

General description

1,3-Butadiene ($\text{CH}_2\text{:CHCH:CH}_2$) (synonyms: *a,g*-butadiene, bivinyl, divinyl, erythrene, biethylene, pyrrolylene and vinylethylene) is a colourless gas with a boiling point of -4.4°C at 1 atmosphere and a density of 0.611g/ml at 20°C . It is a flammable gas and has a mildly aromatic odour. Its vapour pressure is 2100 mmHg at 25°C and the explosive limits are 2–11.5%. Butadiene is slightly soluble in water (735 mg/litre) and is soluble in a number of organic solvents including ethanol, diethyl ether, acetone, benzene, and polar and nonpolar organic solvents. On contact with air, butadiene forms peroxides, and an inhibitor of butadiene peroxidation (4-tertiary-butyl catechol at $\sim 115\text{ ppm}$) is added to commercial butadiene.

Sources

Butadiene is used in the production of resins and plastics including butadiene rubber, styrene rubber, adiponitrile, polychloroprene, nitrile rubber, styrene butadiene latex and acrylonitrile-butadiene-styrene (1). Synthetic rubber made from butadiene is used primarily in the production of car tyres. In 1994, butadiene ranked among the top 20 synthetic organic chemicals produced in the United States, with an annual production of over 3 billion pounds (approximately 1.4 million tonnes) (2).

Two reactive vinyl groups of butadiene make it a useful monomer in numerous polymerization reactions and in the production of hydroaromatic compounds. Spontaneous dimerization of butadiene to 4-vinylcyclohexene occurs at room temperature and more rapidly at higher temperatures.

Occurrence in air

Butadiene is not known to occur as a natural product. Sources of butadiene include cigarette smoke, motor vehicle exhaust, wood smoke and emissions from butadiene production, storage, transport and end-use. Exposure is most likely in industrial settings or in environments where inhalation of the vapour is the major route of exposure. It is unlikely, however, that workers would be exposed to butadiene alone because of its importance in the synthesis of polymers, which also contain other chemicals such as styrene and acrylonitrile.

Few data exist on concentrations of butadiene in ambient air. In general, concentrations in urban air have been reported to range from 1 to 10 ppb (3, 4). A mean concentration of $1.39\text{ }\mu\text{g/m}^3$ (range 0.11–6.94) was reported for 24-hour ambient air samples taken in 19 United States cities in 1987–1988 (5). In Canada, concentrations of butadiene in ambient air were reported to range from undetectable ($< 0.05\text{ }\mu\text{g/m}^3$) to $14.1\text{ }\mu\text{g/m}^3$ (overall mean $0.36\text{ }\mu\text{g/m}^3$) (6). The US Environmental Protection Agency (7) has estimated that butadiene is emitted in motor vehicle exhaust at 8.9–9.9 mg/mile (5.6–6.1 mg/km) and comprises roughly 0.35% of total hydrocarbons in exhaust emissions. Neligan (3) reported concentrations of butadiene in motor vehicle exhaust of 20–60 ppb. Berg et al. (8) reported levels of butadiene of up to 15 ppm in smoke generated during house fires. Löfroth et al. (9) reported butadiene levels equivalent to 0.4 mg/cigarette in sidestream smoke and levels in smoky indoor environments of 10–20 $\mu\text{g/m}^3$. Brunnemann et al. (10) reported an average level of

butadiene equivalent to 205–361 $\mu\text{g}/\text{cigarette}$ in sidestream smoke and 16–75 $\mu\text{g}/\text{cigarette}$ in mainstream smoke. Typical current occupational levels of butadiene are less than 2 ppm (11).

Conversion factors

1 ppm	= 2.21 mg/m^3
1 mg/m^3	= 0.445 ppm

Routes of exposure

Air

Based on its physical properties, butadiene will rapidly vaporize into the atmosphere; air is thus the primary route of entry into the body. The general population is exposed to ppb levels of butadiene. Exposure can also occur from inhalation of petrol fumes, cigarette smoke, and possibly the smoke of other combustible materials such as wood.

In one study, butadiene levels were reported to be 11 and 19 $\mu\text{g}/\text{m}^3$ in indoor tavern air, compared to outside air concentrations of $\leq 1 \mu\text{g}/\text{m}^3$ (9). In another study, slightly lower concentrations (2.6–44 $\mu\text{g}/\text{m}^3$) were reported for a smoke-filled bar (10). Mean levels of butadiene in indoor air in a small number of Canadian homes and offices were 0.3 $\mu\text{g}/\text{m}^3$, with a maximum value of 6.3 $\mu\text{g}/\text{m}^3$ (6).

