1,3-BUTADIENE

This substance was considered by previous working groups in June 1985 (IARC, 1986a; see also correction, IARC, 1987a) and March 1987 (IARC, 1987b). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 106-99-0
Chem. Abstr. Name: 1,3-Butadiene
IUPAC Systematic Name: 1,3-Butadiene
Synonyms: Biethylene; bivinyl; butadiene; buta-1,3-diene; α,γ-butadiene; *trans*-butadiene; divinyl; erythrene; pyrrolylene; vinylethylene

$$CH_2=CH-CH=CH_2$$

C_4H_6 Mol. wt: 54.09

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Colourless gas with mildly aromatic odour; easily liquefied (Sax & Lewis, 1987)
(*b*) *Boiling-point*: –4.4 °C (Weast, 1989)
(*c*) *Melting-point*: –108.9 °C (Weast, 1989)
(*d*) *Density*: 0.6211 g/ml at 20 °C/liquefied (Kirshenbaum, 1978; Verschueren, 1983)
(*e*) *Spectroscopy data*: Ultraviolet (Grasselli & Ritchey, 1975), infrared (Sadtler Research Laboratories, 1980; prism [893[a]], grating [36758]), nuclear magnetic resonance and mass spectral data (US National Institutes of Health/Environmental Protection Agency Chemical Information System, 1983) have been reported.
(*f*) *Solubility*: Very slightly soluble in water (735 mg/l at 20 °C); soluble in ethanol, diethyl ether and organic solvents (Verschueren, 1983; Sax & Lewis, 1987; Budavari, 1989)
(*g*) *Volatility*: Vapour pressure, 1790 mm Hg (239 kPa) at 20 °C (Santodonato, 1985); relative vapour density (air = 1), 1.87 (Verschueren, 1983)

[a]Spectrum number in Sadtler compilation

(*h*) *Stability*: Flash-point, –76 °C (Sax & Lewis, 1987); slowly dimerizes to 4-vinyl-1-cyclohexene (US Occupational Safety and Health Administration, 1990); may form peroxides upon exposure to air (Kirshenbaum, 1978)
(*i*) *Reactivity*: Polymerizes readily, particularly if oxygen is present (Sax & Lewis, 1987)
(*j*) *Conversion factor*[b]: $mg/m^3 = 2.21 \times ppm$

1.1.3 *Technical products and impurities*

1,3-Butadiene is available commercially as a liquefied gas under pressure in several grades of purity, including a special purity or instrument grade of 99.4–99.5 mol% purity, a research grade of 99.86 mol% purity, a technical–commercial grade of 98 mol% purity and a rubber grade (Santodonato, 1985). Analytical, polymer, rubber and liquid grades (Aldrich Chemical Co., 1990; Kuney, 1990) range in minimal purity from 99.0 to 99.5%, with the following typical impurities: 1,2-butadiene, acetaldehyde (see IARC, 1987b), acetylenes (alpha, vinyl), propadiene, butadiene dimer (4-vinylcyclohexene, see IARC, 1986b), peroxides, sulfur and C_5 hydrocarbons. Oxidation/polymerization of 1,3-butadiene is inhibited by addition of hydroquinone, di-*n*-butylamine, *tert*-butylcatechol, aliphatic mercaptans or *ortho*-dihydroxybenzene (Exxon Chemical Co., 1973; Kirshenbaum, 1978; Lyondell Petrochemical Co., 1988; Budavari, 1989).

Crude 1,3-butadiene is also available from many producers for use as a feedstock. Such grades contain a minimum of 36–65% 1,3-butadiene, with specifications typically given for acetylenes, C_3 compounds and lighter hydrocarbons, C_5 compounds and heavier, peroxides, carbonyl compounds, sulfur and organic chlorides. Inhibitors (e.g., *tert*-butylcatechol, 50–200 ppm) are also added (Vista Chemical Co., 1985; Union Carbide Corp., 1987).

1.1.4 *Analysis*

Selected methods for the analysis of 1,3-butadiene in various matrices are listed in Table 1 (methods used previously are given in section 1.3.2).

The specificity and the detection limit of methods for determining simple, small molecules present in packaging materials which migrate into packaged goods have been discussed (Vogt, 1988). 1,3-Butadiene can be determined in plastic polymers, foods and food simulants by chromatographic methods.

Several gas detector tubes are used in conjunction with common colorimetric reactions to detect 1,3-butadiene. The reactions include the reduction of chromate or dichromate to chromous ion and the reduction of ammonium molybdate and palladium sulfate to molybdenum blue (Saltzman & Harman, 1989).

1.2 Production and use

1.2.1 *Production*

1,3-Butadiene was first produced in 1886 by the pyrolysis of petroleum hydrocarbons (Kirshenbaum, 1978). Commercial production started in the 1930s (Kosaric *et al.*, 1987).

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[b]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming normal temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

Table 1. Methods for the analysis of 1,3-butadiene

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Collect on solid sorbent tube; desorb with dichloromethane; chill in ice	GC/FID	0.044 mg/m^3	Eller (1987)
	Collect on solid sorbent tube of charcoal coated with *tert*-butylcatechol; desorb with carbon disulfide	GC/FID	0.35 mg/m^3	Hendricks & Schultz (1986)
	Inject sample into GC using a temperature-programmed, fused-silica, porous layer, open tubular Al_2O_3/KCl column	GC/FID	0.01 ppm by volume (0.01 µl/l)	Locke *et al.* (1987)
	Assay directly	FT-IR	5 ppm (10 mg/m^3)	Harman (1987)
Plastics, liquid foods	Dissolve in *ortho*-dichlorobenzene; inject headspace sample	GC/FID	2–20 µg/kg	US Food and Drug Administration (1987)
Solid foods	Cut or mash sample; inject headspace sample	GC/FID	2–20 µg/kg	US Food and Drug Administration (1987)

Abbreviations: FT-IR, Fourier transform–infrared absorption spectroscopy; GC, gas chromatograph; GC/FID, gas chromatography/flame ionization detection

1,3-Butadiene has been produced commercially by three processes: catalytic dehydrogenation of *n*-butane and *n*-butene (the Houdry process), oxidative dehydrogenation of *n*-butene (the Oxo-D or O-X-D process) and recovery from the C_4 co-product (by-product) stream from the steam cracking process used to manufacture ethylene (the ethylene co-product process). All three processes involve the production of 1,3-butadiene from a C_4 hydrocarbon stream, and solvent extraction and extractive distillation are used in all three to further concentrate the 1,3-butadiene. There has recently been a shift to the use of cheaper, heavier feedstocks for ethylene production, with a concomitant increase in the volume of co-product containing 1,3-butadiene (Krishnan & Corwin, 1987). The ethylene co-product process accounts for approximately 95% of US and 85% of worldwide production (Morrow, 1990).

The production of 1,3-butadiene is thus a two-stage process: (i) production of a C_4 co-product during ethylene manufacture and (ii) recovery of 1,3-butadiene from the co-product. The first stage consists of cracking a hydrocarbon such as naphtha to produce ethylene as the primary product and a co-product stream composed of C_4 hydrocarbons. The amount of 1,3-butadiene in the co-product depends on the feedstock used and the severity of the cracking process: the heavier the feedstock and the more severe the cracking, the more 1,3-butadiene is produced. The 1,3-butadiene content of the co-product C_4 stream is 20–70%; the C_4 feed streams are usually blended with a feed stream containing 40–50% 1,3-butadiene for processing. In the extraction plants, solvents such as dimethylformamide, acetonitrile, furfural, dimethylacetamide and methylpyrrolidone are used (US Occupational Safety and Health Administration, 1990) to alter the volatility of components in a fractional distillation

selectively and to produce a high purity (> 99.0%) 1,3-butadiene monomer (Krishnan & Corwin, 1987).

In 1987, worldwide production of 1,3-butadiene was approximately 5.5 million tonnes (Morrow, 1990). A more detailed accounting of the production of 1,3-butadiene in several countries in 1980–90 is presented in Table 2. Global 1,3-butadiene consumption in 1987 was estimated at 5.5 million tonnes, 1.5 million tonnes of which were used in the USA. As in most years, the US demand exceeded its supply, so approximately 227 thousand tonnes of 1,3-butadiene monomer were imported in 1987 (Morrow, 1990).

Table 2. Trends in production of 1,3-butadiene in several countries (thousand tonnes)

Country	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
Canada	NA	126	118	133	127	132	146	167	182	175	192
France	259	266	258	281	303	288	291	307	335	329	281
Germany[a]	NA	NA	579	717	754	840	683	701	761	717	771
Italy	183	166	159	195	181	NA	NA	NA	NA	NA	NA
Japan	574	518	522	556	627	639	656	707	780	827	827
Mexico	17	12	15	19	20	18	18	21	12	NA	NA
United Kingdom	192	207	228	237	259	297	192	231	239	226	195
USA[b]	1270	1356	869	1068	1113	1062	1156	1329	1437	1417	1435

From Anon. (1984, 1986, 1988, 1991b); NA, not available
[a]Figures prior to 1990 are for western Germany only
[b]Rubber grade

Information available in 1988 indicated that 1,3-butadiene was produced by nine companies in Germany, eight in Japan, four in the United Kingdom and in Brazil, three in France, two in Australia, Belgium, Canada, the Netherlands and Spain, and one each in Argentina, Austria, Bulgaria, China, Czechoslovakia, Finland, India, Italy, Mexico, Poland, Saudi Arabia, Singapore, Taiwan and Yugoslavia (Chemical Information Services, 1988). It was produced by eight companies in the USA in 1991 (Anon., 1991a).

1.2.2 *Use*

1,3-Butadiene is used principally as a monomer in the manufacture of a wide range of polymers and copolymers. Polymerization of styrene and 1,3-butadiene yields styrene–butadiene rubber, the largest single use of butadiene; almost 80% of the styrene–butadiene rubber produced is used in tyres and tyre products. Polymerization of 1,3-butadiene produces polybutadiene, almost all of which used for car and bus tyres. Nitrile rubber is produced by copolymerizing 1,3-butadiene and acrylonitrile; it is used in hoses, gaskets, seals, latexes, adhesives and footwear. Acrylonitrile–butadiene–styrene resins are graft ter-polymers of polybutadiene on a styrene-acrylonitrile copolymer; they are used in automotive parts, pipes, appliances, business machines and telephones. Styrene–butadiene latexes are suspensions of particles or globules of the elastomer in water and are used in paper coatings and paints and as carpet backing (Santodonato, 1985; US Occupational Safety and Health Administration, 1990).

1,3-Butadiene is used as a chemical intermediate in the production of a number of important chemicals. Neoprene is made by chlorinating 1,3-butadiene and treating the resultant chloroprene with sodium hydroxide; two-thirds of the neoprene produced is used for industrial and automotive rubber goods. Adiponitrile is produced by chlorinating 1,3-butadiene and cyanating the product to 1,4-dicyanobutene, which is then reduced to adiponitrile; this is converted to hexamethylenediamine for the production of Nylon 66. 1,4-Hexadiene, made by reacting 1,3-butadiene with ethylene, is used as a monomer for ethylene–propylene terpolymer. Sulfolane, produced by reacting sulfur dioxide and 1,3-butadiene and dehydrogenating the product, is a valuable solvent for extraction. 1,5,9-Cyclodecatriene is produced by trimerizing 1,3-butadiene and is used for the production of various nylon fibres and resins. Some other nonpolymer applications include manufacture of agricultural fungicides (captan and captafol) and anthraquinone dyes (Santodonato, 1985; US Occupational Safety and Health Administration, 1990).

In 1990, 1,3-butadiene was used in the USA for: styrene–butadiene rubber (30%), polybutadiene rubber (20%), adiponitrile/hexamethylenediamine (15%), styrene–butadiene latex (10%), neoprene rubber (5%), acrylonitrile–butadiene–styrene resins (5%), exports (4%), nitrile rubber (3%) and other (including specialty polymers) (8%) (Anon., 1991a).

(For more detailed discussions of the production and use of 1,3-butadiene, see Miller, 1978; Leviton, 1983; Greek, 1984.)

1.3 Occurrence

1.3.1 *Natural occurrence*

1,3-Butadiene is not known to occur as a natural product (Santodonato, 1985).

1.3.2 *Occupational exposure*

On the basis of a National Occupational Exposure Survey, the US National Institute for Occupational Safety and Health (1990) estimated that 52 000 workers were potentially exposed to 1,3-butadiene in the USA in 1981–83. Potential exposure to 1,3-butadiene can occur in the following industrial activities: petroleum refining and related operations (production of C_4 fractions containing 1,3-butadiene, production and distribution of gasoline), production of purified 1,3-butadiene monomer, production of various 1,3-butadiene-based rubber and plastics polymers and other derivatives, and the rubber and plastics products manufacturing industry (production of tyres, hoses and a variety of moulded objects).

In the descriptions below, the accuracy of the levels of exposure to 1,3-butadiene may have been affected by inability to distinguish between 1,3-butadiene and other C_4 compounds, low desorption efficiency at low concentrations, possible sample breakthrough in charcoal tubes and possible loss during storage, in methods used until the mid-1980s (Lunsford *et al.*, 1990). No data are available on levels of exposure to 1,3-butadiene before the 1970s, when different processes and working conditions (e.g., during the Second World War) would have resulted in exposure conditions different from those now prevalent in developed countries.

