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Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

113. 1,3-Butadiene

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ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

A Center for Research on Occupational Health

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Helgi Gudbergsson	Municipal Institute of Public Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute of Occupational Health, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

An editorial work is performed by the Group's Scientific Secretary, Brita Beije, at the National Institute of Occupational Health in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on industrial enzymes was made by prof. Marja Sorsa and Dr. Kimmo Peltonen, Department of Industrial Hygiene and Toxicology, Institute of Occupational Health, Topeliuksenkatu 41 a A, FIN-00250 Helsinki, Finland. The final version was accepted by the Nordic Expert Group June 13-15, 1994 as its document.

Brita Beije
Scientific Secretary

Per Lundberg
Chairman

Contents

1. Introduction

1,3-Butadiene (BD) is an important industrial chemical with an estimated annual world production exceeding 5 million tonnes. BD is used principally as a monomer for producing a wide range of polymers and copolymers, the largest single use being styrene-butadiene rubber for tyres and tyre products.

BD also occurs as an environmental contaminant. It has been estimated that most butadiene emissions derive from mobile sources; although leaks and waste emissions from manufacturing facilities may be locally important. All burning of organic material produces emissions containing minor amounts of BD. Low exposure to BD is thus a common characteristic of the whole human population.

Butadiene is a high priority compound for risk assessment - not only because of its wide exposure - but also considering its known toxicological properties. BD is a multiple organ carcinogen in mice and rats, mouse being by far the more sensitive species. Still, it is not clear whether butadiene, at the low human exposure levels occuring, can be shown carcinogenic, even if epidemiological studies have revealed strong associations between occupational exposure to butadiene and increased risk of haematopoietic cancers.

This report summarizes the main toxicological and exposure data on this important compound to be used as scientific background for standard setting in the Nordic countries.

2. Substance Identification

Common name:	1,3-butadiene
CAS name:	1,3-butadiene
IUPAC name:	1,3-butadiene
Synonyms:	bivinyl, butadiene, buta-1,3-diene, trans-butadiene, divinyl, erythrene, vinylethylene
CAS No:	106-99-0
Chemical group:	unsaturated hydrocarbons
Formula:	C4H6 CH_2=CH-CH=CH_2
Molecular mass:	54.09

3. Physical and Chemical Properties

BD is a colourless, non corrosive gas with a gasoline-like odour. It is a highly reactive chemical which can dimerize to 4-vinylcyclohexene. BD polymerises readily, expecially in the presence of oxygen. BD in air can form acrolein and peroxides (99). Other chemico-physical data are summarized below.

Boiling point:	-4.4°C (115)
Melting point:	-108.9°C (115)
Density:	0.6211 g/ml at 20°C/liquefied (113)
Threshold odour concentrations	1.0 - 3.5 mg/m^3 (6)
Volatility:	vapour pressure, 2.477 hPa Hg at 20 °C, relative vapour pressure, 1.87 (113)
Solubility:	735 mg/l H_2O at 20°C, soluble in ethanol, diethyl ether and organic solvents (19, 99, 113)
Flash point:	-76°C (99)
Spectroscopy:	UV, NMR, MS have been reported (53)
Conversion factors:	1 mg/m^3 = 0.445 ppm 1 ppm = 2.249 mg/m^3 (At 20°C ; 1.013 hPA)

4. Occurrence, Production and Use

4.1. Occurrence of BD

BD is available commercially as a liquefied gas under pressure in several grades of purity, including a special purity, a research grade, a technical-commercial grade and a rubber grade purity. Analytical, polymer, rubber and liquefied grades range in minimal purity from 99.0 to 99.5 %, with the following typical impurities: 1,2- butadiene, acetaldehyde, acetylenes, propadiene, 4-vinylcyclohexene, peroxides, sulfur and C5 hydrocarbons (5, 67). Polymerization

of BD is inhibited by addition of hydroquinone, di-n-butylamine, tert-butylcatecol, aliphatic mercaptans or o-dihydroxybenzene (19).

BD is not known to occur as a natural product, but it is found in organic burnings, house fires etc. (53).

In 1989, total emission of BD to the air in the USA was estimated at approximately 2512 tonnes from 158 locations: total land releases were estimated at 6.7 tonnes (53). Data on annual emissions of BD from US facilities producing BD, polybutadiene, neoprene/chloroprene and styrene-butadiene rubber and from miscellaneous facilities where BD was used were collected in 1984 by the US Environmental Protection Agency (Table 1).

Few data are available on levels of BD in ambient air. Reported concentrations in urban air generally range from less than 2 up to 22 µg/m^3 (27, 88). In the USA, combined levels of BD and 2-butene were 0.01-0.05 mg/m^3 in 1978 in Tulsa, OK (10), and 0-0.042 mg/m^3 1973-74 in Houston TX (102). Levels of BD were 0-0.028 mg/m^3 in various cities in Texas. Urban air in Los Angeles and Riverside, CA contained levels as high as 0.02 mg/m^3 and BD was found in 32 % of 24h ambient air samples taken in 19 US cities in 1987-88, at the mean concentration of 1.4 µg/m^3 (53).

BD has been detected in drinking water in the USA (61). Total releases to ambient water in 1989 were estimated to be 65 tonnes (53).

Levels of 0.2 µg/kg BD were found in retail soft margarine, plastic tubs containing the margarine contained 5-310 µg/kg (105).

The US EPA (1990) estimated that BD is emitted in automobile exhaust at about 6 mg/km and comprises about 0.35% of total hydrocarbon in exhaust emissions. BD has been detected in smoke generated during house fires at up to 33.7 mg/m^3 (15 ppm) (13). In a quantitative survey of carcinogenic outdoor air pollutants, US EPA estimated BD to be the most important single pollutant, after products of incomplete combustion (PIC), as inducer of cancer nationwide (111).

Side stream and mainstream cigarette smoke contain BD at about 200-360 µg and 75 µg/cigarette, respectively. The levels in smoky indoor environments contain typically 2-20 µg/m^3 of BD (18, 75).

4. 2. Production of BD

BD was first produced in 1886 by the pyrolysis of petroleum hydrocarbons and its commercial production started in the 1930s (58). BD has been produced commercially by three processes, catalytic dehydrogenation of n-butane and n-butene (the Houndry process), oxidative dehydrogenation of n-butene (the Oxo-D or O-X-D process) and recovery from the C4 co-product stream from the steam cracking process used to manufacture ethylene. All three processes involve the production of BD from a C4 hydrocarbon stream; solvent extraction and extractive distillation are used in all three to further concentrate the BD. 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

Table 1. 1,3-Butadiene emissions from US manufacturing facilities in 1984-86[1].

Activity of facility	No. of facilities	Total emissions (tonnes/year)		Episodic emissions (1986)		
		Average (kg/min)	Range (kg/min)	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

[1]As cited in IARC (53); 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

BD (65). The ethylene coproduct process accounts for approximately 95% of US and 85% of worldwide production (86).

The production of BD is thus a two-stage process: 1) production of a C4 co-product during ethylene manufacture and 2) recovery of BD from the coproduct. The first stage consists of cracking a hydrocarbon such as naphta to produce ethylene as the primary product and a co-product stream composed of C4 hydrocarbons. The amount of BD 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 BD is produced. BD content of the co-product C4 stream is 20-70% and C4 feed streams are usually blended with a feed stream containing 40-50% BD for processing. In the extraction plants solvents like dimethylformamide, acetonitrile, furfural, dimethylacetamide and methylpyrrolidone are used to alter the volatility of components in the fractional distillation selectively and to produce a high purity BD monomer (65).

Worldwide BD 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 exceed its supply, so approximately 227 thousand tonnes of BD monomer were imported in 1987 (86). A more detailed account of the production of BD in several countries in 1980-90 is presented in Table 2.

4.3. Use of BD

BD is used principally as a monomer in the manufacturing of a wide range of polymers and copolymers. Polymerization of styrene and BD yields styrene-BD rubber, the largest single use of BD. Almost 80% of this styrene-BD polymer is used for car and bus tyres. Nitrile rubber is produced by copolymerizing BD and acrylonitrile. This polymer is used in gaskets, hoses, seals, latexes, adhesives and footwears. Acrylonitrile-butadiene-styrene resins are graft terpolymers 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 carpet backing (53). BD is used as a chemical intermediate in the production of a number of important chemicals. Neoprene is made by chlorinating BD and treating the formed chloroprene with sodium hydroxide. About 70% of the produced neoprene is used for automotive and industrial rubber goods. Adiponitrile is produced by chlorinating BD 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 BD with ethylene, is used as a monomer for ethylene-propylene polymer. Sulfolane, produced by reacting sulfur dioxide and BD and dehydrogenating the product, is a valuable solvent for extracting. 1,5,9-Cyclodecatriene is produced by trimerizating BD and is used for the production of various nylon fibers and resins. Some other nonpolymer applications include manufacture of agricultural fungicides and some dyes (53).

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

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
Finland	~17	~17	~17	~17	~17	~17	~17	~17	~17	~17	~17

[1]As cited in IARC (53); NA = not available; [a]Figures prior to 1990 are for Western Germany only; [b]Rubber grade

In 1990 BD in the USA composed of 30% styrene-butadiene rubber, 20% polybutadiene rubber, 15% adiponitrile/hexamethylenediamine, 10% styrene-butadiene latex, 5% neoprene rubber, 5% acrylonitrile-butadiene-styrene resin, 4% epoxides, 3% nitrile rubber, and 8% other polymers (8).

5. Occupational Exposure

It has been estimated that 52000 workers were potentially exposed to BD in the USA during years 1981-1983. Potential exposure to BD can occur in the petroleum refining and related operations, production of purified BD monomer, production of various BD based rubber and plastics polymers and other derivatives of the rubber and plastics products manufacturing industry (see Table 3). Although gasoline itself contains no or very low amounts of BD, some exposure to BD has been reported in association of different occupations involving handling of gasoline (52).

5.1. Butadiene monomer production

In extraction facilities for the production of pure BD in Germany, the mean exposure level was about 11.3 mg/m^3 with peak levels up to 67.5 mg/m^3 (32).

Additional European monitoring data is available from a Finnish plant producing purified BD. In this plant the BD levels were generally lower than 22.5 mg/m^3 in stationary samples taken from different sites of the plant. In personal samples of 16 process workers, the concentration of BD ranged from lower than 0.2 mg/m^3 to 1 005 mg/m^3. The highest concentrations were measured during sample collection. The workers used protective clothing and respirators during this operation (106). In an other study at the same plant , ambient air concentrations were generally below 22.5 mg/m^3 with peak concentrations up to 674.7 mg/m^3 in a few cases (3).

Table 3. 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[1].

Job area	No. of facilities	Mean (mg/m^3)[a]	Range (mg/m^3)
Production	7	0.53	0.02 - 4.4
Maintenance	6	0.24	0.04 - 0.82
Distribution	1	64.1	
Laboratory	4	0.40	0.16 - 0.88

[1]As cited in IARC (53); [a]Weighted by number of exposed workers

Table 4. Full-shift, time-weighted average exposure levels in personal breathingzone samples at four US 1,3-butadiene monomer production facilities, 1985[1].

Job category	No of samples	Exposure level (mg/m^3) Arithmetic mean	Geometric mean	Range
Process technician	10	1.0	0.2	< 0.04 - 4.1
Control room				
Process technician	28	4.9	1.4	< 0.2 - 77.1
Process area				
Loading area				
Railcar	9	32.4	2.2	0.3 - 273.1
Tank truck	3	5.9	2.3	0.2 - 12.1
Tank farm	5	0.9	0.4	< 0.1 - 3.4
Laboratory technician	29	2.3	0.9	0.1 - 14.0
Cylinder voiding	3	277.4	16.5	0.9 - 825.5

[1]From Krishnan *et al* (65,66)

Detailed hygienic surveys were conducted in 1985 by the US National Institute for Occupational Safety and Health in four of US facilities where BD was produced by solvent extraction of C4 fractions originating as ethylene co-product streams (66). Levels of BD to which workers in various job categories were exposed are summarized in Table 4. Jobs that require workers to handle or transport containers, such as voiding sample cylinders or loading and unloading tank truks or rail cars present the greatest potential exposure. Geometric means of fullshift exposure levels for other job categories were below 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 22.5 mg/m^3 . Full shift area samples indicated that ambient concentrations of BD was highest in the railcar terminals and in the tank storage farm 4.1 and 4.7 mg/m^3, respectively.

In a recent study researchers from the US National Institute for Occupational Safety and Health conducted an extent-of-exposure study of BD monomer, polymer and end-user industries to assess occupational exposure to BD and to evaluate control technologies. Walk-through surveys were conducted in 11 monomer plants and in-depth industrial hygiene surveys were conducted at four monomer plants. Airborne concentrations were measured for various job categories by personal sampling. The data of full-shift and short term air sample measurements are summarized in Tables 5, 6 and 7 (38).

Table 5. 1,3-Butadiene concentrations in personal full-shift air samples in the monomer industry[1].