Toxicokinetics

Absorption

Studies in male B6C3F1 mice and Sprague-Dawley rats indicated that the burden of absorbed ^{14}C equivalents retained in the body following inhalation of ^{14}C -butadiene at a concentration of 0.08–7100 ppm was greater at lower than at higher exposure concentrations (12). For example, the percentage of ^{14}C absorbed and retained at 6 hours decreased from 20% to 4% in mice and from 17% to 2.5% in rats exposed to increasing concentrations. Uptake of butadiene as a percentage of the total inhaled was found to be lower in cynomolgus monkeys than in rats and mice (13).

Distribution

Butadiene and its metabolites are widely distributed throughout the body (14). There were no species differences in the pattern of butadiene distribution in the tissues of rats and mice exposed to ^{14}C -butadiene by inhalation at levels of 670 ppm (rats) or 65 ppm (mice) for 3.4 hours. More than 60% of the ^{14}C -butadiene equivalents quantified in all tissues 1 hour after the end of exposure were nonvolatile, indicating the formation of nonvolatile metabolites. The concentrations of ^{14}C -butadiene equivalents per gram of tissue per micromole of butadiene inhaled were 15–100 times greater in mice than in rats.

Biotransformation

In vitro

Epoxidation is a key initial step in the metabolism of butadiene. Butadiene is a substrate for at least two isozymes of cytochrome P-450 monooxygenase, CYP 2E1 and CYP 2A6 (15, 16). Kinetic analysis of CYP activity in human liver microsomes suggests that CYP 2E1 is a high-affinity, low-

capacity isozyme and CYP 2A6 is a low-affinity, high-capacity isozyme. Epoxybutene undergoes further metabolism to form diepoxybutane and this reaction appears to be catalysed by CYP 2E1 (high-affinity) and CYP 3A4 (low-affinity) (17). CYP 2E1 thus appears to be the principal enzyme responsible for the metabolism of butadiene to epoxybutene and of epoxybutene to diepoxybutane at low butadiene exposure concentrations. In addition to cytochrome P-450, two other enzymes appear to play major roles in the metabolism of epoxybutene and diepoxybutane: glutathione S-transferase and epoxide hydrolase (15, 18, 19).

There are significant species differences in the metabolism of butadiene (20). Comparison of butadiene metabolism in liver and lung microsomes indicates that the rate of metabolism is by far the greatest in mice and is similar in rats and humans (15). In addition, mice show a faster rate of glutathione conjugation with epoxybutene in lung tissues than rats or humans, and humans have faster rates of epoxybutene hydrolysis by epoxide hydrolase compared to rats or mice (15). The rate of cytochrome P-450-mediated epoxidation of epoxybutene to diepoxybutane in liver microsomes is highest in mice; the rates in rats and humans are similar to one another (17). Enzyme-mediated liver glutathione conjugation with diepoxybutane is greatest in mice, followed by rats then by humans (19).

A comparison of the ratio of activation (oxidation) to detoxification (hydrolysis and glutathione conjugation) for butadiene and epoxybutene also reveals striking species differences (21): mice have a significantly higher ratio than rats or humans. For butadiene, ratios were 10 times greater in mice than in rats or humans; for epoxybutene, they were 3–4 times greater in mice than in rats or humans. These ratios are consistent with the higher susceptibility of mice than rats to butadiene-induced tumours (see below).

