6 North America industrial plants. The analysis was based on the follow-up during 1943-1991, with an average follow-up of 25 years and about 25% of the cohort deceased. In the Delzell study, 1,3-butadiene exposure was estimated for each job and work area for each study year, and these estimates were linked to workers' work histories to derive cumulative exposure estimates for each individual worker. Additional information on individual worker exposure information to benzene and styrene

allowed adjustment for these confounding factors. The USEPA quantitative analysis extrapolated the risk from occupational work time exposure to lifetime environmental continuous exposure. USEPA adjusted the 1,3-butadiene exposure parameter estimates calculated by Delzell *et al.* to reflect continuous exposures and converted the relative rate exposure-response relationship to a lifetime additional risk dose-response relationship using life table modeling techniques. The low-exposure extrapolation was done in two ways. 1. The linear relative rate exposure-response model reported by Delzell *et al.* was used to calculate a maximum likelihood estimate (MLE) of 9 E-3 per ppm (equivalent to 4 E-6 per $\mu\text{g}/\text{m}^3$) for lifetime extra risk of leukaemia mortality from continuous environmental exposure to 1,3-butadiene. The 95% upper limit on the estimate is 0.02 per ppm (or 9 E-6 per $\mu\text{g}/\text{m}^3$). 2. A “point of departure” was calculated within the range of observation using any of the appropriate models and then extrapolating to 0 by means of a straight line. EC_{01} (concentration associated with 1% extra risk) was used because 1% was within the observable range of increased leukaemia deaths for the different exposure groups in the Delzell *et al.* study. The cancer potency estimate (MLE) based on the preferred final square root model was 0.022 per ppm (1 E-5 per $\mu\text{g}/\text{m}^3$). The first method is in accordance to the EPA’s 1986 Guidelines for Carcinogen Risk Assessment (USEPA, 1996), and the second approach is in the currently proposed revised guidelines (USEPA, 1996). The geometric mean of the cancer potency estimates (MLE) from the two methods is 6.3 E-6 per $\mu\text{g}/\text{m}^3$.

The Canadian Environmental Protection Act (2000) has identified a TC_{01} , the concentration of butadiene associated with a 1% excess probability of dying from leukaemia, for 1,3-butadiene at 1.7 mg/m^3 . Dividing the *risk*, 10^{-2} , by the *exposure level*, 1700 $\mu\text{g}/\text{m}^3$, gives an *inhalation unit risk* of 5.8 E-6 per ($\mu\text{g}/\text{m}^3$). CEPA based its assessment on the same study as USEPA. The cumulative occupational exposures (ppm-years) estimated for individuals were converted to environmental exposures by assuming 8 hours/day 240 days/year throughout a 45 year working life. Only cases in which leukemia was the underlying cause of death of the worker were analyzed. The TC_{01} was derived in two stages. The first stage involved modeling the relationship between exposure and the death rate due to leukemia. The second stage involved calculating the TC_{01} based on the exposure response relationship and background mortality rates in the Canadian population. Although four different mathematical models were used to fit the data, the TC_{01} generated by the model with the best fit was 1.7 mg/m^3 . The exposure assessment was considered to be of high quality, very comprehensive, and therefore, appropriate for quantification of the exposure response relationship.

Although quantitative estimates of carcinogenic potency for humans have also been derived based on animal data, the values derived based on human data are preferred.

Inhalation-Non-Cancer

USEPA (1998) has developed *RfCs* (daily exposure to humans that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime) for reproductive and developmental effects for 1,3-butadiene.

The RfC for chronic exposure is based on male mediated developmental effects (deemed the most sensitive reproductive/ developmental endpoint) observed in the subchronic dominant lethal study in mice

(Anderson *et al.* 1993, 1995). In this study, CD-1 mice were exposed to 0, 12.5 or 1,250 ppm for 6 h/day, 5 day/week for 10 weeks. The critical effect was decreased litter size at birth or at weaning. An *RfC* was calculated using the benchmark approach. The LEC_{10} (the 95% lower confidence limit on the effective concentration associated with 10% increase in risk) was identified to be 0.15 ppm (adjusted to 24-h daily exposure) from the studies. Applying an uncertainty factor of 810 gives an **RfC of 0.15 ppb (or 3.3 E-1 mg/m³)**. This uncertainty factor accounts for interspecies extrapolation (3), intraspecies variability (10), extrapolation from subchronic to chronic exposure (3), the lack of comprehensive multigenerational reproductive study (3) and “risk reduction” to extrapolate to a level at which no detectable effects are expected (3). Although this *RfC* is for reproductive and developmental effects, it will likely protect against other non-cancer effects.

In addition, an *RfC* for developmental toxicity from **short-term exposures** to 1,3-butadiene of 0.1 ppm (220 $\mu\text{g}/\text{m}^3$) was developed based on mouse foetal weight data (Hackett *et al.* 1987a, b). Female mice and rats were exposed on gestation days 6-15 for 6 h/day to 1,3-butadiene by inhalation at 0, 40, 200 and 1,000 ppm. Developmental toxicity was detected only in mice at these exposure levels. The LEC_{10} for decreased foetal weight was identified to be 14 ppm. The *RfC* was obtained by applying an uncertainty factor of 90 to the LEC_{10} . This uncertainty factor accounts for interspecies extrapolation (3), intraspecies variation (3), and a risk reduction factor to extrapolate the risk to below a detectable level (3).

Finally, an *RfC* for **subchronic exposure** was calculated for the decreased litter size endpoints from the subchronic dominant lethal study (Anderson *et al.* 1993, 1995). Applying uncertainty factors to the LEC_{10} of 0.15 ppm to account for interspecies extrapolation (3), intraspecies variability (3) and risk reduction (3) yields an *RfC* for subchronic exposure of 0.0015 ppm (**3.3 $\mu\text{g}/\text{m}^3$**).

The Canadian Environmental Protection Act (2000) has identified a benchmark dose (BMC_{05} , the dose at which 5% of exposed subjects show an effect) of 0.57 mg/m^3 based on experimental data involving ovarian atrophy of all severities in mice (NTP, 1993). The 95% lower confidence limit (LCL) of BMC_{05} is 0.44 mg/m^3 .

6. References

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