(*a*) *Petroleum refining and production of crude 1,3-butadiene*

Gasoline contains a small percentage of 1,3-butadiene, and exposures of workers in various job groups in the production and distribution of gasoline are shown in Table 3. Table 4 shows the exposures since 1984 of workers in different areas of petroleum refineries and petrochemical facilities where crude 1,3-butadiene is produced (usually a C_4 stream obtained as a by-product of ethylene production).

Table 3. Personal exposures (mg/m^3) to 1,3-butadiene associated with gasoline during 1984–85 in 13 European countries

Activity	Mean	Range	Exposure duration (TWA)
Production on-site (refining)	0.3	ND–11.4	8 h
Production off-site (refining)	0.1	ND–1.6	8 h
Loading ships (closed system)	6.4	ND–21.0	8 h
Loading ships (open system)	1.1	ND–4.2	8 h
Loading barges	2.6	ND–15.2	8 h
Jettyman	2.6	ND–15.9	8 h
Bulk loading road tankers			
Top loading < 1 h	1.4	ND–32.3	< 1 h
Top loading > 1 h	0.4	ND–4.7	8 h
Bottom loading < 1 h	0.2	ND–3.0	< 1 h
Bottom loading > 1 h	0.4	ND–14.1	8 h
Road tanker delivery (bulk plant to service station)	ND		
Railcar top loading	0.6	ND–6.2	8 h
Drumming	ND		
Service station attendant (dispensing fuel)	0.3	ND–1.1	8 h
Self-service station (filling tank)	1.6	ND–10.6	2 min

From CONCAWE (1987); ND, not detected; TWA, time-weighted average

Table 4. Mean 8-h time-weighted average concentrations of 1,3-butadiene to which workers in different jobs in petroleum refineries and petrochemical facilities have been exposed since 1984

Job area	No. of facilities	Mean[a]		Range	
		ppm	mg/m^3	ppm	mg/m^3
Production	7	0.24	0.53	0.008–2.0	0.02–4.4
Maintenance	6	0.11	0.24	0.02–0.37	0.04–0.82
Distribution	1	2.9	64.1		
Laboratory	4	0.18	0.40	0.07–0.4	0.16–0.88

From Heiden Associates (1987)

[a]Weighted by number of exposed workers

(b) Monomer production

Detailed industrial hygiene surveys were conducted by the US National Institute for Occupational Safety and Health in 1985 in four of 10 US facilities where 1,3-butadiene was produced by solvent extraction of C_4 fractions originating as ethylene co-product streams (Krishnan *et al.*, 1987). Levels of 1,3-butadiene to which workers in various job categories were exposed are summarized in Table 5. Jobs that require workers to handle or transport containers, such as voiding sample cylinders or loading and unloading tank trucks or rail cars, present the greatest potential exposure. Geometric means of full-shift exposure levels for other job categories were below 1 ppm [2.2 mg/m^3]. Short-term samples showed that such activities as open-loop sampling and cylinder voiding were associated with peak exposures of 100 ppm [220 mg/m^3]. Full-shift area samples indicated that ambient concentrations of 1,3-butadiene were greatest in the railcar terminals (geometric mean, 1.77 [3.4 mg/m^3]) and in the tank storage farm (2.12 ppm [3.4 and 4.7 mg/m^3]).

Table 5. Full-shift, time-weighted average exposure levels in personal breathing-zone samples at four US 1,3-butadiene monomer production facilities, 1985

Job category	No. of samples	Exposure level (ppm [mg/m^3])		
		Arithmetic mean	Geometric mean	Range
Process technician Control room	10	0.45 [1.0]	0.09 [0.20]	< 0.02–1.87 [< 0.04–4.1]
Process technician Process area	28	2.23 [4.9]	0.64 [1.4]	< 0.08–34.9 [< 0.18–77.1]
Loading area				
Railcar	9	14.64 [32.4]	1.00 [2.2]	0.12–123.57 [0.27–273.1]
Tank truck	3	2.65 [5.9]	1.02 [2.3]	0.08–5.46 [0.18–12.1]
Tank farm	5	0.44 [0.97]	0.20 [0.44]	< 0.04–1.53 [< 0.09–3.4]
Laboratory technician	29	1.06 [2.3]	0.40 [0.88]	0.03–6.31 [0.07–14.0]
Cylinder voiding	3	125.52 [277.4]	7.46 [16.5]	0.42–373.54 [0.93–825.5]

From Krishnan *et al.* (1987)

In 1984, the US Chemical Manufacturers' Association obtained data on personal exposure to 1,3-butadiene before 1984 from 13 monomer-producing companies, categorized broadly by job type (Table 6). These data were collected by an older method and provide a historical perspective on the data reported in Table 5. The highest exposures were in the maintenance and distribution jobs. Out of a total of 1287 samples, 91% were less than or equal to 10 ppm [22.1 mg/m^3] and 68% were less than or equal to 5 ppm [11.1 mg/m^3]. Factors that limit generalization of these data are unspecified sampling and analytical techniques, lack of detailed job descriptions and different or unspecified average times of sampling (JACA Corp., 1987).

Monitoring in a Finnish plant generally indicated ambient air levels of less than 10 ppm [22.1 mg/m^3] at different sites (33 samples; mean sampling time, 5.3 h). In personal samples for 16 process workers, the concentration ranged from < 0.1 to 477 ppm [< 0.22–1054.2

Table 6. Time-weighted average exposure to 1,3-butadiene in 13 US monomer production plants before 1984

Job area	No. of samples	Exposure (ppm [mg/m^3])											
		0.00–5.00 [0–11.05]		5.01–10.00 [11.07–22.12]		10.01–25.00 [22.12–55.25]		25.01–50.00 [55.27–110.50]		50.01–100.00 [110.52–221.23]		> 100.00 [> 221.23]	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Production	562	446	79.4	111	19.7	5	0.9						
Maintenance	329	247	75.1			47	14.3	35	10.6				
Supervisory	64	60	93.8	4	6.2								
Distribution	206	60	29.1	121	58.7	16	7.8	5	2.4	2	1.0	2	1.0
Laboratory	126	58	46.0	68	54.0								
Total	1287	871	67.8	304	23.6	68	5.3	40	3.1	2	0.1	2	0.1

From JACA Corp. (1987)

mg/m^3] (mean, 11.5 ppm [25.4 mg/m^3]; median, < 0.1 ppm [< 0.22 mg/m^3]; 46 samples; mean sampling time, 2.5 h). The highest concentrations were measured during sample collection. Protective clothing and respirators were used during this operation (Arbetsmiljöfonden, 1991).

Potential exposure in the monomer industry other than to 1,3-butadiene includes extraction solvents and components of the C_4 feedstock. Extraction solvents differ among facilities; some common ones are dimethylformamide, dimethylacetamide, acetonitrile, β-methoxypropylnitrile (Fajen, 1985a), furfural and cuprous ammonium acetate (US Occupational Safety and Health Administration, 1990). Stabilizers are commonly used to prevent formation of peroxides in air and polymerization (see p. 238). No information was available on these other exposures, or on exposures to chemicals other than 1,3-butadiene that are produced in some facilities, such as butylenes, ethylene, propylene, polyethylene and polypropylene resins, methyl-*tert*-butyl ether and aromatic hydrocarbons (Fajen, 1985b,c).

(c) *Production of polymers and derivatives*

Detailed industrial hygiene surveys were conducted in 1986 in five of 17 US facilities where 1,3-butadiene was used to produce styrene–butadiene rubber, nitrile–butadiene rubber, polybutadiene rubber, neoprene and adiponitrile (Fajen, 1988). Levels of 1,3-butadiene to which workers in various job categories were exposed are summarized in Table 7. Process technicians in unloading, the tank farm, purification, polymerization and reaction, laboratory technicians and maintenance technicians were exposed to the highest levels. Short-term sampling showed that activities such as sampling a barge and laboratory work were associated with peak exposures to more than 100 ppm [221 mg/m^3]. Full-shift area sampling indicated that geometric mean ambient concentrations of 1,3-butadiene were less than 0.5 ppm [1.1 mg/m^3] and usually less than 0.1 ppm [0.22 mg/m^3] in all locations at the five plants.

Eight-hour time-weighted average (TWA) exposures to 1,3-butadiene in the polymer industry were obtained by personal sampling in 11 North American synthetic rubber plants in 1978–84 and reported by the International Institute of Synthetic Rubber Producers in 1984 (JACA Corp., 1987) (Table 8). The highest exposures were found for tank car loaders (15% of exposures, > 10 ppm [> 22.1 mg/m^3]), reactor operators (18% of exposures, > 10 ppm) and laboratory technicians (6% of exposures, > 10 ppm). Sampling and analytical techniques and job descriptions were not available.

Other data on levels of exposure to 1,3-butadiene have been collected during health surveys and epidemiological studies (Table 9). In a US styrene–butadiene rubber manufacturing plant in 1979, the only two departments in which levels were greater than 10 ppm [22.1 mg/m^3] were tank farm (53.4 ppm [118 mg/m^3]) and maintenance (20.7 ppm [45.8 mg/m^3]) (Checkoway & Williams, 1982). In samples taken at one of two US styrene–butadiene rubber plants in 1976, levels above 100 ppm [221 mg/m^3] were encountered by technical services personnel (114.6 ppm [253.3 mg/m^3]) and an instrument man (174.1 ppm [384.78 mg/m^3]) (Meinhardt *et al.*, 1978). Overall mean 8-h TWA exposure levels differed considerably between the two plants, however: 1.24 ppm [2.74 mg/m^3] in one plant and 13.5 ppm [29.84 mg/m^3] in the other (Meinhardt *et al.*, 1982).

Table 7. Full-shift time-weighted average exposure levels in personal breathing-zone samples at five US plants producing 1,3-butadiene-based polymers and derivatives, 1986

Job category	No. of samples	Exposure level (ppm [mg/m^3])		
		Arithmetic mean	Geometric mean	Range
Process technician				
Unloading area	2	14.6 [32.27]	4.69 [10.37]	0.770–28.5 [1.7–63.0]
Tank farm	31	2.08 [4.60]	0.270 [0.60]	< 0.006–23.7 [< 0.01–52.4]
Purification	18	7.80 [17.24]	6.10 [13.48]	1.33–24.1 [3.0–53.3]
Polymerization or reaction	81	0.414 [0.92]	0.062 [0.14]	< 0.006–11.3 [< 0.01–25.0]
Solutions and coagulation	33	0.048 [0.11]	0.029 [0.06]	< 0.005–0.169 [< 0.01–0.4]
Crumbing and drying	35	0.033 [0.07]	0.023 [0.05]	< 0.005–0.116 [< 0.01–0.26]
Packaging	79	0.036 [0.08]	0.022 [0.05]	< 0.005–0.154 [< 0.01–0.34]
Warehouse	20	0.020 [0.04]	0.010 [0.02]	< 0.005–0.068 [< 0.01–0.15]
Control room	6	0.030 [0.07]	0.019 [0.04]	< 0.012–0.070 [< 0.03–0.16]
Laboratory technician	54	2.27 [5.02]	0.213 [0.47]	< 0.006–37.4 [< 0.01–82.65]
Maintenance technician	72	1.37 [3.02]	0.122 [0.27]	< 0.006–43.2 [< 0.01–95.47]
Utilities operator	6	0.118 [0.26]	0.054 [0.12]	< 0.006–0.304 [< 0.01–0.67]

From Fajen (1988)

The manufacture of butadiene-based polymers and butadiene derivatives implies potential occupational exposure to a number of other chemical agents, which varies according to product and process. These include other monomers (styrene (see IARC, 1987b), acrylonitrile (see IARC, 1987b), chloroprene (see IARC, 1979)), solvents, additives (e.g., activators, antioxidants, modifiers), catalysts, mineral oils (see IARC, 1987b), carbon black (see IARC, 1987b), chlorine, inorganic acids and caustic solution (Fajen, 1986a,b; Roberts, 1986). Styrene, benzene (see IARC, 1987b) and toluene (see IARC, 1989) were measured in various departments of a US styrene–butadiene rubber manufacturing plant in 1979: mean 8-h TWA levels of styrene were below 2 ppm [8.4 mg/m^3], except for tank farm workers (13.7 ppm [57.5 mg/m^3], 8 samples); mean benzene levels did not exceed 0.1 ppm [0.3 mg/m^3], and those of toluene did not exceed 0.9 ppm [3.4 mg/m^3] (Checkoway & Williams, 1982). Meinhardt *et al.* (1982) reported that the mean 8-h TWA levels of styrene were 0.94 ppm [3.9 mg/m^3] (55 samples) and 1.99 ppm [8.4 mg/m^3] (35 samples) in two styrene–butadiene rubber manufacturing plants in 1977; the average benzene level measured in one of the plants was 0.1 ppm [0.3 mg/m^3] (3 samples). Average levels of styrene, toluene, benzene, vinyl cyclohexene and cyclooctadiene were reported to be lower than 1 ppm in another styrene–butadiene rubber plant in 1977 (Burroughs, 1977).

(*d*) *Rubber and plastics products manufacturing industries*

Unreacted 1,3-butadiene was detected as only a trace (0.04–0.2 ng/mg) in 15 of 37 bulk samples of polymers and other chemicals synthesized from 1,3-butadiene and analysed in 1985–86. Only two samples contained measurable amounts of 1,3-butadiene: tetrahydrophthalic anhydride (53 ng/mg) and vinyl pyridine latex (16.5 ng/mg) (JACA Corp., 1987).