In vivo

Numerous *in vivo* data substantiate the *in vitro* metabolism studies, showing that butadiene undergoes oxidation to epoxybutene and that there are significant species differences in metabolism (20). For example, metabolic uptake was greater in mice than in rats exposed to initial butadiene concentrations of 10–5000 ppm (22, 23). Studies by Bond et al. (12) indicated that mice had approximately 2–4 times higher concentrations of epoxybutene in the blood than rats. Following exposure to ¹⁴C-butadiene concentrations of 10, 300 and 8000 ppm, total butadiene metabolites quantified in blood were 5–50 times lower in monkeys than in mice and 4–14 times lower than in rats (13). Himmelstein et al. (24, 25) reported that, following inhalation of butadiene at concentrations of 62.5–1250 ppm and (rats only) 8000 ppm for up to 6 hours, butadiene and epoxybutene blood concentrations in rats and mice were at steady-state after 2–6 hours of exposure and declined rapidly within minutes after the end of exposure. During exposure, peak concentrations of epoxybutene in mice compared to rats were 4–8 times higher in blood, 13–15 times higher in lung and 5–8 times higher in liver. The concentration of diepoxybutane was greatest in the lungs of mice. Diepoxybutane could not be detected in the livers of mice or the lungs and livers of rats. Thornton-Manning et al. (26) reported that in mice and rats exposed to butadiene at a concentration of 62.5 ppm for 4 hours, concentrations of epoxybutene were 3–74 times greater in the tissues of mice than in those of rats. Furthermore, levels of diepoxybutane in blood and tissues of mice were 40–163 times higher than in corresponding rat tissues. It has been demonstrated that inhalation exposure to butadiene results in depletion of glutathione in a number of tissues (25, 27).

Elimination

Urine and exhaled air are the major routes of elimination of butadiene metabolites, accounting for 75–85% of the total elimination (12). Exhalation of parent butadiene and metabolism are major contributors to the overall elimination of this compound. The proportion of butadiene eliminated as carbon dioxide in exhaled air is in the range 4–22% in mice and 12–51% in rats. Epoxybutene is an exhaled metabolite of butadiene in monkeys, rats and mice (12, 13, 22).

Physiologically based toxicokinetic modelling

There are currently four physiologically based pharmacokinetic models for butadiene that have been published and described in significant detail (28–31). In general, the models are very similar in structure, all patterned after the venous-equilibration, flow-limited models for volatile organic chemicals developed by Ramsey & Andersen (32). The four models differ in some of the details within the model compartments in their treatment of the kinetics of the various reactions, especially detoxification, and in their inclusion of hepatic and extrahepatic metabolism. None the less, the conclusions reached by the various investigators are remarkably similar. Predicted differences in epoxybutene concentrations in blood between rats and mice are not of sufficient magnitude to account for the dramatic differences in the carcinogenic potency of butadiene between these two animal species. Diepoxybutane was suggested as the possible carcinogen, although none of the models incorporated distribution of this metabolite. All investigators noted the lack of sufficient experimental data to fully validate their models and specific recommendations were made, most notably regarding the development of data on internal concentrations of butadiene epoxides. The simulations from the various models suggest that it is unlikely that circulating levels of epoxybutene are appropriate for assessing butadiene risk. It is more likely that other epoxides, such as diepoxybutane, will correlate better with species sensitivity towards butadiene.

Biomarkers of exposure

Potential biomarkers of exposure to butadiene include: (a) butadiene haemoglobin adduct levels in laboratory animals and humans (33–35); (b) butadiene metabolite levels in urine (36, 37); and (c) gene mutations and chromosomal aberrations in human lymphocytes (38–40).

Osterman-Golkar et al. (33) measured the *N*-terminal valine haemoglobin adduct of epoxybutene in the blood of Sprague-Dawley rats, B6C3F1 mice and humans exposed to butadiene. Mice and rats were exposed to up to 100 ppm butadiene (6 hours/day, 5 days/week for 4 weeks). Haemoglobin adduct levels in mice increased linearly with butadiene concentration. In rats, adduct levels were lower than in mice and began to level off at an exposure concentration of about 10 ppm. This finding is consistent with the lower concentrations of epoxybutene measured in the blood and tissues of rats compared to mice following exposure to butadiene. Epoxybutene *N*-terminal valine haemoglobin adduct levels of 1.1–2.6 pmol/g haemoglobin were found in male workers exposed to butadiene in a chemical production plant. For the most part, exposure concentrations were less than 1 ppm but may have been as high as 3.5 ppm.

Bechtold et al. (37) investigated the excretion of the urinary metabolites 1,2-hydroxy-4-(*N*-acetylcysteinyl)-butane (M1) and 1-hydroxy-2-(*N*-acetylcysteine)-3-butene (M2) in the urine of humans occupationally exposed to butadiene through inhalation. Humans were similar to monkeys in that M1 was the predominant metabolite in urine derived from the glutathione conjugate of butene diol. This finding is consistent with the higher ratio of M1:(M1 + M2) in humans compared to rats or

mice and the higher rate of epoxide hydrolase activity in the livers of humans compared to rats and mice (15).