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Laboratory technician	29	0.07 - 14.2	2.4	3.6	0.9	9.8
bomb voiding	3	0.9 - 841.1	283.4	483.5	16.7	75.6
Process technician						
control	10	< 0.04 - 4.2	1.0	1.6	0.2	17.8
loading	12	0.2 - 278.9	26.1	79.4	2.2	17.6
production	29	< 0.1 - 78.5	4.9	14.3	1.3	10.0
storage	5	< 0.1 - 3.4	1.0	1.4	0.5	9.6
Total	88	< 0.04 - 841.1	15.7	94.0	1.1	14.6

[1]From Fajen (38)

Table 6. 1,3-Butadiene concentrations in personal short-time air samples in the monomer industry[1].

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Bomb sampling	8	< 1.6 - 330.6	48.4	114.0	7.7	15.4
Bomb voiding	6	< 0.2 - 242.9	51.5	96.3	5.1	41.2
Maintenance	7	0.1 - 37.8	11.6	15.4	2.2	26.1
Process	2	< 0.7 - 0.8	0.6	0.3	0.6	3.7
Total	23	< 0.1 - 330.6	34.0	82.1	3.8	23.0

[1]From Fajen (38)

Table 7. 1,3-Butadiene concentrations in area full-shift air samples in the monomer industry.

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Production	25	< 0.1 - 4.8	1.3	1.3	0.8	7.0
Railcar, loading	20	0.2 - 144.6	23.6	41.4	4.2	19.3
Semi-trailer, loading	4	0.2 - 4.3	1.3	2.0	0.5	9.0
Laboratory	18	0.1 - 13.2	2.3	4.3	0.5	13.1
Tank farm	5	0.3 - 53.5	17.5	23.4	4.8	18.8
Subtotal	72	0.1 - 144.6	8.9	24.5	1.2	15.1
Perimeter	25	< 0.04 - 1.1	0.2	0.3	0.1	6.7
Total	97	< 0.04 - 144.6	6.6	21.3	0.6	17.9

[1]From Fajen (38)

Table 8. Full-shift time-weighted average exposure levels in personal breathing-zone samples at five US plants producing 1,3-butadiene-based polymers and derivatives.[1]

Job category	No of samples	Exposure level (mg/m^3) Arithmetic mean	Geometric mean	Range
Process technician				
Unloading area	2	32.3	10.4	1.7 - 63.0
Tank farm	31	4.6	0.6	< 0.01 - 52.4
Purification	18	17.2	13.5	3.0 - 53.3
Polymerization or reaction	81	0.9	0.1	< 0.01 - 25.0
Solutions and coagulation	33	0.1	0.1	< 0.01 - 0.4
Crumbing and drying	35	0.1	0.1	< 0.01 - 0.3
Packaging	79	0.1	0.1	< 0.01 - 0.3
Warehouse	20	0.04	0.02	< 0.01 - 0.2
Control Room	6	0.1	0.04	< 0.03 - 0.2
Laboratory technician	54	5.0	0.5	< 0.01 - 82.7
Maintenance technician	72	3.0	0.3	< 0.01 - 95.5
Utilities	6	0.3	0.1	< 0.01 - 0.7

[1]From IARC (53)

Table 9. 1,3-Butadiene concentrations in personal full-shift air samples in the polymer industry[1].

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Laboratory technician	49	< 0.01 - 85.2	6.9	15.5	0.7	27.2
Tank farm operator	23	0.02 - 54.0	4.4	11.3	0.6	21.6
Front end (reaction)	108	<0.01 - 55.6	4.0	9.0	0.3	27.2
Maintenance technician	42	0.03 - 96.5	4.1	15.4	0.3	16.7
Back end (finishing)	79	< 0.01 - 16.0	0.8	2.4	0.1	16.0
Other	137	< 0.01 - 0.4	0.1	0.1	0.1	6.8
Total	438	< 0.01 - 96.5	2.6	9.0	0.2	20.8

[1]From Fajen (38)

Table 10. 1,3-Butadiene concentrations in personal short-term air samples in the polymer industry[1].

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Quality control sampling	10	< 0.2 - 629.7	109.5	194.3	21.1	26.5
Maintenance	4	0.2 - 32.4	10.1	15.2	2.4	22.4
Total	14	0.2 - 629.7	81.2	168.5	11.3	28.8

[1]From Fajen (38)

5.2. Polymer production and derivatives

Concentrations at the workplace of German facilities for the manufacture of BD polymer varied greatly, depending on the type and conditions of the process of polymerization and/or preparation. Results from 465 mean shift values and 691 background measurements showed that most exposure levels were between 10 and 40.5 mg/m^3 (32). Industrial hygiene surveys were conducted in 1986 in five of 17 US facilities where BD was used to produce styrene-butadiene rubber, nitrile-butadiene rubber, polybutadiene rubber, neoprene and adiponitrile (53). Levels of BD exposures are summarized in Table 8. Process workers in unloading, the tank farm, purification, polymerization and reaction, lab persons and maintenance workers were exposed to highest levels. Short term sampling showed that activities such as sampling a barge and laboratory work were associated with peak exposures exceeding 22.5 mg/m^3. Full-shift area sampling indicated that geometric mean ambient concentrations of BD were less than 1.1 mg/m^3 and usually less than 0.2 mg/m^3 in all locations at the five plants.

In a recent study, Fajen et al (38) conducted a survey in 17 polymer and two end user plants. During the five in-depth surveys of butadiene polymer facilities, 452 personal samples and 132 area air samples were collected. Tables 9 and 10 provide a breakdown by job category or work activity of the results of full shift and short term personal monitoring, respectively. Fullshift exposures ranged from undetected to a high of 96.7 mg/m^3, whereas the short term exposures ranged from undetected to a high of 629.7 mg/m^3 (38). The highest full-shift personal exposure was 96.7 mg/m^3 for a maintenance technician working on a butadiene compressor. The highest short term exposure of 629.7 mg/m^3 was found for a process technician sampling a barge for BD.

Table 11. 1,3-Butadiene concentrations in area full-shift air samples in the polymer industry[1].

Job category	No. of samples	Butadiene concentration (mg/m^3) Range	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD
Barge	1	0.1 - 0.1	1.1	-	1.1	-
Tank farm	8	0.2 - 3.9	1.5	1.5	0.9	7.5
Laboratory	3	0.1 - 20.3	6.8	11.6	0.4	61.8
Front end (reaction)	50	< 0.01 - 6.3	0.6	1.1	0.2	12.1
Back end (finishing)	19	< 0.01 - 0.1	0.02	0.02	0.01	4.9
Subtotal	81	< 0.01 - 20.3	0.8	2.4	0.1	16.8
Perimeter	51	< 0.01 - 0.4	0.1	0.1	0.03	7.6
Total	132	< 0.01 - 20.3	0.5	1.9	0.1	14.8

[1]From Fajen (38)

Table 11 provides a breakdown by work environment of the results of full shift area monitoring. The BD concentrations in the work areas ranged from undetected to 20.2 mg/m^3. The highest concentration detected was in a quality control laboratory. In the 51 samples taken at the locations near the plant perimeter, an arithmetic mean of 0.07 mg/m^3 and a geometric mean of 0.02 mg/m^3 were calculated (38).

In a recent study Fajen et al (38) conducted a survey in 17 polymer and two end user plants. During the five in-depth surveys of butadiene polymer facilities, 452 personal samples and 132 area air samples were collected. Tables 9 and 10 provide a breakdown by job category or work activity of the results of full shift and short term personal monitoring, respectively. Fullshift exposures ranged from undetected to a high of 96.7 mg/m^3, whereas the short term exposures ranged from undetected to a high of 629.7 mg/m^3 (38). The highest full-shift personal exposure was 96.7 mg/m^3 for a maintenance technician working on a butadiene

5.3. End user industry

Mean 8h time-weighted average concentrations of BD measured in two US styrene-butadiene rubber manufacturing plants at the late 1970s ranged from 0.2 to 130 mg/m^3; however most of the measurements showed air levels below 5 mg/m^3 (53).

A recent study conducted in two different end user plants showed no exposure to BD. The plant used styrene-butadiene, polybutadiene and acrylonitrile-butadiene-rubber. A total of 124 personal samples were collected over the three shifts with 34 in the hose plant and 90 in the tyre factory. The concentrations of BD were below the limit of detection (0.01 mg/m^3 for 25 l sample) in all samples (38).

6. Sampling and Analysis of Substance at Work Place

6.1. Indoor measurements

BD has been measured with various analytical methods from the workroom air, but the collection of the air sample into activated sorbent, desorption of the sample into an organic solvent and subsequent analysis with gas chromatography equipped with flame ionization detector predominates (14, 36, 44, 46, 47, 48, 89).

A short descriptions of the selected methods and recommendations by three authorities are described. All of them share common features with only slight modifications. The institutes are The US National Institute for Occupational Safety and Health (NIOSH), Finnish Institute of Occupational Health (FIOH) and Health and Safety Executive from UK (UK HSE).

NIOSH 1024 method: The air sample is obtained by passing a known volume of air through a set of tandem coconut charcoal tubes, which adsorb BD and remove it from the air stream. The collected BD is then removed from the adsorption tube by extraction with methylene chloride . Injection of the methylene chloride solution into a GC equipped with a flame ionization detector (FID) separates BD from any other interfering compounds that may be present. The choice of chromatography column for this determination is not crucial, as long as it cleanly separates BD from other compounds. The estimated detection of this method is 0.02 µg/ml, with an applicable range of 1-480 µg per sample . The precission of this method appears to change as a function of the concentration being measured, due to the desorption efficiences changing as a function of the sample concentration. With increasing concentration, the preparation of the standard becomes more difficult. In NIOSH method 1024, quantitation of BD is accomplished by comparing the integrated area of the sample's signal to that of the corresponding standard. The preparation and injection of a gaseous BD standard is a difficult procedure, it must be performed carefully or erroneous results may occur. Sample storage appears to dramatically affect the results of the measurement. Samples stored at -4 °C displayed an average recovery of between 93% and 98% over 21 day period, while samples stored at room temperature ranged from 61 to 95 %. Literature methods for the determination of BD in personal air samples overcome some of these problems (89).

UK HSE method: The UK HSE recommended method involves sampling air using a low flow personal sapling pump (10-50 ml/min) onto a Perking Elmer ATD 50 sorbent tube packed with 900 mg of Tenax having a molecular size of 13. The tube is thermally desorbed onto a cold trap held at -30 °C. The trapped components are then re-injected by ballistic heating onto a 50 m PLOT fused silica capillary column held isothermally at 130 °C. BD is completely eluted and separated from all other C4 isomers. The method is suitable for the measurements of airborne BD in the range 0.2 to 100 mg/m^3 for samples of 5 l of air (47, 48).

FIOH method: A method for the monitoring of BD in air has been developed at the Finnish Institute of Occupational Health. Two different methods for sample collection are described, where one is based on passive diffusion into a commercial dosimeter and the other is based on active sample collection on to an activated charcoal tube. Both type of samples are desorbed into acetonitrile and analysed by gas chromatography with FID detection. BD is completely separated from other low molecular compounds if a 50 m PLOT fused silica capillary column is used. The detection limit is 800 ng/m^3 and the recovery around 90 % (0.6 l of air). Two hours sampling time for active sampling is recommended, but eight hours sampling time can be applied to the dosimeters (BD concentrations less than 400 µg).

The NIOSH and FIOH methods are fairly similar. However, the FIOH method has some superior aspects compared to the NIOSH method. The desorption

solvent in FIOH method is acetonitrile which is also used in purification of BD from other C4 compounds. BD forms an azeotrop with acetonitrile, which may be the reason for a good desorption efficiency observed in FIOH study. FIOH and UK HSE methods utilized the same analytical column. As stated, the special PLOT type capillary column is needed if a good separation from other low molecular weight hydrocarbons are required.

The UK HSE method is based on thermodesorption performed with the equipment of one manufacturer This is clearly the weakness of this method, since thermodesorption is not routinely done in all analytical laboratories.

6.2. Urban air monitoring

There are two methods which describe the urban air sampling of BD. The Dutch Expert Committee for Occupational Standards (35) has reviewed methods for environmental monitoring as follows:

By means of a sampling pump 25 l air is sampled over a solid sorbent. The upper limit of the sampler is 220 mg/m^3, the measurement range covers 0.044 to 19 mg/m^3. Desorption is performed with methylene chloride, below 0.9 mg/m^3, the desorption efficiency falls below 75%. BD is analysed by gas chromatograph with FID. Interferences are: pentane, methylacetylene, and vinylidene chloride at high levels. Other hydrocarbons, present at permissible levels, or high humidity (more than 80%) may significantly decrease the capacity of the sampler for BD (89).

Infrared spectrometry can be used for continuous monitoring of BD in air. The detection limit is quite high and disturbance from other sources can be present, but can usually be minimized by suitable choice of wavelength.

There are also some gas detector tubes that use common colorimetric reactions to detect BD. These reactions include the reduction of chromate or dichromate to chromous ion and the reduction of ammonium molybdate plus palladium sulphate to molybdenum blue (96).