Table 8. Time-weighted average exposures to 1,3-butadiene in 11 North American plants producing synthetic rubber, 1978–84

Occupational group	No. of samples	Exposure (ppm [mg/m^3])															
		0.00–5.00 [0–11.05]		5.01–10.00 [11.07–22.12]		10.01–25.00 [22.12–55.25]		25.01–50.00 [55.27–110.50]		50.01–100.00 [110.52–221.23]		100.01–200.00 [221.23–420.00]		200.01–500.00 [442.02–1105.00]		500.01–1000.00 [1105.02–2210.00]	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tank car loader	102	78	76.5	9	8.8	9	8.8	4	3.9	2	2.0						
Vessel cleaner	214	199	93	9	4.2	4	1.9	2	0.9								
Charge solution make-up	89	83	93.2	3	3.4			2	2.3	1	1.1						
Reactor operator	190	133	70	22	11.6	14	7.4	7	3.7	7	3.7	5	2.6	1	0.5	1 1	0.5
Recovery operator	108	100	92.6	5	4.6	2	1.9	1	0.9								
Coagulation operator	185	173	93.5	9	4.9	2	1.1	1	0.5								
Dryer operator	85	84	98.8	1	1.2												
Baler and packager	167	164	98.2	2	1.2	1	0.6										
Warehouseman	22	22	100														
Laboratory technician	116	103	88.8	6	5.2	6	5.2	1	0.9								
Maintenance technician	262	241	92.0	12	4.6	4	1.5	2	0.8	3	1.1						
Supervisor	123	111	90.2	6	4.9	6	4.9										
Waste treatment operator	9	9	100														
Total	1672	1500	89.7	84	5.0	48	2.9	20	1.2	13	0.78	5	0.30	1	0.06	1	0.06

From JACA Corp. (1987)

Table 9. Mean 8-h time-weighted average concentrations of 1,3-butadiene measured in two US styrene–butadiene rubber manufacturing plants

Job classification or department	No. of samples	Concentration		Year of sampling	Reference
		ppm	mg/m^3		
Instrument man	3	58.62	129.55	1976	Meinhardt *et al.* (1978)
Technical services personnel	12	19.85	43.87		
Head production operator	5	15.50	34.26		
Carpenter	4	7.80	17.24		
Production operator	24	3.30	7.29		
Maintenance mechanic	17	3.15	6.96		
Common labourer	17	1.52	3.36		
Production foreman	1	1.16	2.56		
Operator helper	3	0.79	1.75		
Pipefitter	8	0.74	1.64		
Electrician	5	0.22	0.49		
Tank farm	8	20.03	44.3	1979	Checkoway & Williams (1982)
Maintenance	52	0.97	2.14		
Reactor and recovery	28	0.77	1.7		
Solution	12	0.59	1.3		
Factory service	56	0.37	0.82		
Shipping and receiving	2	0.08	0.18		
Storeroom	1	0.08	0.18		

Detailed industrial hygiene surveys were conducted in 1984–87 in a US rubber tyre plant and a US industrial hose plant where styrene–butadiene rubber, polybutadiene and acrylonitrile–butadiene rubber were processed. No 1,3-butadiene was detected in any of a total of 124 personal full-shift samples from workers in the following job categories, which were identified as involving potential exposure to 1,3-butadiene: Banbury operators, mill operators, extruder operators, curing operators, conveyer operators, calendering operators, wire winders, tube machine operators, tyre builders and tyre repair and buffer workers (Fajen *et al.*, 1990).

Measurements taken in 1978 and 1979 in personal 8-h samples in companies where acrylonitrile–butadiene–styrene moulding operations were conducted showed levels of < 0.05–1.9 mg/m^3 (Burroughs, 1979; Belanger & Elesh, 1980; Ruhe & Jannerfeldt, 1980). In a polybutadiene rubber warehouse, levels of 0.003 ppm [0.007 mg/m^3] were found in area samples; area and personal samples taken in tyre plants contained 0.007–0.05 ppm [0.016–0.11 mg/m^3] (Rubber Manufacturers' Association, 1984). In a US tyre and tube manufacturing plant in 1975, a cutter man/Banbury operator was reported to have been exposed to 1,3-butadiene at 2.1 ppm [4.6 mg/m^3] (personal 6-h sample) (Ropert, 1976).

Occupational exposures to many other agents in the rubber goods manufacturing industry were reviewed in a previous monograph (IARC, 1982).

1.3.3 *Air*

In 1989, total emissions of 1,3-butadiene to the air in the USA were estimated at approximately 2512 tonnes from 158 locations; total land releases were estimated at 6.7 tonnes (US National Library of Medicine, 1991).

Data on annual emissions of 1,3-butadiene from US facilities producing 1,3-butadiene, polybutadiene, neoprene/chloroprene and styrene–butadiene rubber and from miscellaneous facilities where 1,3-butadiene was used were collected in 1984 by the US Environmental Protection Agency. Data on episodic emissions were collected from most of the same facilities in 1985–86 (US Environmental Protection Agency, 1987; Mullins, 1990). Average annual emissions, the average rates and durations of episodic emissions and the highest rates for specific types of emissions are presented in Table 10.

Table 10. 1,3-Butadiene emissions from US manufacturing facilities in 1984–86

Activity of facility	No. of facilities	Total emissions (tonnes/year)		Episodic emissions (1986)		
		Average	Range	Average rate (kg/min)	Highest average rate (kg/min)	Average duration (min)
1,3-Butadiene production	10[a]	135.9	6.8–752	355	1600[b] 1100[c]	2170
Polybutadiene production	7	57.4	22.1–176	24	81.4[c] 24.0[d]	7.5
Chloroprene/-neoprene production	2	10, 32.2		2.9	181[b]	38.8
Styrene–butadiene rubber production	17	49.3	0.9–145	3.9	9.9[e] 9.2[c]	49.6
Using 1,3-butadiene	11[f]	63.5	2.2–350	NR	NR	NR

From US Environmental Protection Agency (1987); NR, not reported
[a]Episodic emissions reported for eight facilities
[b]Pressure relief discharges
[c]Accidental liquid releases
[d]Equipment openings
[e]Accidental gas releases
[f]Episodic emissions reported for five facilities

Few data are available on levels of 1,3-butadiene in ambient air; reported concentrations in urban air generally range from less than 1 to 10 ppb [2–22 μg/m^3] (Neligan, 1962; Cote & Bayard, 1990). In the USA, combined levels of 1,3-butadiene and 2-butene were 5.9–24.4 ppb (0.01–0.05 mg/m^3) in 1978 in Tulsa, OK (Arnts & Meeks, 1981), and 0–0.019 ppm (0–0.042 mg/m^3) in 1973–74 in Houston, TX (Siddiqi & Worley, 1977). Levels of 1,3-butadiene were 0.004 mg/m^3 in Denver, CO, and < 0.001–0.028 mg/m^3 in various cities in Texas (Hunt *et al.*, 1984); urban air in Los Angeles and Riverside, CA, contained levels as high as 9 ppb [0.02 mg/m^3] (Parsons & Wilkins, 1976).

1,3-Butadiene was found in 32% of 24-h ambient air samples taken in 19 US cities in 1987–88, at a mean concentration of 1.39 μg/m^3 (range, 0.11–6.94) (US Environmental Protection Agency, 1989).

1.3.4 *Water*

1,3-Butadiene has been detected in drinking-water in the USA (US Environmental Protection Agency, 1978; Kraybill, 1980). Total releases to ambient water in 1989 were estimated to be 65 tonnes (US National Library of Medicine, 1991).

1.3.5 *Food*

Levels of < 0.2 μg/kg 1,3-butadiene were found in retail soft margarine; the plastic tubs containing the margarine contained < 5–310 μg/kg (Startin & Gilbert, 1984).

1.3.6 *Miscellaneous*

The US Environmental Protection Agency (1990) estimated that 1,3-butadiene is emitted in automobile exhaust at 8.9–9.8 mg/mile [5.6–6.1 mg/km] and comprises about 0.35% of total hydrocarbon in exhaust emissions. It has been detected in smoke generated during house fires at up to 15 ppm [33 mg/m^3] (Berg *et al.*, 1978).

Sidestream cigarette smoke contains 1,3-butadiene at approximately 0.4 mg/cigarette, and levels of 1,3-butadiene in smoky indoor environments are typically 10–20 μg/m^3 (Löfroth *et al.*, 1989).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for 1,3-butadiene in some countries and regions are presented in Table 11. Exposure limits were lowered in many countries in the late 1980s.

1,3-Butadiene is regulated by the US Food and Drug Administration (1989) for use in resinous and polymeric coatings in can-end cements; for use only as a coating or coating component and limited to a level not to exceed 1% by weight of paper or paperboard in contact with foods; for use in semi-rigid and rigid acrylic and modified acrylic plastics in repeat-use articles; for use in acrylonitrile–butadiene–styrene copolymers used in closures with sealing gaskets for food containers; and for use in textiles and textile fibres that come in contact with food.

2. Studies of Cancer in Humans

2.1 Cohort studies

The rubber industry, i.e., the manufacture of finished rubber goods, in which there is potential exposure to 1,3-butadiene, among other chemicals, has been evaluated previously; it was concluded that exposure in the rubber industry is carcinogenic to humans (IARC, 1982, 1987b). The epidemiological studies that were evaluated did not, however, include specific information on styrene–butadiene rubber manufacture, and it is these that are summarized below. In these descriptions, the histological descriptions of observed tumours given by the authors are used, with ICD codes when available.

Table 11. Occupational exposure limits and guidelines for 1,3–butadiene

Country or region	Year	Concentration (mg/m^3)	Interpretation[a]
Australia	1990	22 (carcinogen)	
Austria	1982	2200	TWA
Belgium	1990	22 (carcinogen)	TWA
Brazil	1978	1720	TWA
Bulgaria	1984	100	TWA
Czechoslovakia	1990	20	TWA
		40	STEL
Denmark	1990	22 (carcinogen)	TWA
Finland	1987	73 (carcinogen)	TWA
Germany	1989	0 (carcinogen in animals; III A2)	
Hungary	1990	10 (carcinogen)	STEL
Indonesia	1978	2200	TWA
Italy	1978	1000	TWA
Mexico	1983	2200	TWA
Netherlands	1989	110	TWA
Norway	1990	2.2 (carcinogen)	TWA
Poland	1984	100	TWA
Romania	1975	1500[b]	TWA
		2000[b]	Ceiling
Sweden	1990	20 (carcinogen)	TWA
		40	STEL (15-min)
Switzerland	1990	11 (carcinogen)	TWA
Taiwan	1981	2200	TWA
United Kingdom	1991	22	TWA
USA			
ACGIH	1991	22 (suspected human carcinogen; A2)	TWA
OSHA	1989	2200[c]	TWA
USSR	1984	100	MAC
Venezuela	1978	2200	TWA
		2750	Ceiling
Yugoslavia	1971	500	TWA

From Cook (1987); US Occupational Safety and Health Administration (OSHA) (1989); Direktoratet for Arbeidstilsynet (1990); Dutch Expert Committee for Occupational Standards (1990); American Conference of Governmental Industrial Hygienists (ACGIH) (1991); Health and Safety Executive (1991); International Labour Office (1991)

[a]TWA, 8-h time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

[b]Skin notation

[c]The US OSHA has proposed to reduce the permissible exposure limits to 4.4 mg/m^3 for an 8-h TWA, 22 mg/m^3 for a 15-min STEL and 2.2 mg/m^3 for an 8-h TWA 'action level'; for a detailed discussion of this proposal, see US Occupational Safety and Health Administration (1990).

Follow-up of mortality in a cohort of workers who manufactured 1,3-butadiene monomer in Texas (USA) (Downs *et al.*, 1987) was extended through 1985 (Divine, 1990). The cohort comprised men who had been employed for six months or more between the opening of the plant in 1943 and 31 December 1979. Vital status was ascertained through the Social Security Administration or from state health departments. Of 2582 male employees, 1.9% were lost to follow-up and 32.0% were dead, 6% of these with no death certificate. Using US white men as the comparison population, the standardized mortality ratio (SMR) for mortality from all causes was 0.84 (826 deaths; 95% confidence interval [CI], 0.79–0.90) and that for all cancers was 0.80 (163 deaths; 95% CI, 0.69–0.94). The only significantly elevated SMR was for lymphosarcoma and reticulosarcoma (ICD8, 200) (2.29; 9 deaths; 95% CI, 1.04–4.35), thus confirming the earlier report (Downs *et al.*, 1987). Seven of the nine subjects had first been employed before 1946. When analysis was carried out by years of employment, there was no trend in SMR with increasing length of employment for lymphosarcoma or reticulosarcoma, and the only excess was seen for men with fewer than 10 years of employment. On the basis of the department listed on workers' personnel records, exposure to 1,3-butadiene was classified as low (not normally exposed to 1,3-butadiene), routine (exposed to 1,3-butadiene on a daily basis), non-routine (exposed intermittently to 1,3-butadiene, with possible exposure to peak concentrations higher than those with routine exposure) or unknown. Workers ever employed with routine exposure had a significant excess of lympho- and reticulosarcoma (5 deaths; SMR, 5.61; 95% CI, 1.81–13.10); all five deaths were seen in workers who had been employed fewer than 10 years. The rates for cancers of the kidney and large intestine were nonsignificantly increased among men who had worked for more than 10 years. Men who had had non-routine exposure had non-significantly increased risks for leukaemia (ICD8, 204–207) (SMR, 1.85; 6 deaths; 95% CI, 0.68–4.03) and lymphosarcoma and reticulosarcoma (SMR, 1.26; 2 deaths; 95% CI, 0.14–4.54).