Van Sittert & van Vliet (35) compared the haemoglobin adduct level of *N*-(2-hydroxy-3-butenyl)valine in control and butadiene-exposed workers in a naphtha cracking plant; median levels were less than 2 pmol/g haemoglobin in nonsmoking and smoking subjects exposed occupationally to butadiene. Personal air samples collected during the study showed that exposure concentrations were mostly less than 1 ppm (8-hour time-weighted average).

Health effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects

High exposure concentrations of butadiene are required to cause acute toxicity in laboratory animals. For example, Carpenter et al. (41) reported that a concentration of 250 000 ppm in rabbits resulted in anaesthesia and death after 30 minutes of exposure by inhalation. Concentrations of 122 000 and 129 000 ppm caused 50% lethality (LC₅₀) after 4 and 2 hours of exposure in rats and mice, respectively (42).

Non-cancer effects of butadiene include biochemical alterations, reproductive and developmental toxicity, preneoplastic effects (hyperplasia), gonadal atrophy, haematotoxicity, and immunotoxicities. These effects span the range of acute, intermediate and chronic exposures and have been reviewed in Himmelstein et al. (20).

Biochemical effects associated with one-day exposures of rats and mice to butadiene revealed significant depletion (10–95%) of glutathione in lung, liver and heart (23, 25, 27). Reproductive and developmental toxicity of butadiene in laboratory animals have been reported (20).

Carcinogenic effects

Chronic inhalation studies produced evidence that butadiene is carcinogenic in laboratory animals. Sprague-Dawley rats were exposed to concentrations of 0, 1000 and 8000 ppm for 6 hours/day, 5 days/week for 105 weeks (females) or for 111 weeks (males) (43). Four tumour sites were observed in female rats, including mammary gland adenoma and carcinoma, thyroid follicular cell adenoma, uterine sarcoma and Zymbal gland carcinoma. Mammary gland and thyroid follicular cell tumours in females and pancreatic exocrine adenoma and testicular Leydig cell tumours in male rats were considered by the authors to be related to the treatment.

The results of a chronic inhalation study in B6C3F1 mice (44) showed that butadiene was a multiple-organ carcinogen during inhalation exposure to concentrations of 625 and 1250 ppm (6 hours/day, 5 days/week for 60 weeks). This study was designed initially to last 103 weeks, but was cut short because of excessive cancer-related mortality at both exposure concentrations. Early induction and significantly increased incidences of acinar cell carcinomas of the mammary gland, granulosa cell neoplasms of the ovary, and hepatocellular neoplasms were observed in females, and heart haemangiosarcomas, malignant lymphomas, alveolar/bronchioalveolar neoplasms and squamous cell neoplasms of the forestomach were observed in both males and females.

The early deaths in this study were thought to mask the appearance of other tumours, and a second chronic inhalation study in B6C3F1 mice was therefore performed to investigate the relationship between lower exposure concentrations of butadiene and the onset of tumours in various tissues (45). Male and female B6C3F1 mice were exposed to concentrations of 6.25, 20, 62.5, 200 and 625 ppm by inhalation (6 hours/day, 5 days/week for 104 weeks). As in the earlier study, multiple tumour sites were observed in both sexes. The lowest concentration of butadiene for which a significant effect in the lungs of females was observed, compared to control mice exposed to air, was 6.25 ppm. “Stop exposure” studies indicated that concentration of butadiene was a greater determinant than duration of exposure for the development of neoplasms of the forestomach and lymphatic system.

Mutagenic effects

The genotoxic effects of butadiene and certain metabolites of butadiene have been reviewed by de Meester (46), IARC (47) and Himmelstein et al. (20). Butadiene is an indirectly acting mutagen that is metabolized to at least two metabolites, epoxybutene and diepoxybutane, which are themselves directly acting mutagens. Butadiene, epoxybutene, and/or diepoxybutane are genotoxic in a wide variety of test organisms ranging from bacteria, yeasts and *Drosophila* to laboratory mice, and in mammalian cells in culture, including human cells.

Butadiene is genotoxic in mice but not in rats. Inhalation showed a significant increase in the frequency of micronuclei, sister chromatid exchanges and chromosome aberrations in mice, but no effects were observed in rats (48–50). Butadiene causes protein–DNA and DNA–DNA cross-links in the livers of mice, but not in rats (51). Butadiene metabolites were reported to bind to the liver DNA of rats and mice exposed to ¹⁴C-butadiene; the binding was twice as high in mice as in rats (52). These data indicate that the species differences observed in tumour induction by butadiene are paralleled by species differences in genotoxic response.