7. Toxicokinetics

7.1. Uptake and distribution

Uptake of BD occurs via inhalation. BD is well absorbed in the body and is distributed from the alveolar space into the blood and further to different tissues and organs (29). Bond et al (17) conducted experiments using single 6 hr exposures with ^{14}C labelled BD in adult Sprague-Dawley rats and B6C3F$_1$ mice in order to determine the uptake, distribution and metabolism. Mice were exposed (nose-only) from 0.2 to 2 249 mg/m^3 and rats up to 15 968 mg/m^3. Mice had a higher uptake rate than rats and the percentage of ^{14}C absorbed and retained at 6 hrs ranged from 1.5 to 17 % in rats and from 4 to 20 % in mice. In another experiment (45), at low

(23 mg/m^3 or less) exposure levels, mice showed 5 times higher uptake of inhaled BD (20 %) than rats (4 %) or cynomolgus monkeys (3 %).

7.2. Biotransformation

BD is metabolized to 1,2-epoxy-3-butene (BMO) by cytochrome P450-dependent mono-oxygenases and BMO is detoxified by epoxide hydrolases and glutathione transferases, while further epoxidation by monooxygenases transforms BMO into 1,2,3,4-diepoxybutane (DEB), as shown by several authors both *in vitro* and *in vivo* (Fig. 1).

A number of cytochrome P450 isozymes are obviously involved in the metabolism of BD. The major P450 enzyme oxidizing BD to BMO is CYP2E1, the isozyme also involved in the metabolism of styrene (43). This may be of relevance considering the parallel human exposure to these compounds, as pointed out by Filser et al (41).

In experiments conducted on liver and lung tissues from Sprague-Dawley rats, B6C3F$_1$ mice and from human biopsy samples of the same organs indicated significant species specific differences in metabolism (16). B6C3F$_1$ mouse liver microsomes display a capacity for butadiene oxidation exceeding that seen in either human or rat liver microsomes. Except in mice, oxidation of butadiene occurred at rates significantly lower with lung than with liver microsomes. In general, human liver microsomes hydrolysed butadiene monoepoxide at higher rates than either rats or mice. The capacity for glutathione conjugation with butadiene monoepoxide was higher in mice than in humans or rats. The ratios of butadiene activation (P450): detoxification (hydrolysis and conjugation) are markedly different in mouse (74:1), rat (6:1) and human (6:1) liver tissues (16). In mice, the only species examined thus far, bone marrow was found to have much higher levels of butadiene monoepoxide per gram of tissue than did the blood, suggesting formation of the butadiene monoepoxide in the marrow *in situ* (45).

7.3. Elimination

Urine and exhaled air are the major elimination routes for BD, as indicated by ^{14}C experiments (17). No major species differences were seen in elimination. Roughly half of the radioactive material was excreted in urine, 5-10 % in faeces, 5-10 % exhaled as carbon dioxide, 15-20 % exhaled as volatile metabolites and 10-20 % was retained in the body. Monkeys, however, appeared to metabolize the retained ^{14}C-butadiene more completely, as one-half of the internal dose of BD was exhaled as ^{14}C-carbon dioxide (45).

The two main routes for detoxification of BMO *in vivo* were conjugation with glutathione-S-transferase and cleavage of the epoxide with epoxide hydrolase to form 3-butene-1,2-diol. Although these enzyme systems were present in both species, the major route of epoxide detoxification differs between rats and mice. Mouse liver glutathione-S-transferase has a high affinity for BMO while epoxide hydrolase levels are low in mice and high in rats (100). These differences may

have accounted for the fact that BD and BMO metabolic capacities were saturable at lower exposure concentrations in the mouse than in the rat and that glutathione depletion was observed in the mouse.

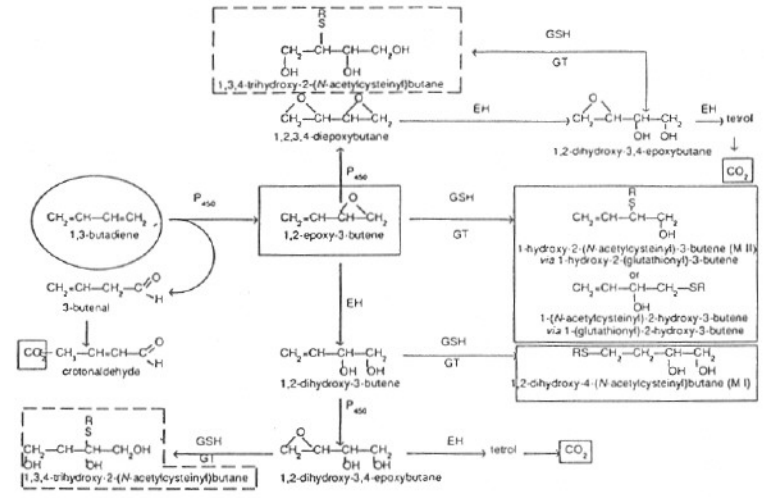
A first-order elimination pattern was observed for BMO in Sprague-Dawley rats following exposure to the epoxide in a closed inhalation chamber at concentrations up to 11 245 mg/m^3; no saturation of BMO metabolism was observed (40, 63). Mice were found to reach metabolic saturation already at a much lower concentration of BMO, ~1 123 mg/m^3 (63). The estimated metabolic V_{max} at saturation level of BMO was 350 µmol/h/kg for mice and over 2 600 µmol/h/kg for rats. At the lower levels where first order elimination kinetics applied, mice had a lower metabolic elimination rate than rats by approximately a factor of five. The key finding in these studies, was that the steady state concentration of BMO in the mouse was about 10-fold higher than in the rat.

When BD metabolism was saturated, BMO was exhaled by both species (15, 63). In addition, when exposed to concentrations of butadiene above 4 498 mg/m^3, the hepatic, non-protein sulfhydryl compounds (NPSH, e.g. glutathione) rapidly became depleted in the mouse, falling to 20 % after 7 h and to 4 % after 15 h. In the rat depletion was much less, 65-80 % of control values after 7 h and then appeared to stabilize (62, 64). A further comparison of both species at several concentrations and tissues showed that a dose dependent NPSH depletion was observed in mouse lung, heart, and liver. In rats NPSH depletion is only seen at high exposure concentrations (33).

Important species differences exist in urinary metabolites of BD (12). The two major metabolites, which have been identified are two mercapturic acids formed from conjugation of glutathione with either butadiene monoepoxide [1-hydroxy-2-(N-acetylcysteinyl)-3-butene; M-II] or the butenediol [1,2-dihydroxy-4-(N-acetylcysteinyl)butane; M-I] (see Fig. 1). The formation of M-I would depend on the ability of animals to hydrolyse butadiene monoepoxide to the butenediol. The ratio of M-I to M-I + M-II was highest in the cynomolgus monkeys and lowest in the mice. Only M-I could be detected in the urine of workers exposed to BD (45).

7.4. Relevant kinetic interactions

BD is widely used in production of styrene copolymers. In manufacturing of SBR (styrene-butadiene-rubber), coexposures to both compounds occur. Both parent compounds are biotransformed by cytochrome P-450 dependent monooxygenases into epoxide form (1,2-epoxy-3-butene and styrene-7,8-oxide), and their pharmacokinetic interactions should therefore be considered relevant. In rats co-exposed to a mixture of BD (45 - 1 349 mg/m^3) and styrene (0 - 1 125 mg/m^3), the metabolic elimination rate of BD was partially inhibited by styrene. The inhibition was competitive upto styrene concentration of 90 ppm, while higher concentrations resulted only in a small additional inhibition (69). BD had no influence on the metabolism of styrene. This finding might be suggestive to support the idea that exposure to BD alone produces more genotoxic/carcinogenic metabolites than coexposure with styrene (see later for epidemiology).



Compounds enclosed in boxes have been identified *in vivo* as metabolites of butadiene; those that have been identified only tentatively are enclosed with broken lines. GSH, glutathione; GT, glutathione *s*-transferase; EH, epoxide hydrolase

Fig. 1. Metabolism scheme for 1,3-butadiene (45).

8. Methods of Biological Monitoring

Standardized methods for assaying BD or its metabolites in biological tissues are not available. However, recently a method was described where the specific N-acetylcysteine conjugates of BD metabolites have been detected in experimental animals exposed to BD (45).

Another potential approach for biological monitoring is to measure the specific adducts to be formed in proteins like haemoglobin or albumin. Adducts of BMO with the N-terminal valine in haemoglobin were determined in male B6C3F$_1$ mice, Sprague-Dawley and Wistar rats following exposures by inhalation (0, 5, 22, 113, 225, 449, 1 125, 2 924 mg BD/m^3, 6h/days, 5 days/week, 2 weeks; animals were sacrified 1 h after the last exposure). The adduct levels increased linearly with BD concentration in mice, wheras a deviation from linearity was observed in rats. After exposure to 23 mg/m^3 BD, the adduct levels were four to five times higher in mice than in rats; at lower concentrations of BD, the species difference was less pronounced (4, 90).

BMO N-terminal valine adduct levels of about 1-3 pmol/g globin were recorded in human nonsmoker subjects, who worked in a production area where BD levels of about 2.2 mg/m^3 had been recorded in a survey conducted three to nine moths prior to blood collection. Increased haemoglobin adduct levels were also observed in cigarette smokers who were not exposed occupationally to BD (90).

9. Effects in *in Vitro* Studies and in Animals

9.1. Irritation and sensitization

Irritation of the mucous membranes resulting in conjunctivitis, nasal and bronchial irritation and finally to respiratory obstruction were the outcome of exposure of mice and rats, for unspecified times, to atmospheres containing 198 000 - 308 000 mg BD/m^3 as reported in the Dutch expert committee (35). Ophthalmoscopic examination of the rabbit eye revealed no signs of injury during or following exposure to atmospheres containing up to 14 740 mg BD/m^3 7.5 h/day, 6 days/week for 8 months. A similar negative result was obtained in a limited study performed concurrently on dogs (35).

9.2. Acute toxicity

Acute toxicity of butadiene is very low. Shugaev (101) reported that the LC_{50} in rats following a 4 hour exposure was 290 121 mg/m^3, while a concentration of 274 378 mg/m^3 resulted in 50 % lethality in mice following 2 hours of exposure. Exposure to 562 250 mg/m^3 for approximately 30 minutes resulted in the death of exposed rabbits (20).

9.3. Short-term toxicity

No treatment related toxic effects, other than increased salivation in female animals, were observed in rats exposed subacutely for 13 weeks (6 hrs/d, 5 d/w) up to 17 992 mg/m^3 of BD (28).

Delays in haemopoietic stem cell maturation were observed when male B6C3F_1 mice were exposed to atmospheres containing 2 750 mg BD/m^3 for up to 31 weeks. Changes were observed in the time course of differentiation of the granulocyte/macrophage precursor cell producing an increase in immature rather than mature pluripotent stem cells in treated animals (72).

Irons et al (55) investigated the effects of BD on peripheral haematology and on bone marrow in male B6C3F_1 mice. These animals were exposed to an air concentration of 2 750 mg/m^3 BD for 6 hr/day, 6 days/week for 3, 6, 12, 18 or 24 weeks. A total of 80 animals was used in this study.

Compartmental analysis of DNA histograms was performed on bone marrow cells isolated from control and BD treated mice after 6 weeks of exposure. The exposure resulted in a 58 % increase in the proportion of cells in the S-phase compared to controls. Significant differences in peripheral haematology were noted between control and treated animals at all time points examined; these included leukopenia. Treatment-related changes in erythrocyte parameters included a significant reduction in the erythrocytes, decreases in haemoglobin and haematocrit, and an increase in the mean corpuscular volume of circulating erythrocytes. No significant increase in circulating reticulocytes was noted and a

5-6 fold increase in circulating micronucleated lymphocytes was observed following treatment. According to the investigators, the alterations in bone marrow and peripheral blood observed as a result of exposure to BD are consistent with a treatment-related macrocytic anemia with little or no haemolytic component. Reductions in circulating leukocytes and the erythrocytes were contrasted with enhanced proliferative activity in bone marrow and essentially normal bone marrow cellularity (55).

9.4. Long-term toxicity/carcinogenicity

Chronic toxicity studies have been conducted by the National Toxicology Program (NTP) in B6C3F_1 mice exposed to 0, 1 406, 2 811 mg/m^3 of BD

32

(6 hr/day, 5 days/week, for 60-61 weeks) (84, 87). Testicular atrophy in male mice and ovarian atrophy in females was noted at 1 406 mg/m^3 (6 hr/day, 5 days/week). In a later study at concentrations 0, 14, 450 or 1406 mg/m^3 bone marrow toxicity was also observed 40 weeks with a decrease in red blood cells, hemoglobin, and packed red cell volume at 141 mg/m^3. An increase in mean corpuscular volume was noted at 1 406 mg/m^3.

The carcinogenicity of BD was examined in male and female B6C3F_1 mice, 50/group, exposed to 0, 1 406 mg/m^3, or 2 811 mg/m^3 butadiene for 60 (male) or 61 (female) weeks (6 hr/day, 5 days/week) (49). The study had been intended to last for 2 years, but early mortality due to the induction of lethal tumors resulted in an earlier study termination. For example, by 60 weeks, less than 20 % of the males exposed to the high concentration and 25 % exposed to the low concentration were still alive. Survival of the controls was greater than 95 % at this time. Malignant T-cell lymphomas were present in both males and females at the low concentration (1 406 mg/m^3) and were the cause of early death in most cases. These thymic lymphomas are distinct from the spontaneous lymphomas occurring in this strain of mouse which are derived from B-cells. Hemangio-sarcomas of the heart, an extremely rare tumor, were also found in both sexes, as were lung and forestomach tumors. The incidence of hemangiosarcomas, lymphomas, and lung tumors was similar at the two concentrations. The decrease in forestomach tumors at the high concentration may well have been due to the excessive early mortality. In addition, tumors were found in the mammary gland, ovary, and liver of female mice at 2 811 mg/m^3. Thus, BD was a multi-site carcinogen in both sexes of B6C3F_1 mice.