Results were available from a study on the mortality of white male workers who had been employed for at least six months in two US styrene–butadiene rubber plants (Meinhardt *et al.*, 1982). A total of 1662 workers employed in plant A between 1943 and 1976 and 1094 workers employed in plant B between 1950 and 1976 were followed-up through 31 March 1976. Nine deaths from cancer of the lymphatic and haematopoietic tissues (ICD7, 200–205) were seen in workers in plant A (SMR, 1.55 [95% CI, 0.71–2.95]); all these deaths occurred among men who had first been employed between January 1943 and December 1945 (SMR, 2.12; [95% CI, 0.97–4.02]), after which the process changed from batch to continuous feed operation. No information was available, however, on the work histories of the subjects. The SMR for leukaemia (ICD7, 204) in plant A among workers employed between 1943 and 1945 was 2.78 (5 deaths [95% CI, 0.65–4.72]); two of the deaths had occurred within three years of first employment. In plant B, the numbers were very small: one death from leukaemia was observed (0.99 expected), which occurred within four years of first employment; the SMR for lymphatic and haematopoietic neoplasms was 0.78 (2 deaths [95% CI, 0.10–2.83]). Time-weighted average exposure to 1,3-butadiene was estimated after 1976 to be about 10 times higher in plant B (mean, 13.5 ppm; SD, 29.9; range, 0.34–174) than in plant A (mean, 1.24 ppm; SD, 1.20; range, 0.11–4.17). Concomitant exposure to styrene had occurred in plants A and B, and to traces of benzene at least in plant A.

Matanoski *et al.* (1990a) investigated mortality patterns from 1943 (synthetic rubber production began in 1942) through 1982 of employees from eight styrene–butadiene rubber plants in Canada and the USA, previously followed up through 1979 by Matanoski and Schwartz (1987). The study included all men who had been employed for at least one year between 1943—or when their plant records were complete—and 1976. Canadian workers were included in the more recent study only if they had worked 10 or more years or had reached age 45 while still employed, since this enabled more complete ascertainment of their vital status through the company's insurance records. Of 12 113 employees, 2441 (20.2%) were deceased, 416 (3.4%) had unknown vital status and 9256 (76.4%) were still living at the end of follow-up. Death certificates were obtained for 97.2% of deceased individuals. On the basis of US death rates for black and white men (since Ontario rates were similar to US rates), the SMRs for the entire cohort were as follows: 0.81 for all causes (2441 deaths; 95% CI, 0.78–0.85); 0.85 for all cancers (518 deaths; 95% CI, 0.78–0.93), 0.61 for lymphosarcoma (ICD8, 200) (seven deaths; 95% CI, 0.25–1.26), 1.20 for Hodgkin's disease (ICD8, 201) (eight deaths; 95% CI, 0.52–2.37), 0.96 for leukaemia (ICD8, 204–207) (22 deaths; 95% CI, 0.60–1.46) and 1.11 for 'other lymphatic' system cancers (ICD8, 202, 203, 208) (17 deaths; 95% CI, 0.64–1.77). The SMR for lymphatic or haematopoietic cancers showed no clear trend of increasing with increasing number of years worked or years since first exposure. When employees were classified according to the job held longest, production workers (presumed by the authors to be those with highest exposures to 1,3-butadiene) had an SMR for deaths from all causes of 0.88 (594 deaths; 95% CI, 0.81–0.95) and a significant excess of other lymphatic cancer (SMR, 2.60; nine deaths; 95% CI, 1.19–4.94). When mortality among production workers was examined by race, the only significant excess was seen for leukaemia in blacks (three deaths; SMR, 6.56; 95% CI, 1.35–19.06). Of 92 deaths among black production workers, six were due to all lymphopoietic cancers (5.07; 1.87–11.07), and three of these were leukaemias (6.56; 1.35–19.06). The rates for haematopoietic cancers among maintenance workers were lower than those of the production workers. Maintenance workers showed increased risk for some digestive cancers, which were not evident in production workers. Workers in the two other job classification categories ('utility' and 'other') showed no significant increase in SMR for any type of cancer. A limitation of this study, pointed out by the authors, was that missing information on 2391 employees meant that they were excluded from the analysis of job department. Since many of these men were active in 1976 and are thus more likely to be alive than dead, the analysis by job is biased toward including more dead workers. The SMRs in this analysis may therefore be higher than those in the total cohort and are thus not directly comparable.

2.2 Case–control studies

In a case–control study nested within a cohort of 6678 US male rubber workers, deaths from cancers at the following sites were compared to those in a sample of the whole cohort: stomach (ICD8, 151) (41 deaths), colorectal (ICD8, 153–154) (63), respiratory tract (ICD8, 160–163) (119), prostate (ICD8, 185) (52), urinary bladder (ICD8, 188) (13), lymphatic and haematopoietic (ICD8, 200–209) (51) and lymphatic leukaemia (ICD8, 204) (14) (McMichael *et al.*, 1976). A 6.2-fold increase in risk for lymphatic and haematopoietic cancers (99.9% CI, 4.1–12.5) and a 3.9-fold increase for lymphatic leukaemia (99.9% CI,

2.6–8.0) were found in association with more than five years' work in manufacturing units producing mainly styrene–butadiene rubber during 1940–60. Of the five other cancer sites investigated, only cancer of the stomach was associated with a significant (two-fold) increase in risk. [The Working Group noted that, although the confidence limits were calculated by a method not used commonly, the results are significant at the 5% level.]

A case–control study nested within the US and Canadian cohort study described above (Matanoski *et al.*, 1990a) involved 59 workers with lymphopoietic cancers, identified using both underlying and contributing causes listed on death certificates. Controls were 193 workers without cancer, matched to the cases for plant, age, sex, date of hire, duration of work and survival up to date of death of the case (Santos-Burgoa, 1988; Matanoski *et al.*, 1990b). Since the exposures to 1,3-butadiene and to styrene were highly correlated, an attempt was made to discern to what extent each exposure contributed to the risk for leukaemia. Four industrial engineers who had no knowledge of the case or control status of the subjects estimated the intensity of exposure in each job, and duration of work was determined from job histories. The sum of the product of intensity and duration for each job resulted in a cumulative ranked exposure index for 1,3-butadiene and styrene separately. When the log of the ranked exposure indexes was dichotomized above and below the mean score for each exposure, 1,3-butadiene alone was associated with a risk for leukaemia (26 deaths) of 7.61 (95% CI, 1.62–35.64), and styrene alone gave a risk of 2.92 (95% CI, 0.83–10.27), each without adjustment for the other chemical. The relative risk for exposure to styrene, adjusted for 1,3-butadiene, was 1.06 (95% CI, 0.23–4.96), while the risk for 1,3-butadiene, adjusted for styrene, was 7.39 (95% CI, 1.32–41.33). The same type of analysis for other lymphatic cancers (18 deaths), including non-Hodgkin's lymphoma (ICD8, 202) and multiple myeloma (ICD8, 203), gave a risk of 0.81 (95% CI, 0.28–2.38) for styrene adjusted for 1,3-butadiene and a risk of 1.68 (95% CI, 0.55–5.15) for 1,3-butadiene adjusted for styrene.

In the population-based case–control study of cancers at multiple sites (excluding leukaemia) carried out in Montréal, Canada (Siemiatycki, 1991), described in detail on p. 95, 4% of the entire study population had been exposed at some time to styrene–butadiene rubber. Elevated odds ratios were seen for cancer of the kidney: 2.0 (90% CI, 1.2–3.4) for 12 cases with 'any' exposure and 2.9 (1.0–8.3) for three cases with 'substantial' exposure. For non-Hodgkin's lymphoma, the odds ratios were 0.9 (0.5–1.7) for seven cases with 'any' exposure and 1.5 (0.4–5.1) for two cases with 'substantial' exposure.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, eight to nine weeks of age, were exposed to 625 or 1250 ppm (1380 or 2760 mg/m^3) 1,3-butadiene (minimum purity, > 98.9%) for 6 h per day on five days per week for 60 weeks (males) or 61 weeks (females). An equal number of animals sham-exposed in chambers served as controls. The study was terminated after 61 weeks because of a high incidence of lethal neoplasms in the exposed animals. The numbers

of survivors were: males—49/50 controls, 11/50 low-dose and 7/50 high-dose; females—46/50 controls, 14/50 low-dose and 30/50 high-dose. Haemangiosarcomas originating in the heart with metastases to various organs were found in: males—0/50 controls, 16/49 ($p < 0.001$) low-dose and 7/49 ($p = 0.006$) high-dose—and females—0/50 controls, 11/48 ($p < 0.001$) low-dose and 18/49 ($p < 0.001$) high-dose (Fisher exact test). [The Working Group noted that the incidence of haemangiosarcomas of the heart in historical controls was 1/2372 in males and 1/2443 in females.] Other types of neoplasm for which the incidences were increased (Fisher exact test) in animals of each sex were malignant lymphomas: males—0/50 controls, 23/50 ($p < 0.001$) low-dose and 29/50 ($p < 0.001$) high-dose; females—1/50 controls, 10/49 ($p = 0.003$) low-dose and 10/49 ($p = 0.003$) high-dose; alveolar bronchiolar adenomas or carcinomas of the lung: males—2/50 controls, 14/49 ($p < 0.001$) low-dose and 15/49 ($p < 0.001$) high-dose; females—3/49 controls, 12/48 ($p = 0.01$) low-dose and 23/49 ($p < 0.001$) high-dose; papillomas or carcinomas of the forestomach: males—0/49 controls, 7/40 ($p = 0.003$) low-dose and 1/44 ($p = 0.473$) high-dose; females—0/49 controls, 5/42 ($p = 0.018$) low-dose and 10/49 ($p < 0.001$) high-dose. Tumours that occurred with statistically significantly increased incidence in females only included hepatocellular adenoma or carcinoma of the liver: 0/50 controls, 2/47 ($p = 0.232$) low-dose and 5/49 ($p = 0.027$) high-dose; acinar-cell carcinoma of the mammary gland: 0/50 controls, 2/49 low-dose and 6/49 ($p = 0.012$) high-dose; and granulosa-cell tumours of the ovary: 0/49 controls, 6/45 ($p = 0.01$) low-dose and 12/48 ($p < 0.001$) high-dose (US National Toxicology Program, 1984; Huff *et al.*, 1985).

Groups of 60 male B6C3F$_1$ and 60 male NIH Swiss mice, four to six weeks of age, were exposed to 0 or 1250 ppm (2760 mg/m^3) 1,3-butadiene (> 99.5% pure) for 6 h per day on five days per week for 52 weeks. A group of 50 male B6C3F$_1$ mice was exposed similarly to 1,3-butadiene for 12 weeks and held until termination of the experiment at 52 weeks. The incidence of thymic lymphomas was 1/60 control B6C3F$_1$ mice, 10/48 B6C3F$_1$ mice exposed for 12 weeks, 34/60 B6C3F$_1$ mice exposed for 52 weeks and 8/57 NIH Swiss mice exposed for 52 weeks. Haemangiosarcomas of the heart were observed in 5/60 B6C3F$_1$ mice and 1/57 NIH Swiss mice (Irons *et al.*, 1989). [The Working Group noted the absence of reporting on NIH Swiss control mice.]

In studies designed to characterize exposure–response relationships further, groups of 70–90 male and 70–90 female B6C3F$_1$ mice, 6.5 weeks of age, were exposed to 0, 6.25, 20, 62.5, 200 or 625 ppm (0.14, 44, 138, 440 or 1380 mg/m^3) 1,3-butadiene (purity, > 99%) for 6 h per day on five days per week for up to two years. Ten animals per group were killed and evaluated after 40 and 65 weeks of exposure. Survival was significantly reduced ($p < 0.05$) in all groups of mice exposed to 1,3-butadiene at 20 ppm or higher; terminal survivors were: males, 35/70 controls, 39/70 at 6.25 ppm, 24/70 at 20 ppm, 22/70 at 62.5 ppm, 3/70 at 200 ppm and 0/90 at 625 ppm; females, 37/70 controls, 33/70 at 6.25 ppm, 24/70 at 20 ppm; 11/70 at 62.5 ppm; 0/70 at 200 ppm and 0/90 at 625 ppm. Tumours for which the rates were significantly increased by exposure to 1,3-butadiene are shown in Table 12 (Melnick *et al.*, 1990).