More recent studies have examined the induction *in vivo* of gene mutation at mutational markers (*lacI* and *lacZ*) in tissues of transgenic mice and at the endogenous *hprt* gene in T lymphocytes. Exposure of transgenic mice to butadiene concentrations of up to 1250 ppm for 4 weeks resulted in a 2- to 4-fold concentration-dependent increase in the bone marrow frequency of the *lacI* mutant (53). In B6C3F1 mice an increased frequency of *hprt* mutant T lymphocytes was found in animals exposed to butadiene (54).

The butadiene metabolites epoxybutene and diepoxybutane induce chromosome aberrations, sister chromatid exchanges and *hprt* mutation in animals, but diepoxybutane is genotoxic at lower concentrations than those required by epoxybutene (46, 47).

The contribution of glutathione S-transferase (GST) genotypes to the differential susceptibility of lymphocytes from individuals to the induction of sister chromatid exchanges by epoxybutene and diepoxybutane has been examined. Lymphocytes from individuals with the GSTM1 null genotype (gene absent) showed an increased sensitivity to sister chromatid exchange induction by epoxybutene (55). In respect of diepoxybutane, sensitive lymphocytes were shown to be from individuals of the GSTT1 null genotype, while the GSTM1 genotype conferred no differential susceptibility (56, 57).

Effects on humans

Toxicological effects

The major effects of acute exposure include irritation and effects on the central nervous system. Workers exposed to butadiene gas during the manufacture of rubber reported irritation of eyes, nasal passages, throat and lungs (58). Carpenter et al. (41) recorded eye irritation and difficulty in focusing on instrument panels in two men during exposures to butadiene at concentrations of 2000 or 4000 ppm for 6–7 hours. High gas concentrations may cause mild skin irritation. Dermal contact with liquid butadiene causes a sensation of cold, followed by a sensation of burning.

Mutagenic and carcinogenic effects

Studies on the *in vitro* induction of sister chromatid exchanges in human lymphocytes by epoxybutene and diepoxybutane showed that the lowest effective concentrations were 25 µmol/litre and 0.5 µmol/litre, respectively (59). In human TK6 lymphoblasts, diepoxybutane was mutagenic at the *hprt* locus at concentrations that were 100 times less than the concentration of epoxybutene required for the same effect (60). Sister chromatid exchanges and *hprt* mutations observed with diepoxybutane occur within the same concentration range and indicate that diepoxybutane is a more potent genotoxic metabolite of butadiene in human cells than epoxybutene.

Three human population monitoring studies for genotoxic endpoints in individuals working in butadiene production facilities have been reported (38–40). In a small pilot study (38), an increased frequency of *hprt* variance was detected in the high-exposure group compared to the low-exposure group and outside-facility controls. There was a correlation between an increase in the *hprt* variance and increased levels of a butadiene metabolite (M1) in the urine. In a separate study using some of the same individuals as the pilot study, there were no significant increases in chromosome aberrations or chromatid breaks in peripheral blood lymphocytes isolated from the high-exposure group (40).

The most important epidemiological studies to date include a cohort mortality study of butadiene monomer (BDM) workers (61), two cohort mortality studies of styrene butadiene rubber (SBR) workers (62, 63) and a lympho-haematopoietic cancer (LHC) case–control study (64) nested within the larger of the SBR cohort studies (63). The two studies of SBR workers included all 10 production plants that were still in operation in 1976.

Several reviews of the epidemiological data have been published (65–70). Landrigan (67) concluded that the data indicate a causal relationship between butadiene and leukaemia and other LHCs, while other authors interpreted the evidence differently.

Cowles et al. (71) evaluated haematological data for 429 BDM workers employed during the period 1982–1989. The results were compared with data for 2600 employees from elsewhere in the petrochemical complex that housed the BDM unit. The findings suggest that there is no evidence for a measurable effect of butadiene on haematological parameters at recent exposure levels in United States industry.