A second carcinogenicity study was conducted by the NTP (84). This study focused on both dose-response relationships and the issue of time to tumor, with the inclusion of stop-exposure studies. Male and female B6C3F_1 mice, 70/group, were exposed to 0, 14, 45, 141, 450 and 1 406 mg/m^3 butadiene for 40, 65, or 104 weeks (6 hr/day, 5 days/week). In addition, mice (50/group/sex) were exposed to 450 mg/m^3 for 40 weeks, 1 406 mg/$m^3$for 13 weeks , 702 mg/m^3 for 52 weeks, or 1 406 mg/m^3 for 26 weeks, resulting in a total exposure of approximately 17 992 or 36 546 mg/m^3-weeks. As in the early study, survival was severely

compromised in both sexes at 1 406 mg/m^3, with all the mice being dead before 70 weeks of exposure. Survival was also decreased at 450 mg/m^3, but this effect was much less severe as the concentration decreased. For example, in females the thymic lymphomas led to reduced survival at 450 mg/m^3. The only concentration at which survival was not affected by exposure to BD was 14 mg/m^3.

As in the earlier study, tumors appeared at multiple sites in both sexes of mice. A significant increase in malignant tumors was detected at 45 mg/m^3 in males and 14 mg/m^3 in female mice. In addition to the lymphomas, hemangiosarcomas, and lung and forestomach tumors seen previously, tumors were now observed in the Harderian gland, preputial gland, and liver in males, and in the Harderian gland, liver, ovary, and mammary gland in females. The detection of these additional sites appears to be due to the disappearance of the thymic lymphomas at the low exposure concentrations. The lymphomas are an early appearing tumor, which can occur in less than 26 weeks following the start of exposure. In contrast, the hemangiosarcomas do not begin to appear until 40 weeks. When the concentration of BD is lower, the lymphomas do not occur, allowing for the development of malignancies in other tissues. A similar pattern is apparent for the induction of lung tumors which also do not begin to appear until approximately 40 weeks of exposure. This tumor is the most sensitive tumor endpoint in the female mouse, occurring with a statistically significant increase at the lowest dose used in the study, at 14 mg/m^3. Examination of the concentration-response curves for the induction of tumors in both male and female mice confirms the observation that the T-cell response is a high-concentration effect. In contrast, a linear relationship was observed between incidence and exposure concentration for the other major tumors (lung, Harderian gland, heart, forestomach).

Studies which maintained a constant concentration-time relationship demonstrated that the high exposure concentration was responsible for the induction of lymphomas. Only 13 weeks of exposure to 1 406 mg/m^3 resulted in a 47 % incidence of thymic lymphomas in male mice, while no significant increase occurred when mice were exposed to 450 mg/m^3 for 40 weeks.

Much fewer long-term carcinogenicity studies have been performed in rats than in mice. Rats of Sprague-Dawley strain were exposed to 0, 2 249 or 17 992 mg/m^3 of BD (6 hr/day, 5 d/week for 111 weeks (males) or 105 weeks (females)). Tumors were significantly increased in pancreas and testes in males and in mammary gland and Zymbal gland in females (91).

Thus, BD causes tumors at multiple sites in both sexes of rats and mice. However, while tumors occur at 14 mg/m^3 in the mouse, the lowest concentration at which tumors were noted in rats was at 2 249 mg/m^3. The only tumor site in common between the two species was the mammary gland in the female. The rat tumors are all in endocrine tissues. BD is thus clearly a potent "sufficient evidence" animal carcinogen (53).

9.5. Genetic toxicity and mutagenicity

BD is a potent indirect mutagen both *in vitro* as well as *in vivo*, and its activity depends on the formation of the reactive metabolites, BMO and/or DEB (see Fig. 1). The genetic toxicity of BD has been reviewed (53, 80).

9.5.1. In vitro studies on BD

The main metabolite BMO reacts with DNA to give two isomeric N7 alkylated guanines and two isomeric N6 alkylated deoxyadenosines (23, 59, 93).

Diepoxybutane induced interstrand cross-links in DNA by reaction at the N7 position of guanine (70). Leuratti et al (73) have also reported a specific N6 adenine adduct, without a sign of cross-linking.

Handling of BD for *in vitro* testing is complicated, and this may be a reason for some discrepant results in *in vitro* studies on the genotoxicity of BD. Gaseous BD clearly increased the frequency of revertant colonies in *Salmonella* strain TA1530 (80). Otherwise, the evidence that rat liver S9 can adequately activate BD is based on weak activity in the same *Salmonella* strain (9) and weak induction of SCE in Chinese hamster ovary cells (97). Gaseous BD did not induce SCE in cultured human lymphocytes, with or without S9 mix (9). However, when it was administered in cooled, liquid form to air-tight cultures, it had a weak, reproducible effect on SCE frequency, regardless of whether S9 mix was used (98). However, erythrocytes do not appear to play a role in the activation of BD, as essentially similar, weak induction of SCEs was observed in whole-blood human lymphocyte cultures and in cultures of isolated mononuclear cells (98). Also gene mutation induction at the *hprt* locus of a human lymphoblastoid cell line, TK 6, has been reported after exposure to BD (24).

9.5.2. In vivo studies on BD

When B6C3F$_1$ mice and Wistar rats were exposed to ^{14}C-BD 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 association with DNA was similar in the two species (62). Acid hydrolysis of DNA isolated from the livers of mice exposed to ^{14}C-BD revealed the presence of two indentifiable N7-alkylguanines. These were not found in similarly exposed rats (57).

After a 7h exposure of mice and rats to BD at 562, 1 126 and 2 249 mg/m^3, alkaline elution profiles from the livers and lungs showed the occurence of protein-DNA and DNA-DNA cross-links at all doses of BD (57). In an other study, there was no evidence of the formation of cross-links in DNA isolated from the livers of BD-treated mice or rats (95).

Recent studies have shown that specific N6 BMO alkylated deoxyadenosine adducts were formed in rats and mice exposed to BD (60). The organs which were studied, and in which adducts were qualitatively detected, were lung, liver and heart. A dose response was reported in rat lung samples, the only organ studied

through the exposure range (exposure regimen 113, 450, 1 126 and 2 924 mg/m^3; 6 h/day, 5 days/week, two weeks).

BD induces both chromosomal effects as well as gene mutations in rodents exposed to this compound. In the bone marrow of mice exposed by inhalation, BD produced chromosomal aberrations (at a dose of 2 811 mg/m^3 for 6 h or 1 406 mg/m^3 for 10 days), SCEs (at 14 - 1 410 mg/m^3 for 10 days) and micronuclei (at 14 - 1 410 mg/m^3 for 10 days, 14 - 1 410 mg/m^3 for 13 weeks or 2 811 mg/m^3 for 3 - 24 weeks) but not aneuploidy (at 2 811 mg/m^3 for 6 h) (30, 54, 56, 109). These findings contrast sharply with the findings in rats exposed by inhalation, in which no SCEs or micronuclei were found in bone marrow and no chromosomal aberrations in lymphocytes after exposure to 225 - 2 249 mg/m^3 BD for two days (30). SCEs thus seem to be the most sensitive endpoint with lowest effective concentration at 14 mg/m^3 in mice (109).

Micronucleus formation has been the most studied cytogenetic endpoint. Victorin et al (114) exposed male NMRI mice for 23 h to 0, 23 or 1 126 mg/m^3 and sampled bone marrow 30 h after the start of exposure. The MN frequency was significantly increased already at the lower concentration (0.82 % micronucleated polychromatic erythrocytes (MPE) in exposed vs 0.14 % MPE in control animals).

Adler et al (2) exposed (102/ElxC3H/El)F$_1$ mice of both sexes to 0, 113, 450, 1 126 or 2 924 mg/m^3 on 6 h/d for 5 days. Significant increases in MN frequencies were already observed at the lowest exposure concentration (0.54 % MPE in exposed vs. 0.13 % MPE in control animals). The dose-response was linear up to 450 mg/m^3. At higher concentrations the curve flattened and the MN frequencies in males were significantly higher than in females. There was no difference between the MN yields in bone marrow and peripheral blood PCE which were also scored.

Autio et al (11) exposed female B6C3F$_1$ mice and male Wistar rats by inhalation to the same concentrations of BD as Adler et al (2). The shape of the dose response curve for bone marrow and peripheral blood MPE was similar as in the study by Adler et al (2), although the actual MN yields were somewhat higher. Contrastingly, the results with rats were not significantly different between exposed (112.5, 449.8 or 1 124.5 mg/m^3) and control animals, neither for bone marrow nor for peripheral blood PCE.

In conclusion, there is a striking difference in the clastogenic response to BD in rats and mice.

Studies by Goodrow et al (42) have demonstrated that protooncogenes are activated in mouse liver and lung tumors and lymphomas following exposure to BD. The activating mutation is in codon 13 of the K-*ras* oncogene, a mutation never seen in spontaneously arising liver tumors. Using transgenic mice (94) have demonstrated *in vivo* activation of transgenes following exposure to BD at 1 410 mg/m^3 level (6 h/d, 5 days). Analysis of mutation spectrum in the target *lac I* gene, revealed BD induced mutations at the A:T base pair while the spontaneous mutations in the control animals were at G:C sites (94, 103).

Table 12. Genotoxicity of 1,3-butadiene *in vivo*.

Species	Endpoint	Result	References
Mouse	Hb adducts	+	4
	DNA alkylation	+	57
	SSBs in DNA	+	57
	SCE	+	109
	MN	+	109
	CA	+	54
	HPRT	+	26
	Fur color spots	+	2
	Dominant lethals	+	1
	Congenital malformations	+	7
Rat	Hb adducts	(+)	4
	DNA alkylation	+	57
	SSBs in DNA	-	57
	SCE	-	30
	MN	-	11
Human	Hb adducts	+	90
	SCE	-	104
	MN	-	104
	CA	-	104
	HPRT	+	71

Two studies have demonstrated the *in vivo* induction of gene mutations at the *hprt* locus in mice. Mice exposed to 1 410 mg BD/m^3 for two weeks had an average *hprt* mutation frequency of 6.2 x 10^{-6} in splenic T cells, whereas that in controls was 1.2 x 10^{-6} (25, 26). A dose dependent increase of *hprt* mutant frequency was observed in splenocytes of mice exposed to 450, 1 126 or 2 924 mg/m^3 of BD (6 hr/d, 5 d). At the highest exposure level a 3-fold increase in the spontaneous mutant frequency was observed (107). The data on the genotoxicity of BD in rats and mice *in vivo* are thus consistent with the clearly more potent carcinogenicity of the compound in mice than in rats (see Table 12).

9.6. Reproductive and developmental toxicity

The developmental and reproductive toxicity of inhaled BD was studied in Sprague-Dawley rats and Swiss (CD-1) mice at 0, 90, 450 or 2 249 mg/m^3 levels of BD for 6 hr/day on days 6 through 15 of gestation and killed on day 18 (mice) or day 20 (rats). In rats, maternal toxicity was observed in the 2 249 mg/m^3 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 in rats. In contrast, results of the mouse developmental toxicity study indicated that the fetus may be more susceptible than the dam to inhaled BD. Maternal toxicity was observed in mice at the

450 and 2 249 mg/m^3 inhalation exposure levels, whereas 90 mg/m^3 and higher concentrations of BD caused significant exposure-related reductions in the mean body weights of male fetuses. Mean body weights of female fetuses were also reduced at the 450 and 2 249 mg/m^3 exposure levels. No increased incidence of malformations was observed in either study (85).

A small, but concentration related, increase in abnormal sperm morphology was observed in B6C3F$_1$ mice 5 weeks following exposure to 450, 2 249 or 11 245 mg BD/m^3 (6 hr/d, 5 d/w) (85).

Altogether three dominant lethal mutation studies have been performed with BD. Morrissey et al (85) reported that exposure of male B6C3F$_1$ mice to levels as low as 450 mg/m^3, BD caused an increase in the percentage of females with two or more dead implants in the first week following exposure. In both the first and second weeks following exposure, there were increases in the number of dead implantations (early), although strict atmospheric concentration-response relationships were not observed. These results suggested that more mature cells of spermatogenesis (spermatozoa and spermatids) might be adversely affected.

This finding of germ cell mutagenicity of BD was independently confirmed by two later studies using mice of strain CD-1 (7) or 102/El x C3H/EI-F$_1$ hybrids (1). In both studies a significant dominant lethal effect was observed at exposure level 2 811 mg/m^3 (6 h/d, 5 d/w for 10 weeks) in the Anderson et al (7) study and at 2 924 mg/m^3 (6 h/d for 5 days) in the Adler et al (1) study.