Groups of 50 male B6C3F$_1$ mice, 6.5 weeks of age, were exposed to 1,3-butadiene (purity, > 99%) for 6 h per day on five days per week at 200 ppm (442 mg/m^3) for 40 weeks, 625 ppm (1380 mg/m^3) for 13 weeks, 312 ppm (690 mg/m^3) for 52 weeks or 625 ppm

Table 12. Tumour incidences (I) and percentage mortality-adjusted tumour rates (R) in mice exposed to 1,3-butadiene for up to two years

Tumour	Sex	Exposure concentration (ppm)											
		0		6.25		20		62.5		200		625	
		I	R	I	R	I	R	I	R	I	R	I	R
Lymphoma	M	4/70	8	3/70	6	8/70	19	11/70	25[a]	9/70	27[a]	69/90	97[a]
	F	10/70	20	14/70	30	18/70	41[a]	10/70	26	19/70	58[a]	43/90	89[a]
Haemangiosarcoma of the heart	M	0/70	0	0/70	0	1/70	2	5/70	13[a]	20/70	57[a]	6/90	53[a]
	F	0/70	0	0/70	0	0/70	0	1/70	3	20/70	64[a]	26/90	84[a]
Alveolar-bronchiolar adenoma and carcinoma[b]	M	22/70	46	23/70	48	20/70	45	33/70	72[a]	42/70	87[a]	12/90	73[a]
	F	4/70	8	15/70	32[a]	19/70	44[a]	27/70	61[a]	32/70	81[a]	25/90	83[a]
Forestomach papilloma and carcinoma	M	1/70	2	0/70	0	1/70	2	5/70	13	12/70	36[a]	13/90	75[a]
	F	2/70	4	2/70	4	3/70	8	4/70	12	7/70	31[a]	28/90	85[a]
Harderian gland adenoma and adenocarcinoma	M	6/70	13	7/70	15	11/70	25	24/70	53[a]	33/70	77[a]	7/90	58[a]
	F	9/70	18	10/70	21	7/70	17	16/70	40[a]	22/70	67[a]	7/90	48
Preputial gland adenoma and carcinoma	M	0/70	0	0/70	0	0/70	0	0/70	0	5/70	17[a]	0/90	0
Hepatocellular adenoma and carcinoma	M	31/70	55	27/70	54	35/70	68	32/70	69	40/70	87[a]	12/90	75
	F	17/70	35	20/70	41	23/70	52[a]	24/70	60[a]	20/70	68[a]	3/90	28
Adenocarcinoma of the mammary gland	F	0/70	0	2/70	4	2/70	5	6/70	16[a]	13/70	47[a]	13/90	66[a]
Benign and malignant granulosa-cell tumour of the ovary	F	1/70	2	0/70	0	0/70	0	9/70	24[a]	11/70	44[a]	6/90	44

From Melnick *et al.* (1990)

[a]Increased compared with chamber controls (0 ppm), $p < 0.05$, based on logistic regression analysis

[b]The Working Group noted that the incidence in control males and females was in the range of that in historical controls (Haseman *et al.*, 1985).

(1380 mg/m^3) for 26 weeks. After the exposures were terminated, the animals were placed in control chambers for up to 104 weeks. A group of 70 males served as chamber controls (0 ppm). Survival was reduced in all treated groups; the numbers of survivors at the end of the study were 35 controls, nine exposed to 200 ppm, five exposed to 625 ppm for 13 weeks, one exposed to 312 ppm and none exposed to 625 ppm for 26 weeks. Tumours for which the rates were significantly increased by exposure to 1,3-butadiene are shown in Table 13 (Melnick *et al.*, 1990).

3.1.2 *Rat*

Groups of 100 male and 100 female Sprague–Dawley rats, five weeks of age, were exposed to 0, 1000 or 8000 ppm (2200 or 17 600 mg/m^3) 1,3-butadiene (minimal purity, 99.2%) for 6 h per day on five days per week for 111 weeks (males) or 105 weeks (females). Survival was reduced in low- and high-dose females and in high-dose males; the numbers of survivors were: males—45 control, 50 low-dose and 32 high-dose; females—46 control, 32 low-dose and 24 high-dose. Tumours that occurred at significantly increased incidence in males were exocrine adenomas and carcinomas of the pancreas (3 control, 1 low-dose, 11 ($p < 0.05$) high-dose) and Leydig-cell tumours of the testis (0 control, 3 low-dose, 8 ($p < 0.01$) high-dose). Those that occurred at significantly increased incidence (Fisher exact test) in females were follicular-cell adenomas and carcinomas of the thyroid gland (0 control, 4 low-dose, 11 ($p < 0.001$) high-dose) and benign and malignant mammary gland tumours (50 control, 79 low-dose and 81 high-dose, with a significant, dose-related trend ($p < 0.001$); most of the latter were fibroadenomas: 40 control, 75 ($p < 0.001$) low-dose, 67 ($p < 0.01$) high-dose. Tumours that occurred only with positive trends (Cochran–Armitage trend test) in females were sarcomas of the uterus ($p < 0.05$; 1 control, 4 low-dose, 5 high-dose) and carcinomas of the Zymbal gland ($p < 0.01$; 0 control, 0 low-dose, 4 high-dose) (Owen *et al.*, 1987; US Occupational Safety and Health Administration, 1990). [The Working Group noted that differences in tumour incidence between groups were not analysed using statistical methods that took into account differences in mortality between control and treated groups.]

3.2 Carcinogenicity of metabolites

Mouse: D,L-1,2:3,4-Diepoxybutane (IARC, 1976), an intermediate of 1,3-butadiene metabolism, induced 10/30 papillomas and 6/30 squamous-cell carcinomas of the skin when applied at 3 mg three times per week for life to the skin of female Swiss mice (Van Duuren *et al.*, 1965). 1,2-Epoxy-3-butene (vinyloxirane), another intermediate in 1,3-butadiene metabolism, induced 4/30 skin tumours when applied at 100 mg three times per week to the skin of male Swiss mice (Van Duuren *et al.*, 1963). Subcutaneous injection of D,L-1,2:3,4-diepoxybutane at 0.1 and 1.1 mg/animal in tricaprylin once per week for one year induced local fibrosarcomas in 5/50 and 5/30 female Swiss mice; no tumour was observed in three solvent-treated control groups. Administration of D,L-1,2:3,4-diepoxybutane at 1 mg/animal in tricaprylin once per week for one year induced local fibrosarcomas in 9/50 Sprague–Dawley rats, compared with none in controls (Van Duuren *et al.*, 1966).

Table 13. Tumour incidences (I) and percentage mortality-adjusted tumour rates (R) in male mice exposed to 1,3-butadiene in stop-exposure studies (After exposures were terminated, animals were placed in control chambers until the end of the study at 104 weeks.)

Tumour	Exposure									
	0		200 ppm, 40 wk		625 ppm, 13 wk		312 ppm, 52 wk		625 ppm, 26 wk	
	I	R	I	R	I	R	I	R	I	R
Lymphoma	4/70	8	12/50	35[a]	24/50	61[a]	15/50	55[a]	37/50	90[a]
Haemangiosarcoma of the heart	0/70	0	15/50	47[a]	7/50	31[a]	33/50	87[a]	13/50	76[a]
Alveolar–bronchiolar adenoma and carcinoma	22/70	46	35/50	88[a]	27/50	87[a]	32/50	88[a]	18/50	89[a]
Forestomach squamous-cell papilloma and carcinoma	1/70	2	6/50	20[a]	8/50	33[a]	13/50	52[a]	11/50	63[a]
Harderian gland adenoma and adenocarcinoma	6/70	13	27/50	72[a]	23/50	82[a]	28/50	86[a]	11/50	70[a]
Preputial gland carcinoma	0/70	0	1/50	3	5/50	21[a]	4/50	21[a]	3/50	31[a]
Renal tubular adenoma	0/70	0	5/50	16[a]	1/50	5	3/50	15[a]	1/50	11

From Melnick *et al.* (1990)

[a]Increased compared with chamber controls (0 ppm), $p < 0.05$, based on logistic regression analysis

3.3 Activated oncogenes

Tumours from the study of Melnick *et al.* (1990) were evaluated in independent studies for the presence of oncogenes. Activated K-*ras* oncogenes were detected in 6/9 lung adenocarcinomas, 3/12 hepatocellular carcinomas and 2/11 lymphomas obtained from $B6C3F_1$ mice exposed to 1,3-butadiene. A specific codon 13 mutation (guanine to cytosine transversion) was found in most of the activated K-*ras* genes (Goodrow *et al.*, 1990). Activated K-*ras* genes have not been found in spontaneously occurring liver tumours or lymphomas from $B6C3F_1$ mice (Reynolds *et al.*, 1987; Goodrow *et al.*, 1990) and were observed in only 1/10 spontaneous lung tumours in this strain of mice (Goodrow *et al.*, 1990).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

1,3-Butadiene was reported to be metabolized to 1,2-epoxy-3-butene by a single human postmitochondrial liver preparation; no metabolism was observed in a single lung sample (Schmidt & Loeser, 1985). [The Working Group was unable to determine whether the lung and the liver samples were from the same individual.] Incubations of 1,3-butadiene with human liver microsomes from four subjects produced the chiral antipodes 1,2-epoxy-3-butene at ratios of 52–56% *R*- to 44–48% *S*-epoxybutene (Wistuba *et al.*, 1989).

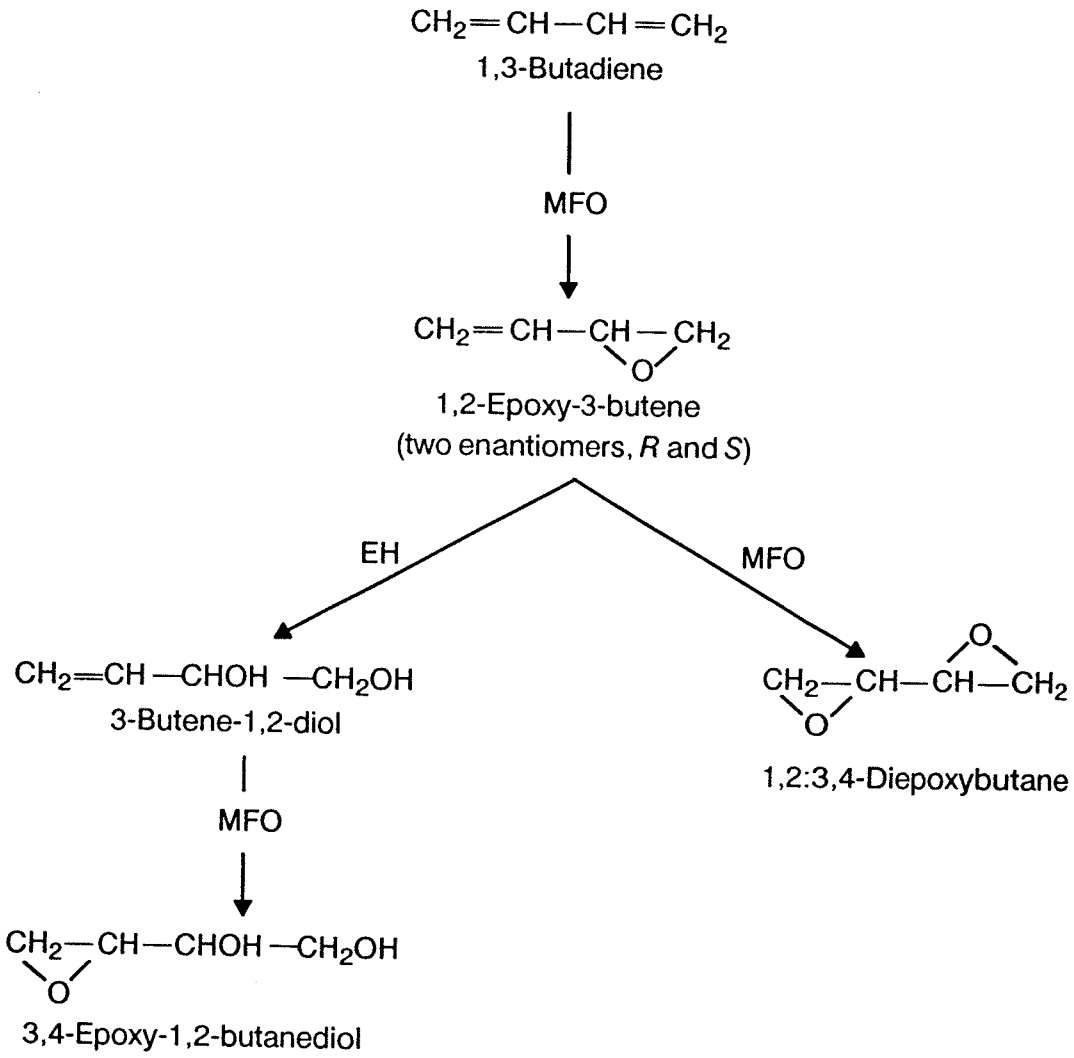
1,2-Epoxy-3-butene is further transformed by epoxide hydrolase and glutathione *S*-transferase, as measured by disappearance of the epoxide by human liver microsomes and cytosol (Kreuzer *et al.*, 1991).

4.1.2 *Experimental systems*

Male Sprague-Dawley rats were exposed in closed inhalation chambers to various initial concentrations of 1,3-butadiene to study the pharmacokinetic behaviour of the compound. Analysis of the resulting concentration decline curves of 1,3-butadiene in the gas phase revealed that its metabolism was saturable. At less than 800–1000 ppm [1800–2200 mg/m^3], 1,3-butadiene was metabolized according to first-order kinetics; at higher exposure concentrations (> 1500 ppm [> 3300 mg/m^3], saturation range), a maximal metabolic rate of 220 μmol/h per kg bw was observed; this was enhanced by pretreatment with Aroclor 1254 (Bolt *et al.*, 1984). In similar experiments in male $B6C3F_1$ mice, saturation of 1,3-butadiene metabolism was observed at higher exposure concentrations (> 2000 ppm [> 4400 mg/m^3]) at a maximal metabolic rate of 400 μmol/h per kg bw. Pharmacokinetic analysis of the data suggested that the species-related difference in the effect of 1,3-butadiene was due to more rapid uptake of the compound from the gas phase by mice (Kreiling *et al.*, 1986a).