The epidemiological studies, while relatively few in number, involve approximately 18 000 workers followed over periods spanning 33–43 years. There are sufficient data to support a relationship

between butadiene exposure and LHC. Although data have not yet been published, preliminary information (presented at the 1995 International Symposium on the Evaluation of Butadiene and Isoprene Health Risks) suggests that there is an association between exposure to butadiene and leukaemia in workers in the synthetic rubber industry. One published study reported a strong relationship between butadiene and leukaemia (63, 64), but the magnitude of this relationship was implausible based on the findings of a cohort study of the same population (68). That same study found no relationship between butadiene exposure and other LHCs. IARC (47) considered all the epidemiological studies, with the exception of the latest update by Divine et al. (61) and categorized the epidemiological evidence as limited. Landrigan (69) has expressed the contrary view that the LHC findings in the butadiene epidemiological studies have all the hallmarks of causal relationships.

Evaluation of human health risks

Exposure evaluation

In a survey of butadiene monomer, polymer and end-user industries in the United States, the geometric mean concentration for full-shift exposure for all job categories was 0.098 ppm and the arithmetic mean was 2.12 ppm (11).

Although data for ambient air levels in Europe are limited, reported concentrations in urban air generally ranged from less than 2 $\mu\text{g}/\text{m}^3$ to 20 $\mu\text{g}/\text{m}^3$ (3, 4). Mean levels in indoor air in a small number of Canadian homes and offices were 0.3 $\mu\text{g}/\text{m}^3$ (6). Sidestream cigarette smoke contains 1,3-butadiene at approximately 0.4 mg/cigarette, and levels of butadiene in smoky indoor environments are typically 10–20 $\mu\text{g}/\text{m}^3$ (9).

Health risk evaluation

Irritation or effects on the central nervous system may be associated with acute exposure to high concentrations of butadiene. However, carcinogenicity is considered to be the critical effect for the derivation of air quality guidelines.

1,3-Butadiene has induced a wide variety of tumours in rats and mice, with mice being considerably more sensitive than rats (Table 1). There are widely divergent points of view as to which animal species – the rat or the mouse – is most appropriate for use in human risk assessments for butadiene (21, 72).

Epidemiological studies, while relatively few in number, suggest that there is equivocal evidence for an association between exposure to butadiene and LHC. In 1992, IARC classified butadiene in Group 2A (probably carcinogenic to humans). Preliminary (unpublished) reports suggest, however, that there may be an association between butadiene exposure and leukaemia in workers in the synthetic rubber industry.

The genotoxicity of butadiene has been studied in a variety of *in vitro* and *in vivo* mutagenicity assays, and the data overwhelmingly suggest that the induction of cancer requires the metabolism of butadiene to its DNA-reactive metabolites. Butadiene is mutagenic in both bacterial and mammalian systems. The butadiene metabolites epoxybutene and diepoxybutane are also carcinogenic and genotoxic *in vivo*. Butadiene is metabolized to epoxides to a significantly lesser extent in human tissues than in mice and rats. The differences between mice and rats observed *in vitro* are

supported by *in vivo* studies, indicating that mice form very high levels of epoxides compared to rats when exposed to butadiene. In general, the data support the conclusion that the metabolism of butadiene in humans is more similar to that in rats, a relatively insensitive species to butadiene carcinogenicity, than to that in mice, a highly sensitive species. It should be recognized, however, that inter-individual differences in butadiene metabolism may exist that will influence the extent to which butadiene epoxides are formed.

Table 1. Risk estimates for exposure of humans to butadiene^a

Reference	Tumour data source	Cancer model	Extra risk of death from cancer at 1 ppm butadiene ^b
EPA (73) ^c	Pooled male mouse tumours (74)	One-hit	213 (344)
	Pooled female mouse tumours (74)	One-hit	85 (111)
	Male mouse haemangiosarcomas (74)	One-hit	40 (57)
EPA (75) ^c	Pooled male and female mouse tumours ^d (74)	Multistage	16 (175)
	Pooled male rat tumours (76)	Multistage	0 (6)
	Pooled female rat tumours (76)	One-hit	64 (84)
OSHA (77) ^c	Pooled male mouse tumours ^{e,f} (74)	One-hit	2613 (3500)
	Pooled female mouse tumours (74)	Multistage	859 (1591)
CMA (78)	Pooled male mouse tumours ^g (74)	Hartley-Sielken ^h	47 (55)
	Pooled male rat tumours ⁱ (43)	Multistage	1 (7)
	Pooled male rat tumours ⁱ (43)	Weibull	0 (6)
	Pooled male rat tumours ⁱ (43)	Mantel-Bryan	2 (4)
	Pooled female rat tumours ^j (43)	Multistage	6 (8)
	Pooled female rat tumours ^j (43)	Weibull	6 (8)
	Pooled female rat tumours ^j (43)	Mantel-Bryan	3 (6)
OSHA (79)	Pooled female mouse tumours (74)	One-hit	95 (120)
		Two-hit	0.6 (80)
	Female mouse heart tumours (74)	One-hit	28 (37)
		Two-hit	27 (37)
	Pooled female rat tumours (43)	One-hit	66 (90)
		Two-hit	23 (3)
	Pooled female rat tumours ⁱ (43)	One-hit	3 (5)
		Two-hit	3 (5)