The results indicated that the dominant lethal effect observed after 10 weeks of exposure is representative of the last three treatment weeks, i.e. treated spermatozoa and spermatids. The results of the three independent experiments strengthen the conclusion that BD is a germ cell mutagen.

The germ cell mutagenicity of BD observed in male mice might be the mechanistic explanation for the quite unusual finding of male-mediated malformations in offspring of CD-1 male mice exposed for 10 weeks to 28 mg/m^3 or 2 811 mg BD/m^3 (6 hr/d, 5 d/w). The lower dose also increased the frequency of malformations and late deaths, but did not affect early deaths (7).

9.7. Immunotoxicity

The immunotoxicity of BD was examined in male B6C3F$_1$ mice exposed to 2 811 mg/m^3 (6 hr/day, 5 days/wk) for 12 weeks. No effects were noted in either humoral or cell-mediated immunity (108).

10. Studies in Humans

10.1. Acute effects

BD is practically non-toxic by inhalation and shows very weak irritative properties. Concentrations of several thousand ppm of BD has been reported to irritate the skin, eyes, nose and throat (53). In a study on volunteer workers, only minor irritation of eyes was observed after 6-8 hrs exposure to 4 498 mg/m^3 of BD (20).

Dermal contact with liquid BD causes cold burns and frostbite; no data of sensitization is available (37).

10.2. Effects of repeated exposure

Some indications of altered hematological parametres were reported in workers exposed to 45 mg BD/m^3 together with various solvents (22).

Studies have been reported on the effects of occupational exposure to BD mainly from the former USSR and Bulgaria. Only few of the reports are substantiated by details on the atmospheric concentrations or duration of the exposure. The effects reported include haematological disorders, kidney malfunctions, laryngotracheitis, upper-respiratory-tract irritation, conjunctivitis, gastritis, various skin disorders and a variety of neurasthenic symptoms, as well as hypertension and neurological disorders (53).

10.3. Genotoxic effects

Very few human studies have been reported. In a study from BD manufacturing industry in Finland cytogenetic analysis of peripheral blood lymphocytes of workers exposed to low levels of BD (generally less than 2.2 mg/m^3) revealed no exposure related effects in the frequencies of chromosomal aberrations (CA), sister chromatid exchanges (SCE) or micronuclei (MN) (3).

Similarly, negative results were obtained from studies of two other worker populations exposed to slightly higher levels of BD in manufacturing (generally less than 2.2 mg/m^3) and in styrene-butadiene rubber production (generally less than 4.5 mg/m^3) in two plants located in Portugal and the Czech Republic. Although smoking related effects were seen for SCE and for MN and age related increase was observed for CA and MN (in females), none of the cytogenetic parametres correlated with exposure to BD which was measured by personal monitoring (104).

So far the only positive BD induced effects of genotoxicity in humans are the preliminary findings of increased *hprt* mutations in workers employed at a BD manufacturing plant in Texas, USA. The exposure levels were generally 2.2 - 6.7 mg/m^3 of ambient BD. Only nonsmoking workers took part in the study, where the specific urinary metabolite of BD, "MI" (1,2-dihydroxy-4-(N-

acetylcysteinyl) butane) was used as an individual exposure marker. A significant correlation was observed between the level of the MI metabolite in urine and the frequency of *hprt* mutants in lymphocytes (71).

10.4. Carcinogenic effects

Both cohort and case-control studies on BD exposure at work have been reported. A general problem in the studies has been the difficulties in retrospective exposure assessment. In US plants, the mean of nearly 4 000 air measurements is 17.8 mg/m^3 with very wide deviation (SD 54.0) (76, 77).

One US cohort of workers who manufactured BD 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 BD (34).

In a US study of workers employed in two styrene-BD rubber plants, there was a suggested increase of risk for leukaemia with exposure to BD in one of the plants. No increase in risk was seen for cancers of the lymphatic and haematopoietic system other than leukaemia (81, 82).

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 (79).

In a study of styrene-BD 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 (78).

One study, therefore, specifically related increased risks for leukaemia to exposure to BD 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 BD or styrene-BD rubber.

A later analysis of estimated high exposures and lymphohematopoietic cancers within the cohort focused on specific work areas with exposure to butadiene and increased risk for leukaemia and Hodgkin's disease (76) (Table 13).

Table 13. Standardized mortality ratios (SMRs) in relation to lymphohematopoietic cancers among workers in three plants.

Cause of death	Observed	SMR	95 % CI
All lymphohaematopoietic cancers	34	1.63	1.13 - 2.27
Lymphosarcoma and reticulosarcoma	5	1.16	0.37 - 2.70
Hodgkin's disease	5	2.43	0.78 - 5.68
Leukaemia and aleukaemia	15	1.81	1.01 - 2.99
Other lymphatic tissue	9	1.49	0.68 - 2.82

CI, confidence interval

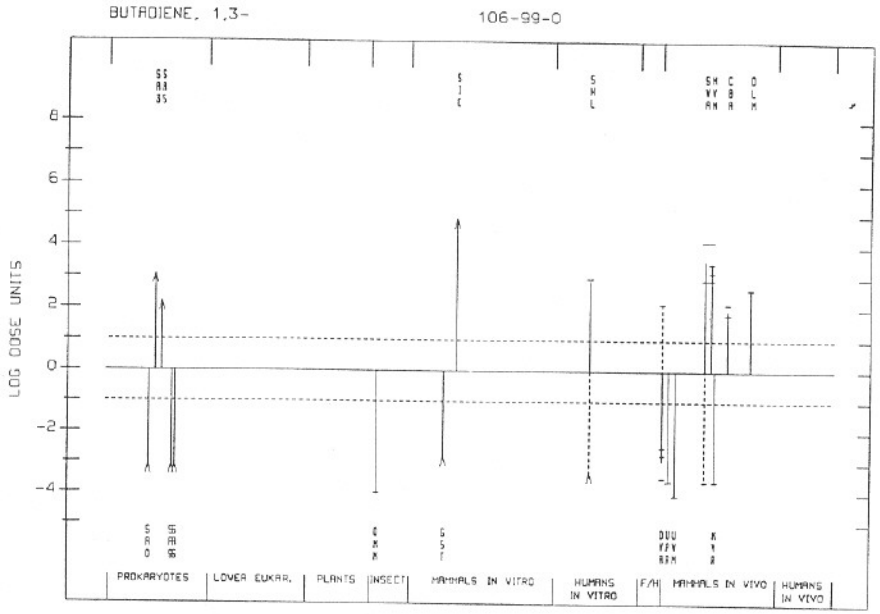


Fig. 2. Genetic activity profile of BD (53).

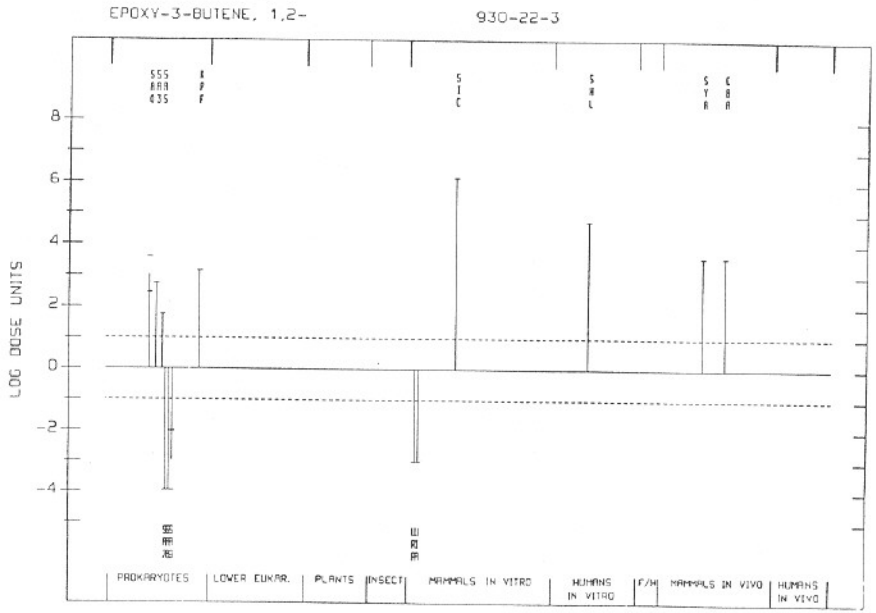


Fig. 3. Genetic activity profile of BME (53).

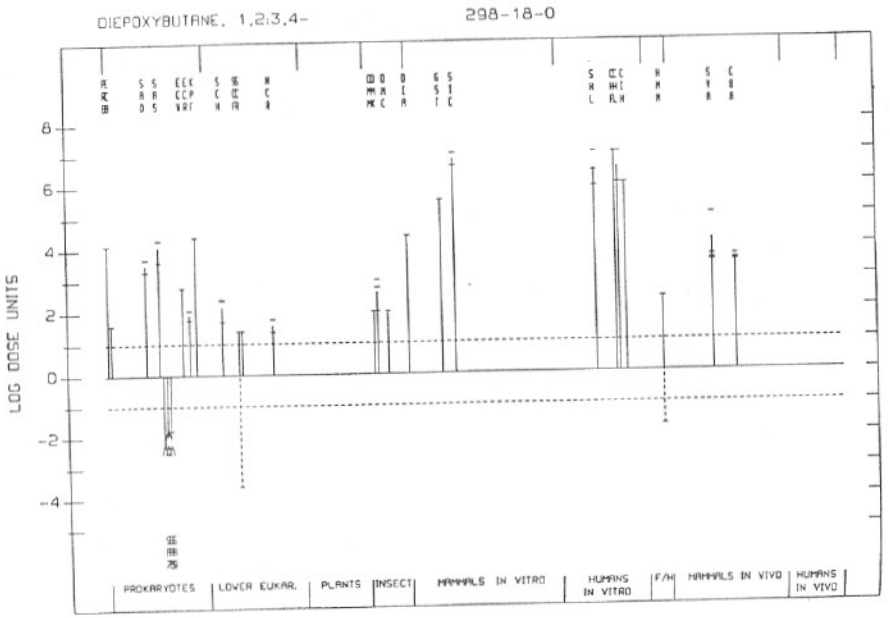


Fig. 4. Genetic activity profile of DEB (53).

11. Dose-Effect and Dose-Response Relationships

11.1. Short-term tests for genetic toxicity

The recent carcinogenicity evaluation by IARC (53) included the dose-related activity profiles for genetic and related effects on BD as well as the two epoxide metabolites, 1,2-epoxy-3-butene (BMO) and 1,2,3,4-diepoxybutane (DEB) (Figs. 2, 3, 4).

The EPA developed activity profile represents the bioassays in phylogenetic sequence by endpoint, and the values on the y-axis represent the logarithmically transformed lowest effective doses (LED) and highest ineffective doses (HID) tested. The term 'dose', as used in this report, does not take into consideration the length of treatment or exposure and may therefore be considered synonymous with concentration. In practice, the concentrations used in all the *in vitro* tests were converted to µg/ml, and those for *in vivo* tests were expressed as mg/kg bw. Because dose units are plotted on a log scale, differences in molecular weights of compounds do not, in most cases, greatly influence comparisons of their activity profiles.

Table 14. Incidences of primary tumours in Sprague-Dawley rats exposed to 1,3-butadiene for two years (83).

Sex	Organ	Neoplasm	Exposure concentration (mg/m³)*		
			0	2 249	17 992
Males	Pancreas	Exocrine[a]	3	1	11[b]
	Testis	Leydig-cell[a]	0	3	8[b]
	Brain	Glial cell[a]	1	4	5
Females	Uterus	Stromal sarcoma[a]	1	4	5
	Zymbal gland	Carcinoma[a]	0	0	4
	Thyroid gland	Follicular cell[a]	0	4	11[b]
	Mammary gland	Fibroadenoma[a]	32	64[b]	55[b]
		Carcinoma	18	15	26
		Total[a]	50	79[b]	81[b]
	Average no. of mammary gland fibroadenomas/ fibroadenoma-bearing rat[c]		1.38	3.70	3.33

From Owen et al (92)

* Exposure concentrations are given as ppm in the original article

[a] Increasing trend, $p<0.05$

[b] Increased in comparison with chamber controls (0 mg/m³), $p<0.05$

[c] From US Occupational Safety and Health Administration (112)

Tabell 15. Incidence of primary tumours in B6C3F1 mice exposed to 1,3-butadiene for 60-61 weeks (83).

Target	Neoplasm	Exposure concentration (mg/m³)*					
		Males			Females		
		0	1 406	2 811	0	1 406	2 811
Haemotopoietic system	Malignant lymphoma	0/50[a]	23/50[b]	29/50[b]	1/50[a]	10/49[b]	10/49[b]
Heart	Haemangiosarcoma	0/50[a]	16/49[b]	7/49[b]	0/50[a]	11/48[b]	18/49[b]
Lung	Alveolar-bronchiolar	2/50[a]	14/49[b]	15/49[b]	3/49[a]	12/48[b]	23/49[b]
Forestomach	Squamous-cell	0/49	7/40[b]	1/44	0/49[a]	5/42[b]	10/49[b]
Mammary gland	Acinar-cell	0/50	0/50	0/50	0/50[a]	2/49	6/49[b]
Ovary	Granulosa-cell	-	-	-	0/49[a]	6/45[b]	12/48[b]
Liver	Hepatocellular	8/50	6/49	2/49	0/50[a]	2/47	5/49[b]

From Huff et al (49)

* Exposure concentrations are given as ppm in the original article

[a] Increasing trend, $p<0.05$; incidences of neoplastic lesions analysed by life table methods and by the Fisher exact test for pairwise comparisons of high-dose or low-dose groups with controls

[b] Increased in compariosn with chamber control (0 mg/m³), $p<0.05$

Table 16. Incidences of primary tumours in male B6C3F1 mice exposed to 1,3-butadiene for up to two years (taken from ref 83).