1,3-Butadiene is converted to 1,2-epoxy-3-butene by mixed-function oxidases in rat liver microsomes *in vitro*. Pretreatment of rats with phenobarbital increases enzyme activity (Malvoisin *et al.*, 1979; Bolt *et al.*, 1983). 1,2-Epoxy-3-butene is further metabolized to 1,2:3,4-diepoxybutane and 3-butene-1,2-diol; the latter product is metabolized by mixed-function oxidases to 3,4-epoxy-1,2-butanediol (Malvoisin & Roberfroid, 1982) (Fig. 1).

Fig. 1. Possible pathways for metabolism of 1,3-butadiene by rat liver microsomes



From Malvoisin and Roberfroid (1982); MFO, mixed-function oxidases; EH, epoxide hydrolase

Cytochrome P-450-mediated formation of 1,2-epoxy-3-butene from 1,3-butadiene also occurs in the presence of mouse liver microsomes, and crotonaldehyde has been shown to be a further metabolite (Elfarra *et al.*, 1991).

1,2-Epoxy-3-butene is present in the expired air of rats and mice exposed to 1,3-butadiene (Bolt *et al.*, 1983; Kreiling *et al.*, 1987). When male Sprague-Dawley rats were exposed in closed exposure chambers to concentrations of 1,3-butadiene higher than 2000 ppm [4400 mg/m^3], which result in the maximum possible metabolic rate, about 4 ppm [8.8 mg/m^3] 1,2-epoxy-3-butene were measured in the gas phase under steady-state conditions. Kinetic analysis revealed that only 29% of the predicted value of 1,3-butadiene metabolite under these conditions was available systemically as 1,2-epoxy-3-butene, which was considered to be related to a first-pass metabolism of the 1,2-epoxy-3-butene originating in the

liver (Filser & Bolt, 1984). The exhalation of 1,2-epoxy-3-butene by two male Sprague–Dawley rats and six male B6C3F$_1$ mice exposed in a closed system to 2000–4000 ppm [4400–8800 mg/m^3] 1,3-butadiene for 15 h was compared (Kreiling *et al.*, 1987). After about 2 h, rats had built up a constant concentration of 1,2-epoxy-3-butene at about 4 ppm [8 mg/m^3], with no sign of toxicity. 1,2-Epoxy-3-butene concentrations in the experiment with mice increased to about 10 ppm [22 mg/m^3] after 10 h; and after 12 h, animals showed signs of acute toxicity.

Studies on the disposition of inhaled (nose only) ^{14}C-labelled 1,3-butadiene in Sprague–Dawley rats and B6C3F$_1$ mice confirmed that mice metabolize 1,3-butadiene to a greater extent than rats. Radiolabelled metabolites present in blood were separated according to their volatility by vacuum line–cryogenic distillation (Dahl *et al.*, 1984). Blood samples taken from mice during exposure to 13 000 mg/m^3 (7100 ppm) (*sic*) for 6 h contained two to five times more radiolabelled 1,2-epoxy-3-butene than did the blood of rats (Bond *et al.*, 1987). Three male cynomolgus monkeys (*Macaca fascicularis*) were exposed by nose only to 10, 310 or 7760 ppm [22, 680 or 17 150 mg/m^3] ^{14}C-butadiene for 2 h. For exposures equivalent to those in mice and rats, the concentrations of total 1,3-butadiene metabolites in blood were 5–50 times lower in monkeys than in mice. The ranking of species was thus mice > rats > monkeys (Dahl *et al.*, 1991).

Metabolic species differences were also investigated *in vitro* using liver preparations from rats (Sprague–Dawley, Wistar), mice (NMRI and B6C3F$_1$), rhesus monkeys and humans (Schmidt & Loeser, 1985). The ranking of species for 1,2-epoxy-3-butene formation was: female mice > male mice > rats (humans) > monkeys. [The Working Group noted that the quantitative data on the human rate were derived from a single sample of liver.]

Repeated pretreatment of male Sprague–Dawley rats and male B6C3F$_1$ mice (inhalation by nose only) with 1,3-butadiene at 13 600 mg/m^3 (7600 ppm) for 6 h per day for five days had no effect on the ability of liver microsomes isolated from these animals to metabolize 1,3-butadiene. The metabolism of 1,3-butadiene *in vitro* was depressed significantly, however, in microsomes from lungs of pre-exposed rats and mice compared to unexposed controls (Bond *et al.*, 1988). Formation of 1,2-epoxy-3-butene was also observed after incubation of 1,3-butadiene with mouse and rat lung tissue but not after incubation with lung tissue from monkeys or humans (Schmidt & Loeser, 1985). [The Working Group noted that the quantitative data on the human rate were derived from a single sample of lung.]

The inhalation pharmacokinetics of the metabolite 1,2-epoxy-3-butene were studied in male Sprague–Dawley rats and male B6C3F$_1$ mice in closed chambers. Whereas in rats no indication of saturation kinetics could be obtained up to exposure concentrations of 5000 ppm [11 000 mg/m^3], saturation occurred in mice exposed to 500 ppm [1100 mg/m^3] or more (Kreiling *et al.*, 1987; Laib *et al.*, 1990).

4.2 Toxic effects

4.2.1 *Humans*

The toxic effects of combined exposures to 1,3-butadiene and other agents (e.g., styrene, chloroprene, hydrogen sulfide, acrylonitrile) have been reviewed (Parsons & Wilkins, 1976). Concentrations of several thousand parts per million of 1,3-butadiene irritate the skin, eyes, nose and throat (Carpenter *et al.*, 1944; Wilson *et al.*, 1948; Parsons & Wilkins, 1976).

Several studies have been reported on the effects of occupational exposure to 1,3-butadiene, mainly from the ex-USSR and Bulgaria. Few are substantiated by details on the atmospheric concentration or duration of exposure, and control data are generally not provided. The effects reported include haematological disorders (Batkina, 1966; Volkova & Bagdinov, 1969), kidney malfunction, laryngotracheitis, irritation of the upper respiratory tract, conjunctivitis, gastritis, various skin disorders, a variety of neuraesthenic symptoms (Parsons & Wilkins, 1976) and hypertension and neurological disorders (Spasovski *et al.*, 1986).

Checkoway and Williams (1982) reported minimal changes in haematological indices among eight workers exposed to about 20 ppm (44.2 mg/m^3) 1,3-butadiene, 14 ppm (59.5 mg/m^3) styrene and 0.03 ppm (0.1 mg/m^3) benzene, as compared to those among 145 workers exposed to less than 2 ppm (4.4 mg/m^3) 1,3-butadiene, 2 ppm (8.5 mg/m^3) styrene and 0.1 ppm (0.3 mg/m^3) benzene. Changes included a slight decrease in haemoglobin level and a slight increase in red-cell mean corpuscular volume. [The Working Group considered that these changes cannot be interpreted as an effect of 1,3-butadiene on the bone marrow, particularly as alcohol intake was not evaluated.]

4.2.2 *Experimental systems*

LC_{50} values for 1,3-butadiene were reported to be 270 000 mg/m^3 [122 170 ppm] in mice exposed for 2 h and 285 000 mg/m^3 [129 000 ppm] in rats exposed for 4 h; after 1 h of exposure, rats were in a state of deep narcosis (Shugaev, 1969). Oral LD_{50} values of 5.5 g/kg bw for rats and 3.2 g/kg bw for mice have been reported (US National Toxicology Program, 1984).

In female rats exposed to 1–30 mg/m^3 (0.45-14 ppm) 1,3-butadiene for 81 days, morphological changes were observed in liver, kidney, spleen, nasopharynx and heart (G.K. Ripp reported in Crouch *et al.*, 1979). In groups of 24 rats exposed to 600–6700 ppm [1300–14 800 mg/m^3] 1,3-butadiene for 7.5 h per day on six days per week for eight months, no adverse effect was noted, except for a slight retardation in growth with the highest concentration (Carpenter *et al.*, 1944). Rats exposed to 2200–17 600 mg/m^3 (1000–8000 ppm) 1,3-butadiene for 6 h per day on five days per week for three months showed no treatment-related effect other than increased salivation in females (Crouch *et al.*, 1979).

Groups of 110 male and 110 female CD Sprague–Dawley rats were exposed to atmospheres containing 0, 1000 or 8000 ppm [0, 2200 or 17 600 mg/m^3] 1,3-butadiene for 6 h per day on five days per week. The study was terminated when it was predicted that survival would drop to 20–25% (105 weeks for females, 111 weeks for males). Ten animals of each sex from each group were killed at 52 weeks. Treatment was associated with changes in clinical condition and lowering of body weight gain during the first 12 weeks, then nonsignificant changes, reduced survival and increases in certain organ weights and in the incidences of uncommon tumour types (for details, see p. 257). Increased mortality in high-dose males was accompanied by an increase in the severity of nephropathy (Owen *et al.*, 1987; Owen & Glaister, 1990).

B6C3F$_1$ mice exposed to 0, 625 or 1250 ppm [1380 or 2760 mg/m^3] 1,3-butadiene for 6 h per day on five days per week for 60–61 weeks had increased prevalences of atrophy of the ovary and testis, atrophy and metaplasia of the nasal epithelium, hyperplasia of the

respiratory and forestomach epithelium and liver necrosis (see also pp. 254–255) (US National Toxicology Program, 1984).

Haematological changes in male B6C3F$_1$ mice exposed to 62.5, 200 or 625 ppm [138, 440 or 1375 mg/m^3] 1,3-butadiene for 6 h per day on five days per week for 40 weeks included decreased red blood cell count, haemoglobin concentration and packed red cell volume and increased mean corpuscular volume. Similar changes occurred in female mice exposed to 625 ppm [1375 mg/m^3] 1,3-butadiene (for details, see pp. 255–257) (Melnick *et al.*, 1990).

The role of murine retroviruses on the induction of leukaemias and lymphomas following inhalation of 1,3-butadiene was evaluated in a series of studies reviewed by Irons (1990). Exposure of groups of male B6C3F$_1$ mice, which have the intact ecotropic murine leukaemia virus, to 1250 ppm [2750 mg/m^3] 1,3-butadiene for 6 h per day on 6 days per week for 6–24 weeks resulted in a decrease in the number of circulating erythrocytes, in total haemoglobin and in haematocrit and an increase in mean corpuscular volume. Leukopenia, due primarily to a decrease in the number of segmented neutrophils, and an increase in the number of circulating micronuclei were observed (Irons *et al.*, 1986a). Persistent immunological defects were not detectable after this treatment (Thurmond *et al.*, 1986). Exposure of male NIH Swiss mice, which do not possess intact endogenous ecotropic murine leukaemia virus, produced similar results (Irons *et al.*, 1986b).

A further study was conducted to examine the expression and behaviour of endogenous retroviruses in these strains during the preleukaemic phase of 1,3-butadiene exposure. Chronic exposure of B6C3F$_1$ mice to 1,3-butadiene (1250 ppm [2740 mg/m^3]) for 6 h per day on five days per week for 3–21 weeks increased markedly the quantity of ecotropic retrovirus recoverable from the bone marrow, thymus and spleen. Expression of other endogenous retroviruses (xenotropic, MCF-ERV) was not enhanced. No virus of any type was found in similarly treated NIH Swiss mice (Irons *et al.*, 1987a).

Enhanced susceptibility to 1,3-butadiene-induced leukaemogenesis as a result of the ability to express the retrovirus was suggested by the finding that exposure to 1250 ppm 1,3-butadiene for one year resulted in a 57% incidence of thymic lymphoma in B6C3F$_1$ mice (with expression of the virus) and a 14% incidence in NIH Swiss (without viral expression) (Irons *et al.*, 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Fertility was reported to be unimpaired in mating studies in rats, guinea-pigs and rabbits exposed to 600, 2300 or 6700 ppm [1300, 5000 or 14 800 mg/m^3] 1,3-butadiene by inhalation for 7.5 h per day on six days per week for eight months (Carpenter *et al.*, 1944). [The Working Group noted the incomplete reporting of this study].

Pregnant Sprague–Dawley rats (24–28 per group) and Swiss (CD-1) mice (18–22 per group) were exposed to atmospheric concentrations of 0, 40, 200 or 1000 ppm [0, 88, 440 or 2200 mg/m^3] 1,3-butadiene for 6 h per day on days 6–15 of gestation and killed on gestation day 18 (mice) or 20 (rats). Subsequently, the uterine contents were evaluated; individual fetal

body weights were recorded; and external, visceral and skeletal examinations were performed. In rats, maternal toxicity was observed in the 1000-ppm group in the form of reduced extragestational weight gain and, during the first week of treatment, decreased body weight gain. Under these conditions, there was no evidence of developmental toxicity. Maternal toxicity was observed in mice given 200 and 1000 ppm 1,3-butadiene; 40 ppm and higher concentrations of 1,3-butadiene caused significant exposure-related reductions in the mean body weights of male fetuses. Mean body weights of female fetuses were reduced at the 200 and 1000 ppm exposure levels. No increased incidence of malformations was observed in either species. The frequency of fetal variations (supernumerary ribs, reduced sternebral ossification) was significantly increased in mice exposed to 200 and 1000 ppm. In a study of sperm-head morphology, groups of 20 male B6C3F$_1$ mice were exposed to atmospheric concentrations of 0, 200, 1000 or 5000 ppm [0, 440, 2200 or 11 000 mg/m^3] 1,3-butadiene for 6 h per day for five consecutive days. Small, concentration-related increases in the frequency of abnormal sperm morphology were seen five weeks after exposure (the only time of examination) (Hackett *et al.*, 1987; Morrissey *et al.*, 1990). [The Working Group noted that sequential examinations were not conducted after exposure to determine the effect of 1,3-butadiene on all stages of gamete development.]