NIOSH (80)	Female mouse lung (81)	Weibull/multistage	305 (-) ^{f,l}
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^a Adapted from US Occupational Safety and Health Administration (OSHA) (79) and Himmelstein et al. (25).

^b Numbers in parentheses are 95% upper confidence limit estimates for deaths per 10 000 workers.

^c Only upper confidence limits used in quantitative risk assessment; OSHA calculated corresponding maximum likelihood estimates.

^d Numbers are not adjusted for the early termination of the study.

^e Numbers are adjusted for the early termination of the study.

^f Estimate excluded high-dose (625 ppm) group owing to nonlinear metabolism.

^g Pooled tumour incidence excludes incidence of lymphoma.

^h Time-to-tumour model.

ⁱ Pooled tumour incidence excludes incidence of Zymbal gland carcinoma.

^j Pooled tumour incidence excludes incidence of mammary fibroadenoma.

^k Mouse dose was extrapolated to humans using body weight to the three fourths power.

^l Number is the maximum likelihood estimate for excess (extra) risk taken from Table 2 of NIOSH (80).

^m Mouse dose was extrapolated to humans using body surface area to the two thirds power.

In the only published human study, of 40 individuals occupationally exposed to butadiene at levels typical of an industrial setting (1–3 ppm), there were no significant increases in chromosome aberrations, micronuclei formation or sister chromatid exchanges in peripheral blood lymphocytes compared to controls (30 individuals) (39). This observation is of particular interest since butadiene concentrations as low as 6.25 ppm increased the occurrence of the same indicators of genetic damage in the bone marrow and peripheral blood lymphocytes of mice.

Several different risk assessments have been conducted for butadiene, and a number of these for occupational exposure have been summarized by the US Occupational Safety and Health Administration (79). The estimates in these risk assessments were based on different assumptions. Some were adjusted for absorbed dose, since changes in butadiene absorption in animals will occur with changes in the inhaled concentration (11). For the most part, they were based on the multistage model. There was considerable variation in human cancer risk estimates depending on the animal species used for the calculations, with those based on tumour data in mice being 100–1000 times higher than those based on tumour data in rats.

Unit risk estimates for cancer associated with continuous lifetime exposure to butadiene in ambient air have been reported. Values estimated by the Californian Air Resources Board (82), based on adjustment of dose for absorption (12) and tumour incidence in mice (45) and rats (43), were 0.0098 and 0.8 per ppm, respectively. The value estimated by the US Environmental Protection Agency, which was based on linearized multistage modelling of data from an earlier, limited bioassay in mice, was 2.8×10^{-4} per $\mu\text{g}/\text{m}^3$ (83). Values estimated by RIVM (84), based on linearized multistage modelling of the incidence of lymphocytic lymphoma and haemangiosarcoma of the heart in mice in the most recent NTP bioassay (45), were in the range $0.7\text{--}1.7 \times 10^{-5}$ per $\mu\text{g}/\text{m}^3$.

Estimates of human cancer risk could be improved by the inclusion of mechanistic information such as *in vivo* toxicokinetic data, genotoxicity data and data from the recent epidemiological reassessment. For example, new data on levels of butadiene epoxides in blood and tissues in laboratory animals (24–26) could be used to replace the earlier absorption data (11). In addition, physiologically based pharmacokinetic models have been greatly improved since earlier attempts to apply this approach to risk assessment, most notably by the incorporation of model parameters that

have been experimentally measured rather than empirically estimated. Nevertheless, none of the models published to date incorporates the necessary information on the formation, removal and distribution of diepoxybutane.

Guideline

Quantitative cancer risk estimates vary widely, depending in particular on the test species used. No definitive conclusions can yet be made as to which species should be used for risk estimates. As yet unpublished epidemiological data might have an impact on the risk estimates and hence on the derivation of a guideline value. In the light of these considerations, no guideline value can be recommended at this time.

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