Target	Neoplasm	Exposure concentration[a]				
		0 Control	450 mg/m^3 40 weeks (18000)[b]	1406 mg/m^3 13 weeks (18278)[b]	702 mg/m^3 52 weeks (36504)[b]	1406 mg/m^3 26 weeks (36556)[b]
Haematopoietic system	Lymphoma	4/50 (9.0%)	8/50 (24.1%)	22/50 (56.1%)**	8/50 (35.0%)*	33/50 (87.2%)**
Heart	Haemangio-sarcoma	0/50 -	15/50 (47.1%)**	7/50 (30.9%)**	33/50 (85.2%)**	13/50 (74.5%)**
Lung	Alveolar-bronchiolar adenoma or carcinoma	21/50 (47.5%)	36/50 (88.6%)**	28/50 (89.5%)**	32/50 (88.0%)**	17/50 (87.2%)**
Forestomach	Squamous-cell papilloma or carcinoma	1/50 (2.3%)	3/50 (10.2%)	7/50 (28.7%)**	9/50 (39.2%)**	10/50 (60.7%)**
Harderian gland	Adenoma or carcinoma	6/50 (13.5%)	27/50 (72.1%)**	23/50 (82.0%)**	30/50 (88.6%)**	13/50 (76.5%)**
Liver	Hepatocellular adenoma or carcinoma	21/50 (44.6%)	33/49 (82.4%)**	24/49 (80.3%)**	25/50 (75.9%)**	13/50 (77.3%)*
Preputial gland	Carcinoma	0/50 -	1/50 (3.5%)	5/50 (21.2%)**	4/50 (21.2%)**	3/50 (30.6%)**

Incidence, number of tumour-bearing animals/number of animals examined; tumour rates, adjusted for intercurrent mortality by the poly-3 quantal response method, are given in parentheses
[a] Exposure concentrations are given as ppm in the original article
[b] Total cumulative exposure expressed as mg/m^3 x weeks
* Significantly different ($p<0.05$) from chamber controls (0 mg/m^3)
** $p<0.01$

Profile-line height (the magnitude of each bar) is a function of the LED or HID, which is associated with the characteristics of each individual test system. For negative test results, the highest dose tested without appreciable toxicity is defined as the HID. Similarly, for positive results, the LED is recorded.

The indirect mutagenicity of BD is reflected in Fig. 2; the activity is seen only when the metabolic activation system is provided *in vitro* or in the *in vivo* systems. The potency difference between the epoxides is 1 - 2 orders of magnitude higher with DEB (Fig. 4) as compared with BME (Fig. 3) in the same assay system.

Table 17. Incidence of primary tumours in female B6C3F1 mice exposed to 1,3-butadiene for up to two years (83).

Target	Neoplasm	Exposure concentration (mg/m^3)[a]					
		0	14.1	45	141	450	1 406
Haematopoietic system	Lymphoma	6/50 (13.1%)	12/50 (27.2%)	11/50 (27.5%)	7/50 (20.2%)	9/50 (40.1%)*	32/80 (85.5%)**
Heart	Haemangio-sarcoma	0/50 -	0/50 -	0/50 -	1/49 (3.1%)	21/50 (71.9%)**	23/80 (83.4%)**
Lung	Alveolar-bronchiolar adenoma or carcinoma	4/50 (8.8%)	15/50 (33.0%)*	19/50 (46.5%)**	24/50 (61.1%)**	25/50 (81.5%)**	22/78 (82.4%)**
Forestomach	Squamous-cell papilloma or carcinoma	0/50 -	0/50 -	3/50 (7.8%)	2/50 (6.1%)	4/50 (22.5%)**	22/80 (82.6%)**
Harderian gland	Adenoma or carcinoma	8/50 (17.5%)	10/50 (22.7%)	7/50 (17.4%)	15/50 (41.2%)*	20/50 (70.9%)**	9/80 (58.0)**
Liver	Hepatocellular adenoma or carcinoma	15/49 (33.3%)	14/49 (30.3%)	15/50 (36.4%)	19/50 (51.4%)	16/50 (64.9%)*	2/80 (21.7%)
Ovary	Granulosa-cell tumour	1/49 (2.3%)	0/49 -	1/48 (2.6%)	9/50 (26.3%)**	8/50 (41.1%)**	6/79 (46.5%)**
Mammary gland	Carcinoma or adeno-acanthoma	0/50 -	2/50 (4.5%)	4/50 (10.2%)*	12/50 (32.6%)**	15/50 (56.4%)**	16/80 (66.8%)**

Incidence, number of tumour-bearing animals/number of animals examined; tumour rates, adjusted for intercurrent mortality by the poly-3 quantal response method, are given in parentheses
[a] Exposure concentrations are given as ppm in the original article
*Significantly different ($p<0.05$) from chamber controls (0 mg/m^3)
**$p<0.01$

11.2. Long-term exposure

The main carcinogenicity bioassays have been performed in Sprague-Dawley rats, exposed for 2 years (92) and in B6C3F$_1$ mice exposed for 60 - 61 weeks (49) and up to 2 years (84).

BD was carcinogenic in rats at multiple organ sites at exposure concentrations of 2 249 and 17 992 mg/m^3 (Table 14). The fact that in rats, the metabolism of

BD is saturated at concentrations above 2 249 mg/m^3 (68), may explain the plateau in tumour incidences in the brain, uterus and mammary gland.

In mice, the incidences of lymphomas, haemangiosarcomas of the heart and neoplasms of the lung were significantly increased in both sexes at both exposure concentration (Table 15). A second study in mice was performed to characterize the exposure-response relationship better using lower concentrations of BD. Also in this study, the very unusual haemangiosarcomas of the heart were increased in male (Table 16) and female (Table 17) mice. The incidence of lung tumours was increased in male mice from 141 mg/m^3, while in females the lowest carcinogenic concentration for lung tumors was as low as 14 mg/m^3. These data demonstrate an unusually strong carcinogenic potency of BD in mice.

12. Previous Evaluations by International Bodies

Various international bodies have evaluated the toxicity of BD. The carcinogenicity of BD has been evaluated in three occasions by IARC (50, 51, 53). The most recent evaluation of 1992 considered the evidence on animal carcinogenicity as "sufficient", while human epidemiology was considered "limited". The overall evaluation of carcinogenic risk to humans was classified into group 2A, thus considering BD probably carcinogenic to humans.

In the Nordic countries, the carcinogenicity classification for BD in Norway is category I ("sufficient evidence of carcinogenicity") with potency grading K2 ("intermediate potency carcinogen"). In Sweden it is classified into labelling category "C" entailing a risk phrase "May cause cancer after frequently repeated exposure". In Finland, BD is in the class 3 of carcinogenic agents requiring the application of the Labour Protection Act to carcinogenic substances.

The scientific evidence in relation to carcinogenicity of BD has been reviewed by the CEC expert group (21). The European Union category for BD is 2 ("substances which should be regarded as if they were carcinogenic to man").

13. Evaluation of Human Health Risks

13.1 Assessment of health risks

Occupational exposure to BD is highest in the monomer production industry. A survey carried out in the USA indicated full-shift exposure levels in all categories of butadiene industry (monomer and polymer) to be below 22.5 mg/m^3 (38, 39). Measurements from Finland indicated exposure levels below 2.3 mg/m^3 in the monomer production (3), while slightly higher levels still mainly below 6.7 mg/m^3 TWA were observed in studies performed in BD production facilities in Portugal and the Czech Republic (104).

Although the environmental levels of BD, as compared to occupational exposure levels, are several orders of magnitude lower (average concentration in US city air was estimated to be 1.4 µg/m^3), BD is a compound to which everybody is exposed to, as it is a product of organic combustion (tobacco smoke, automobile exhaust, fire emissions).

The high risk exposures relate to manufacturing of BD, where short term exposures can exceed 22.5 mg/m^3 and even 224.9 mg/m^3, especially in cylinder sampling, voiding and maintenance (39).

The health risk estimations on BD are based on extrapolations from experimental data. The epidemiological studies reported to date give strong evidence for increased incidences of leukemia and/or lymphohematopoietic neoplasms in relation to work in BD industry and many have suggested an excess of stomach cancers in the styrene-BD rubber industry. While exposures in these industries are complex, the studies reviewed have not convincingly strongly associated the increased risks to exposure to BD specifically.

If the risk assessment is based on mouse carcinogenicity data using a multistage Weibull time-to-tumor model (31), the expected risk becomes very high in comparison to present occupational standards and exposure levels. The risk estimates were extrapolated from mice to humans on the basis of body weight raised to the three-fourths power, and the median lifespan of mice was equated with a human lifespan of 74 years. Estimates of excess risk for lifetime occupational exposure (8 h/day, 5 days/week, 50 weeks/year, for 45 years) to 4.5 mg BD/m^3 ranged from 0.2 per 10 000 workers, based on female mouse heart hemangiosarcomas, to 600 per 10 000 workers, based on female mouse lung tumours. Although important species differences may exist in uptake, metabolism and elimination, these results suggest that exposures to BD in the workplace should be reduced to the lowest feasible level.

13.2. Recommended basis for an occupational exposure limit

BD is an unusually potent genotoxic carcinogen with high potency in mice and medium potency in rats. Its carcinogenicity in epidemiologic studies needs to be confirmed, but the overall strength of association and biological plausibility strongly suggests its carcinogenicity in humans.

The occupational standard for BD is 22.5 mg/m^3 (TLV 8 h) in Norway and 1 mg/m^3 in Sweden, while the Finnish standard (HTP 8 h) still is 110 mg/m^3. The ACGIH suggested standard for BD is 4.4 mg/m^3. See Appendix.

It should be noted that BD is a genotoxic carcinogen and no safe level of exposure can therefore be given. The data presented in this document urge for reconsideration of the present occupational standards of BD in the Nordic countries.

14. Research Needs

Research still remains to be done to elucidate the risks to humans of exposures to BD. Studies are needed to identify the possible hazards of end-points, such as reproductive toxicity and germinal mutagenicity that are currently not well defined. Physiologically based pharmacokinetic dose-response models should be refined in order to elucidate (i) the relationship between exposure, the dose that reaches the target and biological effects and (ii) the basic biological mechanisms that are responsible for the effects that are observed; the latter is crucial to the extrapolation of data from animals to humans and from high to low doses. Biological markers of exposure, effects and susceptibility in human populations should be developed so that adverse effects can be detected earlier and control action taken to reduce the risks to public health of exposures to BD.

15. Summary

Sorsa M, Peltonen K. 113. 1,3-Butadiene. Nordic Expertgroup for Criteria Documentaton of Chemical Health Risks. *Arbete och Hälsa* 1994;36:1-42.

1,3-Butadiene (BD) is an important industrial chemical with an estimated annual world production exceeding 5 million tons. BD is used principally as a monomer for producing a wide range of polymers and copolymers, the largest single use being styrene-BD rubber for tyres and tyre products.

BD also occurs as an environmental contaminant in urban air, traffic exhausts and tobacco smoke. This report is a survey of the relevant literature to form a basis for a discussion on occupational exposure limits in urban air, traffic exhausts and tobacco smoke. Low exposure to BD is thus a common characteristic of the whole human population. BD requires metabolic activation to reactive epoxides in order to bind to DNA and initiate events leading to mutations and cancer. Species differences in metabolism, including both activation and detoxification, are therefore very relevant for its toxic manifestations and for risk assessments. The epoxide metabolites of BD are highly mutagenic in various assay systems.

BD is a high priority compound for risk assessments not only because of its wide exposure but also considering its known toxicological properties. BD is practically nontoxic acutely, but it is a multiple organ carcinogen in mice and rats, mouse being by far the more sensitive species. Still, it is not clear whether BD, at the low human exposure levels occurring, can be shown carcinogenic, although epidemiological studies have revealed associations between occupational exposure to BD and excess mortality due to lymphatic and hematopoietic cancers.

Keywords: Butadiene, carcinogenicity, mutagenicity, occupational exposure limits, species differences in metabolism.

16. Summary in Swedish

Sorsa M, Peltonen K. 113. 1,3-Butadien. Nordiska expertgruppen för kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1994;36:1-42.

1,3-Butadien är en viktig industriell kemikalie med en uppskattad världsomfattande produktion som överstiger 5 miljoner ton. DB används huvudsakligen som monomer för produktion av en bred skala av polymerer och kopolymerer. Det största individuella användningsområdet är produktionen av styren-butadiengummi för bilringar och närbesläktade produkter.