4.4 Genetic and related effects

4.4.1 *Humans*

In an abstract of a study of workers engaged in the manufacture of 1,3-butadiene in Finland, cytogenetic analysis revealed no increase in the frequency of sister chromatid exchange, chromosomal aberrations or micronucleus formation in peripheral blood. The ambient air concentrations of 1,3-butadiene were generally < 1 ppm [< 2.2 mg/m^3], and the workers used protective clothing and respirators (Sorsa *et al.*, 1991).

4.4.2 *Experimental systems* (see also Tables 14–16 and Appendices 1 and 2)

The genetic toxicology of 1,3-butadiene has been reviewed (Rosenthal, 1985; de Meester, 1988; Brown, 1990). Additional information on 1,3-butadiene is included in a review by the Dutch Expert Committee for Occupational Standards (1990). The genetic and related effects of two main metabolites of 1,3-butadiene (1,2-epoxy-3-butene and 1,2:3,4-diepoxybutane) were reviewed by Ehrenberg and Hussain (1981) and de Meester (1988).

(*a*) *1,3-Butadiene*

1,3-Butadiene was mutagenic to *Salmonella typhimurium* TA1530 in the presence of liver S9 from phenobarbital- or Aroclor 1254-pretreated rats but was not mutagenic in the presence of uninduced rat liver S9 (de Meester *et al.*, 1980). It was also mutagenic to TA1535 in the presence of Arcolor 1254-induced rat S9, uninduced rat S9 and uninduced mouse S9 but was not mutagenic in the presence of uninduced human S9 (Arce *et al.*, 1990).

1,3-Butadiene gave negative results in tests for somatic mutation and recombination in *Drosophila melanogaster*.

1,3-Butadiene was not active in the L5178Y mouse lymphoma forward mutation assay. A weak positive response was reported for sister chromatid exchange induction in Chinese hamster ovary (CHO) cells.

In one study, sister chromatid exchange was induced weakly in human whole blood lymphocyte cultures after treatment with 1,3-butadiene in the presence and absence of Aroclor-1254-induced rat liver S9. No sister chromatid exchange was induced in another study in which S9 from a variety of sources was used, including mouse and human.

When B6C3F$_1$ mice and Wistar rats were exposed to ^{14}C-1,3-butadiene in a closed exposure system, radiolabel was associated with hepatic nucleoproteins and DNA from both species. The association of radiolabel with nucleoproteins was about two times stronger in mice than in rats, but the association with DNA was similar in the two species (Kreiling *et al.*, 1986b). Acid hydrolysis of DNA isolated from the livers of mice exposed to ^{14}C-1,3-butadiene revealed the presence of two identifiable alkylation products: 7-*N*-(1-hydroxy-3-buten-2-yl)guanine and 7-*N*-(2,3,4-trihydroxybutyl)guanine. These were not found in similarly exposed rats (Jelitto *et al.*, 1989).

After a 7-h exposure of mice and rats to 1,3-butadiene at 250, 500 or 1000 ppm (550, 1100 or 2200 mg/mg^3), alkaline elution profiles from the livers and lungs showed the occurrence of protein–DNA and DNA–DNA cross-links with all doses of 1,3-butadiene in mice but not in rats. This finding was interpreted as a biological effect in mice of the bifunctional alkylating metabolite, 1,2:3,4-diepoxybutane (Jelitto *et al.*, 1989). In another study, there was no evidence of the formation of cross-links in DNA isolated from the livers of 1,3-butadiene-treated mice or rats (Ristau *et al.*, 1990).

No unscheduled DNA synthesis was evident in the livers of either Sprague-Dawley rats or B6C3F$_1$ mice after exposure to 10 000 ppm [22 000 mg/m^3] 1,3-butadiene.

1,3-Butadiene increased the frequency of sister chromatid exchange in bone-marrow cells of mice, but not of rats, exposed *in vivo*. Chromosomal aberrations and micronuclei, but not aneuploidy, were induced in mice by 1,3-butadiene, but, in a single study, micronuclei were not induced in rats.

In a study of dominant lethal mutations, male Swiss CD-1 mice were exposed to 0, 70, 200, 1000 or 5000 ppm [155, 440, 2200 or 11 050 mg/m^3] 1,3-butadiene for 6 h per day for five days and then mated weekly for eight weeks. After one week, a significant increase was observed in the number of dead implants in females mated with males exposed to 1000 ppm (smaller increases were seen at 200 and 5000 ppm). Two weeks after exposure, the proportion of dead implants was increased in the 200- and 1000-ppm groups [details not given]. Sperm-head abnormalities were induced in exposed males (Morrissey *et al.*, 1990).

(*b*) *1,2-Epoxy-3-butene*

1,2-Epoxy-3-butene reacts with DNA to give two main alkylated products, 7-(2-hydroxy-3-buten-1-yl)guanine and 7-(1-hydroxy-3-buten-2-yl)guanine (Citti *et al.*, 1984).

1,2-Epoxy-3-butene was mutagenic to bacteria in the absence of an exogenous metabolic system. It did not induce unscheduled DNA synthesis in rat or mouse hepatocytes but induced sister chromatid exchange in CHO cells and in cultured human lymphocytes. In a single study, it induced sister chromatid exchange and chromosomal aberrations in mouse bone marrow *in vivo*.

(*c*) *1,2:3,4-Diepoxybutane*

1,2:3,4-Diepoxybutane induced interstrand cross-links in DNA by reaction at the *N*7 position of guanine (Lawley & Brookes, 1967).

Table 14. Genetic and related effects of 1,3-butadiene

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	1300.0000	Arce *et al.* (1990)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	-	+	86.0000	de Meester *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	(+)	650.0000	Arce *et al.* (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	1300.0000	Arce *et al.* (1990)
SAS, *Salmonella typhimurium* TA97, reverse mutation	-	-	1300.0000	Arce *et al.* (1990)
DMM, *Drosophila melanogaster*, wing spot mutation	-	0	10000.0000	Victorin *et al.* (1990)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	-	-	650.0000	McGregor *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	-	(+)	1.3500	Sasiadek *et al.* (1991a)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	-	2160.0000	Arce *et al.* (1990)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	+	108.0000	Sasiadek *et al.* (1991b)
DVA, DNA-DNA cross-links, Sprague-Dawley rats *in vivo*	-	0	310.0000 inhal. 8 h/d, 7 d	Ristau *et al.* (1990)
DVA, DNA-DNA cross-links, B6C3F1 mice *in vivo*	-	0	3100.0000 inhal. 8 h/d, 7 d	Ristau *et al.* (1990)
BVD, DNA alkylation, male Wistar rat liver cells *in vivo*	-	0	550.0000	Jelitto *et al.* (1989)
BVD, DNA alkylation, male B6C3F1 mouse liver cells *in vivo*	+	0	680.0000	Jelitto *et al.* (1989)
DVA, DNA-DNA cross-links, Sprague-Dawley rat liver/lung *in vivo*	-	0	550.0000	Jelitto *et al.* (1989)
DVA, DNA-DNA cross-links, B6C3F1 mouse liver/lung *in vivo*	+	0	680.0000	Jelitto *et al.* (1989)
UPR, Unscheduled DNA synthesis, Sprague-Dawley rats *in vivo*	-	0	4000.0000 inhal.[c]	Arce *et al.* (1990)
UPR, Unscheduled DNA synthesis, Sprague-Dawley rats *in vivo*	-	0	4000.0000 inhal.[d]	Arce *et al.* (1990)
UVM, Unscheduled DNA synthesis, B6C3F1 mice *in vivo*	-	0	11600.0000 inhal.[c]	Arce *et al.* (1990)
UVM, Unscheduled DNA synthesis, B6C3F1 mice *in vivo*	-	0	11600.0000 inhal.[d]	Arce *et al.* (1990)
SVA, Sister chromatid exchange, male B6C3F1 mouse bone marrow *in vivo*	+	0	116.0000 inhal. 6 h/d[e]	Cunningham *et al.* (1986)
SVA, Sister chromatid exchange, male Sprague-Dawley rat bone marrow *in vivo*	-	0	4000.0000 inhal. 6 h/d[e]	Cunningham *et al.* (1986)
SVA, Sister chromatid exchange, male B6C3F1 mouse bone marrow *in vivo*	+	0	7.0000 inhal. 6 h/d, 10 d	Tice *et al.* (1987)
MVM, Micronucleus test, male B6C3F1 mouse bone marrow *in vivo*	+	0	116.0000 6 h/d[e]	Cunningham *et al.* (1986)
MVM, Micronucleus test, male B6C3F1 mouse peripheral blood *in vivo*	+	0	70.0000 inhal. 6 h/d, 10 d	Tice *et al.* (1987)
MVM, Micronucleus test, male B6C3F1 mouse peripheral blood *in vivo*	+	0	7.0000[f]	Jauhar *et al.* (1988)
MVM, Micronucleus test, NMRI mouse bone marrow *in vivo*	+	0	35.0000 inhal. 23 h	Victorin *et al.* (1990)

Table 14 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVR, Micronucleus test, male Sprague-Dawley rat bone marrow *in vivo*	-	0	4000.0000[e]	Cunningham *et al.* (1986)
CBA, Chromosomal aberrations, male B6C3F1 mouse bone marrow *in vivo*	+	0	1500.0000[g] inhal. 6 h[g]	Irons *et al.* (1987b)
CBA, Chromosomal aberrations, male NIH Swiss mouse bone marrow *in vivo*	+	0	1500.0000[g] inhal. 6 h[g]	Irons *et al.* (1987b)
CBA, Chromosomal aberrations, male B6C3F1 mouse bone-marrow *in vivo*	+	0	700.0000	Tice *et al.* (1987)
*Aneuploidy, male NIH Swiss mouse bone marrow *in vivo*	-	0	1500.0000 inhal. 6 h[g]	Irons *et al.* (1987b)
*Aneuploidy, male B6C3F1 mouse bone marrow *in vivo*	-	0	1500.0000 inhal. 6 h[g]	Irons *et al.* (1987b)
DLM, Dominant lethal test, Swiss CD-1 mouse	+	0	233.0000	Morrissey *et al.* (1990)
SPM, Sperm abnormality test, mouse	+	0	1165.0000	Morrissey *et al.* (1990)

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] 6 h treatment on day 1, 3 h on day 2, liver sampled 2 h later
[d] 6 h treatment on days 1 and 2, liver sampled 18 h later
[e] For two days, killed 24 h after the second exposure
[f] Five days/week for 13 weeks
[g] Killed at 24, 48, 72 and 96 h after cessation of exposure
*Data not displayed on profiles

Table 15. Genetic and related effects of 1,2-epoxy-3-butene

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	350.0000	de Meester *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	26.0000	Gervasi *et al.* (1985)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	+	0	175.0000	de Meester *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	1750.0000	de Meester *et al.* (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	8750.0000	de Meester *et al.* (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	0	8750.0000	de Meester *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	8750.0000	de Meester *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	105.0000	Gervasi *et al.* (1985)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	0	0.0000	Hemminki *et al.* (1980)
KPF, *Klebsiella pneumoniae*, fluctuation test	+	0	70.0000	Voogd *et al.* (1981)
URP, Unscheduled DNA synthesis, rat hepatocytes *in vitro*	-	0	1000.0000	Arce *et al.* (1990)
UIA, Unscheduled DNA synthesis, mouse hepatocytes *in vitro*	-	0	1000.0000	Arce *et al.* (1990)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	0.0700	Sasiadek *et al.* (1991a)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	1.7500	Sasiadek *et al.* (1991b)
SVA, Sister chromatid exchange, male C57Bl/6 mouse bone marrow *in vivo*	+	0	25.0000	Sharief *et al.* (1986)
CBA, Chromosomal aberrations, male C57Bl/6 mouse bone marrow *in vivo*	+	0	25.0000	Sharief *et al.* (1986)

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

Table 16. Genetic and related effects of 1,2:3,4-diepoxybutane

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage induction, *Bacillus megaterium*	+	0	0.0000	Lwoff (1953)
PRB, Prophage induction, *Pseudomonas pyocyanea*	+	0	0.0000	Lwoff (1953)
PRB, Prophage induction, *Escherichia coli* K-12	+	0	7.5000	Heinemann & Howard (1964)
ECB, *Escherichia coli* H540, DNA repair induction	+	0	2500.0000	Thielmann & Gersbach (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	50.0000	Dunkel *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	20.0000	Gervasi *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	25.0000	McCann *et al.* (1975)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5.0000	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5.0000	Dunkel *et al.* (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	50.0000	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	60.0000	Gervasi *et al.* (1985)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	(+)	(+)	167.0000	Dunkel *et al.* (1984)
ECR, *Escherichia coli* B, reverse mutation	+	0	1720.0000	Glover (1956)
ECR, *Escherichia coli* B/r, reverse mutation	+	0	860.0000	Glover (1956)
KPF, *Klebsiella pneumoniae*, fluctuation test	+	0	4.0000	Voogd *et al.* (1981)
**Saccharomyces cerevisiae* D7, gene conversion	+	+	130.0000	Sandhu *et al.* (1984)
SCH, *Saccharomyces cerevisiae* D4, mitotic gene conversion	+	0	430.0000	Zimmermann (1971)
SCH, *Saccharomyces cerevisiae* D81, mitotic crossing-over	+	0	2000.0000	Zimmermann & Vig (1975)
SCH, *Saccharomyces cerevisiae* D3, mitotic recombination	+	+	400.0000	Simmon (1979)
**Saccharomyces cerevisiae* D7, mitotic crossing-over	+	+	130.0000	Sandhu *et al.* (1984)
**Saccharomyces cerevisiae*, reverse mutation	+	0	4000.0000	Polakowska & Putrament (1979)