BD förekommer också som miljökontaminant i stadsluften, trafikutsläpp och tobaksrök. Denna rapport är en översikt av den relevanta litteraturen för diskussion av arbetsrelaterade exponeringsgränsvärden. Låg exponering för BD är karakteristiskt för hela människosläktet. BD kräver metabolisk aktivering till reaktiva epoxider för att kunna bindas till DNA och initiera en kedja av händelser som leder till mutationer och cancer. Skillnader i metabolismen mellan olika djurarter, inkluderande både aktivering och detoxifiering, är därför mycket relevanta för dess toxiska verkningar och för riskuppskattning. Epoxidmetaboliterna av BD är mycket mutagena i olika testsystem.

BD är en substans med hög prioritet vid riskuppskattning, inte endast på grund av den omfattande exponeringen, men också med tanke på dess kända toxikologiska egenskaper. BD:s akuta toxicitet är mycket låg, men den orsakar tumörer i ett flertal organ hos möss och råttor. Möss har visat sig vara mycket känsligare än råttor. Trots detta är det fortfarande oklart i vilken grad BD orsakar cancer hos människa vid de konstaterade låga exponeringsnivåerna, även om epidemiologiska studier har avslöjat associationer mellan arbetsmässig exponering för BD och ökad dödlighet av lymfatiska och hematopoetiska cancertyper.

Nyckelord: Artskillnader i metabolism, butadien, carcinogenicitet, hygieniska gränsvärden, mutagenicitet.

17. References

1. Adler I-D, Anderson D. Dominant lethal effects after inhalation exposure to 1,3-butadiene. *Mutation Res* 1994;309:295-297.
2. Adler I-D, Cao J, Filser JG, Gassner P, et al. Mutagenicity of 1,3-butadiene inhalation in somatic and germinal cells of mice. *Mutation Res* 1994;309:307-314.
3. Ahlberg RW, Sorsa M, Pfäffli P, Mäki-Paakkanen J, Viinanen R. Genotoxicity and exposure assessment in the manufacture of 1,3-butadiene. In: *WHO Occupational Health in the Chemical Industry*. Copenhagen: WHO,1992:199-204.
4. Albrecht OE, Filser JG, Neumann HG. Biological monitoring of 1,3-butadiene: species diffrences in haemoglobin binding in rat and mouse. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:135-143.
5. Aldrich Chemical Co. *Aldrich Catalog/Handbook of fine chemicals 1994-1995*. Milwaukee WI: Aldrich Chemical Co, 1994: 255.
6. Amoore J, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-290.
7. Anderson D, Edwards AJ, Brinkworth MH. Male-mediated F_1 effects in mice exposed to 1,3-butadiene. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:171-183.
8. Anonymous. Chemical profile: butadiene. *Chem Mark Rep* 1991;239:50.
9. Arce GT, Vincent DR, Cunningham MJ, Choy WN, Sarrif AM. In vitro and in vivo genotoxicity of 1,3-butadiene and metabolites. *Environ Health Perspectives* 1990;86:75-78.
10. Arnts RR, Meek SA. Biogenic hydrocarbon contribution to the ambient air of selected areas. *Atmosph Environ* 1981;15:1643-1651.
11. Autio K, Renzi L, Catalan J, Albrecht OE, Sorsa M. Induction of micronuclei in peripheral blood reticulocytes and bone marrow cells of rats and mice exposed to 1,3-butadiene by inhalation. *Mutation Res* 1994;309:315-320.
12. Bechtold WE, Strunk MR, Ward JB Jr, Henderson RF. Species differences in urinary butadiene metabolites: comparison of metabolite ratios in mice, rats and humans. *Toxicol Appl Pharmacol* 1994, in press.
13. Berg S, Frostling H, Jacobsson S. Chemical analysis of fire gases with gas chromatography-mass spectrometry. *Proceedings of International Symposium on the Control of Air Pollution in the Work Environment, Part 1*. Stockholm: Arbetarskyddsfonden 1978:309-321.
14. Bianchi A, Cook HA. Modified method for analysis of C2-C5 hydrocarbons in an aromatic-alkene matrix. *J Chrom* 1988;449:175-181.
15. Bolt HM, Schmiedel G, Filser JG, et al. Biological activation of 1,3-butadiene to vinyl oxirane by rat liver microsomes and expiration of the reactive metabolite by exposed rats. *J Cancer Res Clin Oncol* 1983;106:112-116.
16. Bond JA, Csanady GA, Leavens T, Medinsky MA. Research strategy for assessing target tissue dosimetry of 1,3-butadiene in laboratory animals and humans. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:45-56.
17. Bond JA, Dahl AR, Henderson RF, Dutcher JS, Mauderly JL, Birnbaum LS. Species differences in the disposition of inhaled butadiene. *Toxicol Appl Pharmacol* 1986;84:617-627.

18. Brunnemann KD, Kagan MR, Cox JE, Hoffmann D. Analysis of 1,3-butadiene and other selected gas phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. *Carcinogenesis* 1990;11:1863-1868.

19. Budavari S, Rahway NJ, eds. *The Merck Index*, 11th ed. Merck & Co, 1989:230-231.

20. Carpenter CP, Shaffer CB, Weil CS, Smyth HF. Studies of the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J Ind Hyg Toxicol* 1944;26:69-78.

21. CEC (Commission of the European Communities). *The Toxicology of chemicals. Carcinogenicity, Vol. III. 1,3-Butadiene*. 1991:111-119 (EVR13765 EN).

22. Checkoway H, Williams TM. A hematology survey of workers at a styrene-butadiene synthetic rubber manufacturing plant. *Am Ind Hyg Assoc Ass J* 1982;43:164-169.

23. Citti L, Gervasi PG, Turchi G, Bellucci G, Bianchini R. The reaction of 3,4-epoxy-1-butene with deoxyguanosine and DNA in vitro: synthesis and characterization of the main adducts. *Carcinogenesis* 1984;5:47-52.

24. Cochrane JE, Craft TR, Cariello NF, Skopek TR. Mutagenicity and toxicity of 1,2-epoxybutane and diepoxybutene in human lymphoblasts. *Environ Mol Mutag* 1991;19:17.

25. Cochrane JE, Skopek TR. Mutagenicity of 1,3-butadiene and its epoxide metabolites in human TK6 cells and in splenic T cells isolated from exposed B6C3F1 mice. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:195-204.

26. Cochrane JE, Skopek TR. Mutagenicity of butadiene and its epoxide metabolites: I. Mutagenic potential of 1,2-epoxybutene, 1,2,3,4-diepoxybutane and 3,4-epoxy-1,2-butanediol in cultured human lymphocytes. *Carcinogenesis* 1994;15:713-717.

27. Cote IL, Bayard SP. Cancer risk assessment of 1,3-butadiene. *Environ Health Persp* 1990;86:149-153.

28. Crouch CN, Pullinger DM, Gaunt IF. Inhalation toxicity studies with 1,3-butadiene - 23 Month toxicity studies in rats. *Am Ind Hyg Assoc* 1979;40:796-802.

29. Csanady GA, Guengerich FP and Bond JA. Comparison of the biotransformation of 1,3-butadiene and its metabolite, butadiene monoepoxide, by hepatic and pulmonary tissues from humans, rats and mice. *Carcinogenesis* 1992;13:1143-1153.

30. Cunningham MJ, Choy WN, Arce GT, et al. In vivo sister chromatid exchange and micronucleus induction studies with 1,3-butadiene in B6C3F_1 mice and Sprague-Dawley rats. *Mutagenesis* 1986;1:449-452.

31. Dankovic DA, Smith RJ, Stayner LT, Bailer AJ. Time-to-tumour risk assessment for 1,3-butadiene based on exposure of mice to low doses by inhalation. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:335-344.

32. Deutscher Ausschuss für Gefahrstoffe. TRK-Wert für 1,3-Butadien. *TRGS* 1992;102:37-41.

33. Deutschmann S, Laib RJ. Concentration-dependent depletion of non-protein sulfhydryl (NPSH) content in lung, heart and liver tissue of rats and mice after acute inhalation exposure to butadiene. *Toxicol Lett* 1989;45:175-183.

34. Downs TD, Crane MM, Kim KW. Mortality among workers at a butadiene facility. *Am J Ind Med* 1987;12:311-329.

35. Dutch Expert Committee for Occupational Standards. *Health-based recommended occupational exposure limits for 1,3-butadiene*. Ministry of Social Affairs and Employment, The Hague RA:1990:1-43 (5/90).

36. Eller PM, ed. *NIOSH Manual of Analytical Methods*, 3rd ed, suppl 2. Washington, DC: US Government Printing office, 1987:1024. (DHHS Publ. No. 84-100.)

37. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). *Special Report No. 1, 1,3-Butadiene*. ECETOC, 1993:1-111.

38. Fajen JM, Lunsford RA, Roberts DR. Industrial exposure to 1,3-butadiene in monomer, polymer and end-user industries. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:3-14.

39. Fajen JM, Roberts DR, Ungers LJ, Krishnan ER. Occupational exposure of workers to 1,3 butadiene. *Environ Health Persp* 1990;86:11-18.

40. Filser JG, Bolt HM. Inhalation pharmacokinetics based on gas uptake studies. VI. Comparative evaluation of ethylene oxide and butadiene monoxide as exhaled reactive metabolites of ethylene and 1,3-butadiene in rats. *Arch Toxicol* 1984;55:219-223.

41. Filser JG, Johanson G, Kessler W, et al. A pharmacokinetic model to describe toxicokinetic interactions between 1,3-butadiene and styrene in rats: predictions for human exposure. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:65-78.

42. Goodrow T, Reynolds S, Maronpot R, Anderson M. Activation of K-ras by codon 13 mutations in C57BL/6 x C3HF_1 mouse tumours induced by exposure to 1,3-butadiene. *Cancer Res* 1990;50:4818-4823.

43. Guengerich FP, Kim D-H, Iwasaki M. Role of human cytochrome P450IIE1 in the oxidation of many low molecular weight cancer suspects. *Chem Res Toxicol* 1991;4:168-179.

44. Harman JN. Infrared absorption spectroscopy. In: Lodge JP, ed. *Methods of Air Sampling and Analysis*, 3rd ed. Chelsea, MI: Lewis Publisher, 1987:78-86.

45. Henderson RF, Bechtold WE, Sabourin PJ, Maples KR, Dahl AR. Species differences in the metabolism of 1,3-butadiene in vivo. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:57-64.

46. Hendricks WD, Shultz GR. A sampling and analytical method for monitoring low ppm air concentrations of 1,3-butadiene. *Appl Ind Hyg* 1986;1:186-190.

47. HSE (UK Health and Safety Executive). *Methods for the determination of hazardous substances (MDHS) 53 - pumped, molecular sieve*. London: HMSO, 1986.

48. HSE (UK Health and Safety Executive). *Methods for the determination of hazardous substances (MDHS) 63 - diffusive, molecular sieve*. London: HMSO, 1989.

49. Huff JE, Melnick RL, Solleveld HA, Haseman JK, Powers M, Miller RA. Multiple organ carcinogenicity of 1,3-butadiene in B6C3F_1 mice after 60 weeks of inhalation exposure. *Science* 1985;227:548-549.

50. IARC. Some Chemicals Used in Plastics and Elastomers. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol 39*, 1986:155-179.

51. IARC. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Suppl. 7*, 1987:1-440.

52. IARC. Monograph on Gasoline. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans Vol 45*. 1989:159-201.

53. IARC. Monograph on 1,3-Butadiene. *Monographs on the Evaluation of the Carcinogenic Risk to Humans.Vol 54*; 1992:237-285.

54. Irons RD, Oshimura M, Barrett JC. Chromosome aberrations in mouse bone marrow cells following in vivo exposure to 1,3-butadiene. *Carcinogenesis* 1987;8:1711-1714.

55. Irons RD, Smith CN, Stillman WS, Shah RS, Steinhagen WH, Leiderman LJ. Macrocytic-megaloblastic anemia in male B6C3F_1 mice following chronic exposure to 1,3-butadiene. *Toxicol Appl Pharmacol* 83;1986:95-100.

56. Jauhar PP, Henika PR, MacGregor JT, et al. 1,3-Butadiene: induction of micronucleated erythrocytes in the peripheral blood of B6C3F_1 mice exposed by inhalation for 13 weeks. *Mutation Res* 1988;209:171-176.

57. Jelitto B, Vangala RR, Laib RJ. Species differences in DNA damage by butadiene: role of diepoxybutane. *Arch Toxicol* 1989; Suppl. 13:246-249.

58. Kosaric N, Duvnjak Z, Farkas A, et al. Ethanol. In: Gerharz W, ed. *Ullmann's Encyclopedia of Industrial Chemistry, Vol A9* 5th rev.ed. . New York, NY: VHC Publisher, 1987:590.

59. Koivisto P, Neagu I, Kaltia S, Kostiainen R, Peltonen K. Alkylation of purine bases with 3,4-epoxy-1-butene, an reactive metabolite of 1,3-butadiene. In: Hemminki K, Dipple A, Shuker D, Kadlubar F, Segerback D, Bartsch H, eds. *DNA adducts: Identification and biological significance. IARC Scientific Publications* 1993;125:337-341.

60. Koivisto P, Peltonen K, Sorsa M. Analysis of 1,3-butadiene exposure using DNA adducts as a marker of internal dose. *EEMS 24th Annual meeting, Human biomonitoring in assessment of genetic risk*, Poznan, Poland, 1994.