Table 16 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCF, *Saccharomyces cerevisiae*, cytoplasmic petite mutation	-	0	4000.0000	Polakowska & Putrament (1979)
**Saccharomyces cerevisiae*, mitochondrial mutation	+	0	4000.0000	Polakowska & Putrament (1979)
**Saccharomyces cerevisiae* D7, reverse mutation	+	+	130.0000	Sandhu *et al.* (1984)
NCR, *Neurospora crassa*, reverse mutation	+	0	4300.0000	Kölmark & Westergaard (1953)
NCR, *Neurospora crassa*, reverse mutation	+	0	1720.0000	Pope *et al.* (1984)
DMM, *Drosophila melanogaster*, recombination and mutation, spot test	+	0	1000.0000	Graf *et al.* (1983)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	100.0000	Bird & Fahmy (1953)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	175.0000	Sankaranarayanan *et al.* (1983)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	1000.0000	Fahmy & Fahmy (1970)
DMC, *Drosophila melanogaster*, chromosomal deletion	+	0	1000.0000	Fahmy & Fahmy (1970)
DIA, DNA-DNA cross-links, B6C3F1 mouse liver DNA *in vitro*	+	0	4.0000	Ristau *et al.* (1990)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	0	0.3000	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	0	0.0250	Perry & Evans (1975)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	+	0.0100	Sasiadek *et al.* (1991a)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.1250	Wiencke *et al.* (1982)
SHL, Sister chromatid exchange, human lymphocytes[c] *in vitro*	-	0	0.0100	Porfirio *et al.* (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.0100	Porfirio *et al.* (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	+	0.0400	Sasiadek *et al.* (1991b)
CHF, Chromosomal aberrations, human skin fibroblasts[d] *in vitro*	+	0	0.0100	Auerbach & Wolman (1978)
CHF, Chromosomal aberrations, human skin fibroblasts *in vitro*	-	0	0.0100	Auerbach & Wolman (1978)
CHL, Chromosomal aberrations, human lymphoblastoid cell lines[e]	+	0	0.0100	Cohen *et al.* (1982)
CHL, Chromosomal aberrations, human lymphocytes[a] *in vitro*	+	0	0.1000	Marx *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	0	0.1000	Marx *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	-	0	0.0100	Porfirio *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes[c] *in vitro*	+	0	0.0100	Porfirio *et al.* (1983)

Table 16 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIH, Chromosomal aberrations, human bone-marrow cells[c] *in vitro*	(+)	0	0.1000	Marx *et al.* (1983)
CIH, Chromosomal aberrations, normal human bone-marrow cells *in vitro*	(+)	0	0.1000	Marx *et al.* (1983)
HMM, Host-mediated assay, mutation, *S. typhimurium* TA1530 in mice	+	0	444.0000	Simmon (1979)?
HMM, Host-mediated assay, mitotic recombination, *S. cerevisiae* D3 in mice	-	0	56.0000	Simmon *et al.* (1979)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+	0	1.0000	Conner *et al.* (1983)
SVA, Sister chromatid exchange, mouse alveolar macrophages *in vivo*	+	0	1.0000	Conner *et al.* (1983)
SVA, Sister chromatid exchange, mouse regenerating liver cells *in vivo*	+	0	1.0000	Conner *et al.* (1983)
SVA, Sister chromatid exchange, NMRI mouse bone-marrow cells *in vivo*	+	0	22.0000[f]	Walk *et al.* (1987)
SVA, Sister chromatid exchange, NMRI mouse bone-marrow cells *in vivo*	+	0	29.0000	Walk *et al.* (1987)
SVA, Sister chromatid exchange, Chinese hamster bone-marrow cells *in vivo*	+	0	34.0000[g]	Walk *et al.* (1987)
SVA, Sister chromatid exchange, Chinese hamster bone-marrow cells *in vivo*	+	0	32.0000	Walk *et al.* (1987)
CBA, Chromosomal aberrations, NMRI mouse bone marrow *in vivo*	+	0	22.0000[f]	Walk *et al.* (1987)
CBA, Chromosomal aberrations, NMRI mouse bone marrow *in vivo*	+	0	29.0000	Walk *et al.* (1987)
CBA, Chromosomal aberrations, Chinese hamster bone marrow *in vivo*	+	0	34.0000[g]	Walk *et al.* (1987)
CBA, Chromosomal aberrations, Chinese hamster bone marrow *in vivo*	+	0	32.0000	Walk *et al.* (1987)

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, mg/ml; in-vivo tests, mg/kg bw
[c] Fanconi's anaemia (homozygotes and heterozygotes)
[d] Fanconi's anaemia (heterozygotes)
[e] Fanconi's anaemia (homozygotes and heterozygotes), ataxia telangiectasia, xeroderma pigmentosum, normal
[f] Calculated to give 22 (F) and 23 (M) mg/kg
[g] Calculated to give 34 (F) and 42 (M) mg/kg
*Not displayed on profile

Addition of an exogenous metabolic system was not required for genotoxic activity of this compound *in vitro*. In bacteria, it induced prophage, DNA repair and mutation. It induced mutation, gene conversion and mitotic recombination in yeast and mutation in fungi. In *Drosophila melanogaster*, it induced mutation and small chromosomal deletions.

1,2:3,4-Diepoxybutane induced DNA cross-links in mouse hepatocytes, dose-related increases in the frequency of sister chromatid exchange in cultured CHO cells and, in a single study, mutations in cultured mouse lymphoma L5178Y cells at the *tk* locus. It induced a dose-related increase in the frequency of sister chromatid exchange in cultured human lymphocytes from normal donors and from patients with a variety of solid tumours, but not from Fanconi's anaemia homozygotes or heterozygotes. It induced chromosomal aberrations in early-passage skin fibroblasts from Fanconi's anaemia heterozygotes, in primary lymphocytes from Fanconi's anaemia homozygotes and heterozygotes and in long-established lymphoblastoid cell lines from normal donors, Fanconi's anaemia homozygotes and heterozygotes and patients with xeroderma pigmentosum and ataxia telangiectasia. Bone-marrow cultures from Fanconi's anaemia patients and control individuals also showed increased frequencies of chromosomal aberrations after exposure to 1,2:3,4-diepoxybutane. Chromosomal aberrations were not induced in normal lymphocytes in two studies, but small increases were observed in another one.

1,2:3,4-Diepoxybutane induced mutations in *S. typhimurium* TA1530 in the mouse host-mediated assay, but it did not induce mitotic recombination in *Saccharomyces cerevisiae* D3.

Significant, dose-related increases in the frequency of sister chromatid exchange were observed in bone marrow and in alveolar macrophages from both intact and partially hepatectomized mice and in the regenerating liver of hepatectomized mice. 1,2:3,4-Diepoxybutane induced chromosomal aberrations and sister chromatid exchange in bone-marrow cells of male and female NMRI mice and Chinese hamsters exposed by inhalation or intraperitoneal injection.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Butadiene has been produced on a large scale since the 1930s. It is used to manufacture a wide range of polymers and copolymers, including styrene–butadiene rubber, polybutadiene, nitrile rubber, acrylonitrile–butadiene–styrene resins and styrene–butadiene latexes. It is also an intermediate in the production of various other chemicals.

Occupational exposure to 1,3-butadiene occurs in the production of monomeric 1,3-butadiene, of butadiene-based polymers and butadiene-derived products. The mean concentrations reported have usually been < 10 ppm (< 22 mg/m^3), although that level may be exceeded during some short-term activities. 1,3-Butadiene is not usually found at detectable levels in the manufacture of finished rubber and plastic products. Because gasoline contains 1,3-butadiene, loading of gasoline and other gasoline-related operations entail exposure to 1,3-butadiene.

1,3-Butadiene has also been detected in automobile exhaust and, at levels of < 0.02 ppm (< 0.04 mg/m^3), in urban air.

5.2 Human carcinogenicity data

One US cohort study of workers who manufactured 1,3-butadiene monomer showed a significant excess risk for lymphosarcoma and reticulosarcoma. Although there was no overall excess risk for leukaemia, there was a suggested increase in risk in a subgroup of workers with 'non-routine' exposure to 1,3-butadiene.

In a US study of workers employed in two styrene–butadiene rubber plants, there was a suggested increase of risk for leukaemia with exposure to 1,3-butadiene in one of the plants. No increase in risk was seen for cancers of the lymphatic and haematopoietic system other than leukaemia.

In a study of styrene–butadiene rubber workers in eight plants in the USA and Canada, there was no overall increased risk for leukaemia; however, a subgroup of production workers had a significantly increased risk. There was no apparent increased risk for 'other lymphatic system' cancers, although a significant risk was seen for production workers.

In a case–control study nested within this cohort of styrene–butadiene rubber workers, a large excess of leukaemia was found which was associated with exposure to 1,3-butadiene and not to styrene.

In a case–control study in the rubber industry, a large excess of lymphatic and haematopoietic cancers, including lymphatic leukaemia, was seen among workers employed in styrene-butadiene rubber production.

One study, therefore, specifically related increased risks for leukaemia to exposure to 1,3-butadiene and not to styrene. In other studies, the increased risks for leukaemia and other lymphatic cancers occurred among workers whose exposure had been in the manufacture of 1,3-butadiene or styrene–butadiene rubber.

5.3 Animal carcinogenicity data

1,3-Butadiene was tested for carcinogenicity by inhalation exposure in four experiments in mice and one in rats. Tumours were induced at all exposure concentrations studied, ranging from 6.25 to 8000 ppm (13.8–17 600 mg/m^3). 1,3-Butadiene produced tumours at multiple organ sites in animals of each sex of both species, including tumours of the haematopoietic system and an uncommon neoplasm of the heart in male and female mice. Neoplasms at multiple organ sites were induced in mice after only 13 weeks of exposure. 1,3-Butadiene induced dose-related increases in the incidence of tumours at many sites.

Two metabolites, 1,2-epoxy-3-butene and 1,2:3,4-diepoxybutane, were carcinogenic to mice and rats when administered by skin application or subcutaneous injection.

Activated K-*ras* oncogenes have been detected in lymphomas and in liver and lung tumours induced in mice by 1,3-butadiene.

5.4 Other relevant data

In rats, mice and monkeys, 1,3-butadiene is metabolized to an epoxide, 1,2-epoxy-3-butene, for which quantitative differences in metabolic rates (mice > rat > monkey) have been observed. Because 1,2-epoxy-3-butene is exhaled by rats and mice exposed to 1,3-butadiene, the epoxide must undergo systemic circulation. Two experiments with human liver tissue demonstrated conversion of 1,3-butadiene to 1,2-epoxy-3-butene, suggesting that humans are not qualitatively different from animals in terms of epoxide formation.

Developmental toxicity, in the form of reduced fetal weight and skeletal variations, has been observed in mice, but not rats, exposed by inhalation to 1,3-butadiene.

Genotoxic effects were generally observed in mice but not in rats *in vivo*. This apparent species difference was highlighted in a comparison of liver DNA adducts from the two species. 1,3-Butadiene induced dominant lethal effects, sperm-head abnormalities, chromosomal aberrations, micronucleus formation and sister chromatid exchange *in vivo* in mice; it did not induce micronuclei or sister chromatid exchange in rats. Unscheduled DNA synthesis was not induced in either rats or mice after exposure of 1,3-butadiene. The compound did not induce mutation in the mouse lymphoma forward mutation assay and was not genotoxic to *Drosophila melanogaster*. It induced mutation in bacteria in the presence of an exogenous metabolic system.

1,2-Epoxy-3-butene, one of the main metabolites of 1,3-butadiene, induced sister chromatid exchange and chromosomal aberrations in mice *in vivo* and sister chromatid exchange in cultured human lymphocytes and rodent cells. It did not induce unscheduled DNA synthesis in isolated rat or mouse hepatocytes. 1,2-Epoxy-3-butene induced point mutation in bacteria in the absence of exogenous metabolic systems. It also reacted with purified DNA.

1,2:3,4-Diepoxybutane, another metabolite of 1,3-butadiene, induced chromosomal aberrations and sister chromatid exchange in mice and Chinese hamsters exposed *in vivo*. It induced chromosomal aberrations and sister chromatid exchange in cultured human cells and both sister chromatid exchange and mutation in cultured mammalian cells. 1,2:3,4-Diepoxybutane induced chromosomal deletions and gene mutation in *Drosophila*. It was mutagenic to bacteria in a mouse host-mediated assay as well as *in vitro*. It induced bacterial prophage and DNA repair. In one study, it induced DNA–DNA cross-links in mouse liver DNA *in vitro*; it induced DNA interstrand cross-links *in vitro*.

5.5 Evaluation[1]

There is *limited evidence* for the carcinogenicity in humans of 1,3-butadiene.

There is *sufficient evidence* for the carcinogenicity in experimental animals of 1,3-butadiene.

Studies *in vitro* suggest that the metabolism of 1,3-butadiene is qualitatively similar in humans and experimental animals. 1,3-Butadiene is metabolized in mammals to epoxy metabolites which interact with DNA. Base-substitution mutations are induced in bacteria. Similar mutations in the K-*ras* oncogene have been reported in tumours induced in mice by 1,3-butadiene.

Overall evaluation

1,3-Butadiene is *probably carcinogenic to humans (Group 2A)*.

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

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