61. Kraybill HF. Evaluation of public health aspects of carcinogenic/mutagenic biorefractories in drinking water. *Prev Med* 1980;9:212-218.

62. Kreiling R, Laib RJ, Bolt HM. Alkylation of nuclear proteins and DNA after exposure of rats and mice to [1,4-^{14}C]1,3-butadiene. *Toxicol Lett* 1986b;30:131-136.

63. Kreiling R, Laib RJ, Filser JG, Bolt HM. Inhalation pharmacokinetics of 1,2-epoxybutene-3 reveal species differences between rats and mice sensitive to butadiene-induced carcinogenesis. *Arch Toxicol* 1987;61:7-11.

64. Kreiling R, Laib RJ, Filser JG, Bolt HM. Species differences in butadiene metabolism between mice and rats evaluated by inhalation pharmacokinetics. *Arch Toxicol* 1986;58:235-238.

65. Krishnan ER, Corwin TK. Control of occupational exposure to 1,3-butadiene. *Proceedings of 80th Annual Meeting of Air Pollution Control Association, Vol 5.*, Air and Waste Management Association, Pittsburgh, PA, 1987:2-14. (Report 87-84A.14.)

66. Krishnan ER, Ungers LJ, Morelli-Schroth PA, Fajen JM. *Extent-of-exposure study: 1,3-butadiene monomer production industry*. National Institute for Occupational Safety and Health, Cincinnati, OH, 1987.

67. Kuney JH, ed. *Chemencyclopedia 91, Vol 9*. Washington, DC: American Chemical Society, 1990:50.

68. Laib RJ, Filser JG, Kreiling R, Vangala RR & Bolt HM. Inhalation pharmacokinetics of 1,3-butadiene and 1,2-epoxybutene-3 in rats and mice. *Environ Health Perspect* 1990;86:57-63.

69. Laib RJ, Tucholski M, Filser JG, Csanady GA. Pharmacokinetic interaction between 1,3-butadiene and styrene in Sprague-Dawley rats. *Arch Toxicol* 1992;66:310-314.

70. Lawley PD, Brooks P. Interstrand cross-linking of DNA by difunctional alkylating agents. *J Med Biol* 1967;25:143-160.

71. Legator MS, Au WW, Ammenheuser M, Ward JB Jr. Elevated somatic cell mutant frequencies and altered DNA repair responses in nonsmoking workers exposed to 1,3-butadiene. In: Sorsa M, Peltonen K, Vainio H and Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 127;1993:253-263.

72. Leiderman LJ, Stillman WS, Shah RS, Steinhagen WH, Irons RD. Altered hematopoietic stem cell development in male B6C3F$_1$ mice following exposure to 1,3-butadiene. *Exp Mol Pathol* 1986;44:50-56.

73. Leuratti C, Jones NJ, Marafante E, Peltonen K, Kostiainen R, Waters R. Biomonitoring of exposure to 1,3-butadiene: detection by high-performance liquid chromatography and ^{32}P-postlabelling of an adenine adduct formed by diepoxybutane. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:143-150.

74. Lundberg P. Scientific basis for Swedish occupational standards VII. *Arbete och Hälsa* 1986;35:22-29.

75. Löfroth G, Burton RM, Forehand I, et al. Characterization of environmental tobacco smoke. *Environ Sci Technol* 1989;23:610-614.

76. Matanoski G, Francis M, Correa-Villasenor A, et al. Cancer epidemiology among styrene-butadiene rubber workers. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:363-374.

77. Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Health Perspect* 1990;86:107-117.

78. Matanoski GM, Schwartz L. Mortality of workers in styrene-butadiene polymer production. *J Occup Med* 1987;29:675-680.

79. McMichael AJ, Spirtas R, Gamble JF, Tousey PM. Mortality among rubber workers: relationship to specific jobs. *J Occup Med* 1976;18:178-185.

80. de Meester C, Poncelet F, Roberfroid M, Mercier M. The mutagenicity of butadiene towards Salmonella typhimurium. *Toxicol Lett* 1980;6:125-130.

81. Meinhardt TJ, Lemen RA, Crandall MS, Young RJ. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. Mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand J Work Environ Health* 1982;8:250-259.

82. Meinhardt TJ, Young RJ, Hartle RW. Epidemiologic investigations of styrene-butadiene rubber production and reinforced plastic production. *Scand J Work Environ Health* 1978;4, Suppl 2:240-246.

83. Melnick RL, Huff JE. 1,3-Butadiene induces cancer in experimental animals at all concentration from 6.25 to 8000 parts per million. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 127;1993:309-322.

84. Melnick RL, Huff J, Chou BJ, Miller RA. Carcinogenicity of 1,3-butadiene in C57BL/6 x C3HF^1 mice at low exposure concentrations. *Cancer Res* 1990;50:6592-6599.

85. Morrissey RE, Schwetz BA, Hackett PL, et al. Overview in reproductive and developmental toxicity studies of 1,3-butadiene in rodents. *Environ Health Perspect* 1990;86:79-84.

86. Morrow NL. The industrial production and use of 1,3-butadiene. *Environ Health Persp* 1990;86:7-8.

87. National Toxicology Program (NTP). *Toxicology and Carcinogenesis Studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (Inhalation Studies)*. National Institute of Environmental Health Sciences, Research Triangle Park, NC, 1984. (NTP TR No. 288. NIH Publication No. 84-2544.)

88. Neligan RE. Hydrocarbons in Los Angeles atmosphere. A comparison between the hydrocarbons in automobile exhaust and those found in Los Angeles atmosphere. *Arch Environ Health* 1962;5:581-591.

89. NIOSH (US National Institute for Occupaitonal Safety and Health. *Manual of analytical methods*, 3rd ed. 2nd supp, US DHHS, Cincinnati, OH:1987.

90. Osterman-Golkar SM, Bond JA, Ward JBLegator MS. Use of haemoglobin adducts for biomonitoring exposure to 1,3-butadiene. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:127-137.

91. Owen PE, Glaister JR. Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. *Env Health Persp* 1990;86:19-25.

92. Owen PE, Glaister JR, Gaunt IF, Pullinger DH. Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. *Am Ind Hyg Assoc J* 1987;48:407-413.

93. Peltonen K, Koivisto P, Neagu I, Kostiainen R, Kilpeläinen I, Sorsa M. Estimating internal dose of 1,3-butadiene: preliminary date on use of modified purine bases as markers of exposure. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:309-322.

94. Recio L, Bond JA, Pluta LJ, Sisk SC. Use of transgenic mice for assessing the mutagenicity of 1,3-butadiene in vivo. In: Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. Butadiene and Styrene: Assessment of Health Hazards. *IARC Scientific Publications* 1993;127:235-243.

95. Ristau C, Deutschmann S, Laib RJ, Ottenwälder H. Detection of diepoxybutane-induced DNA-DNA closslinks by cesium trifluoracetate (CsTFA) density-gradient centrifugation. *Arch Toxicol* 1990;64:343-344.

96. Saltzman BE, Harman JN. Direct reading colorimetric indicators. In: Lodge JP, ed, *Methods of Air Sampling and Analysis*, 3rd ed. Chelsea, MI: Lewis Publisher, 1989:171-187.

97. Sasiadek M, Järventaus H, Sorsa M. Sister-chromatid exchanges induced by 1,3-butadiene and its epoxides in CHO cells. *Mutation Res* 1991;263:47-50.

98. Sasiadek M, Norppa H, Sorsa M. 1,3-Butadiene and its epoxides induce sister-chromatid exchanges in human lymphocytes in vitro. *Mutation Res* 261;1991:117-121.

99. Sax NI, Lewis RJ. *Hawleys Condensed Chemical Dictionary*, 11th ed. New York, NY: Van Nostrand Reinhold, 1987:177.

100. Schmidt U, Loeser E. Species differences in the formation of butadiene monoxide from 1,3-butadiene. *Arch Toxicol* 1985;57:222-225.

101. Shugaev BB. Concentrations of hydrocarbons in tissues as a measure of toxicity. *Arch Environ Health* 1969;18:878-882.

102. Siddigi AA, Worley FL. Urban and industrial air pollution in Houston, Texas. I. Hydrocarbons. *Atmosph Environ* 1977;11:131-143.

103. Sisk SC, Pluta LJ, Bond JA, Recio L. Molecular analysis of lacI mutants from bone marrow of B6C3F1 transgenic mice following inhalation exposure to 1,3-butadiene. *Carcinogenesis* 1994;15:471-477.

104. Sorsa M, Autio K, Demopoulos NA, et al. Human cytogenetic biomonitoring of occupational exposure to 1,3-butadiene. *Mutation Res* 1994;309:321-326.

105. Startin JR, Gilbert J. Single ion monitoring of butadiene in plastics and food by coupled mass spectrometry-automatic headspace gas chromatography. *J Chrom* 1984;294:427-430.

106. Swedish Work Environment Fund. *Development and evaluation of biological and chemical methods for exposue assessment of 1,3-butadiene*. FIOH, Helsinki Finland and Univ Stockholm, Stockholm, Sweden, 1991. (Final report 1991-03-31.)

107. Tates AD, van Dam FJ, de Zwart FA, van Teylingen CMM, Natarajan AT. Use of a cloning assay with high cloning efficiency to detect induction of 6-thioguanine resistant lymphocytes in spleen of adult mice following in vivo inhalation exposure to 1,3-butadiene. *Mutation Res*, 1994, in press.

108. Thurmond LM, Lauer LD, House RV, et al. Effect of short-term inhalation exposure to 1,3-butadiene on murine immune functions. *Toxicol Appl Pharmacol* 1986;86:170-179.

109. Tice RR, Boucher R, Luke CA, Shelby MD. Comparative cytogenetic analysis of bone marrow damage induced in male B6C3F$_1$ mice by multiple exposures to gaseous 1,3-butadiene. *Environ Mutagen* 1987;9:235-250.

110. Työministeriö. HTP-arvot 1993. *Turvallisuustiedote* 1993;25:1-44. (In Finnish.)

111. US Environmental Protection Agency. *Cancer risk from Outdoor Exposure to Air Toxics, vol I*. US Environmental Protection Agency, Research Triangle Park, NY. 1990: ES-1-4-10. Final Report (EPA-450/1-90-004a).

112. US Occupational Safety and Health Administration. *Occupational Exposure to 1,3-Butadiene*. US Occupational Safety and Health Administration: 1990. (Fed Regist 55, 32736-32826.)

113. Verschueren K. *Handbook of Environmental Data on Organic Chemicals*, 2nd ed. New York, NY: Van Nostrand Reinhold, 1983:295-297.

114. Victorin K, Busk L, Cederberg H & Magnusson J. Genotoxic activity of 1,3-butadiene and nitrogen dioxide and their photochemical reaction products in Drosphila and in the mouse bone marrow micronucleus assay. *Mutation Res* 1990;228:203-209.

115. Weast RC, Astle MJ, Beyer WH, eds. *CRC Handbook of Chemistry and Physics*, 69th ed. Boca Raton, FL: CRC Press, 1989: C-161, D-212.

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Appendix 1.

Permitted or recommended maximum levels of 1,3-butadiene in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	10	22		1988	1
Finland	50	110		1993	2
Iceland	10 20	20 40	C STV	1989	3
Netherlands	50	110		1994	4
Norway	1	2.2	K	1989	5
Sweden	0.5 5	1 10	C STV	1993	6
USA (ACGIH)	2	4.4	A2	1994-95	7
(NIOSH)			lowest feasible value, X	1990-91	8

A2: suspected human carcinogen
C: regarded as carcinogen
K: possible carcinogen
STV: short term value
X: carcinogen with no further categorization

References

1. *Grænsværdier for stoffer og materialer.* Køpenhavn: Arbejdstilsynet,1988 (Anvisning Nr.3.1.0.2) .
2. *HTP-värden 1993.* Tammerfors: Arbetsministeriet, 1993 (Säkerhetsmeddelande 25). ISBN 951-47-8343-3.
3. *Mengunarmörk og adgerdir til ad draga úr mengun.* Skrá yfir mengunarmörk. Reykjavik: Vinnuefürlit Rikisins,1989.
4. *De Nationale MAC-lijst 1994.* Den Haag: 1994 (Arbeidsinspectie P 145). ISBN 90-399-0600-9.
5. *Administrative normer for forurensinger i arbeitsatmosfaere.* Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for arbeidstilsynet, 1989 (Bestillingsnr. 361).
6. *Hygieniska gränsvärden..* Stockholm: Arbetarskyddsstyrelsen, 1993 (AFS 1993:9). ISBN 91-7930-046-4.
7. *Threshold Limit Values and biological exposure indices for 1994-95.* Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists,1994. ISBN 1-882417-06-2.
8. Rules and Regulations. *Federal Register Vol.54.* Washington: US Government, 1990:2329-2984.

CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
2-Diethylaminoethanol	Arbete och Hälsa 1994:25*N
Diethylamine, Diethylenetriamine, Dimethylamine & Ethylenediamine	Arbete och Hälsa 1994:23*
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6
Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*
Ethylenediamine	Arbete och Hälsa 1994:23*
Ethylene glycol	Arbete och Hälsa 1980:14