European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

Existing Substances

European Union Risk Assessment Report

CAS No: 106-99-0

EINECS No: 203-450-8

1,3-butadiene

1st Priority List

Volume: 20

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European Union Risk Assessment Report

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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

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RISK ASSESSMENT

Final Report, 2002

United Kingdom

This document has been prepared by the UK rapporteur on behalf of the European Union. The scientific work on the environmental part was prepared by the Building Research Establishment (BRE) Ltd, under contract to the rapporteur.

Contact point

Human Health: Health & Safety Executive
Industrial Chemicals Unit
Magdalen House, Stanley Precinct
Bootle, Merseyside, L20 3QZ
United Kingdom

Environment: Environment Agency
Chemicals Assessment Section
Ecotoxicology & Hazardous Substances National Centre
Isis House, Howbery Park
Wallingford, Oxfordshire, OX10 8B
United Kingdom

Date of Last Literature Search:	**2000**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2002**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

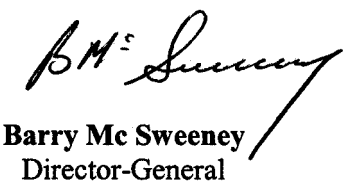
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS no: 106-99-0
EINECS no: 203-450-8
IUPAC name: 1,3-Butadiene

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

There are no concerns for any effects on the environment.

Human health

Human health (toxicity)

Workers

Conclusion (iiib) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iiib) is reached for manufacture of butadiene monomer and for production of polymers, in view of the carcinogenic and genotoxic nature of 1,3-butadiene.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is reached for all occupational exposure scenarios for all other endpoints of potential concern.

Consumers

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Estimations indicate that consumer exposure is very low. Although thresholds cannot be reliably identified, the risk of mutagenicity and/or carcinogenicity is considered to be very low.

Humans exposured via the environment

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low.

This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Conclusion (iiia) is reached for all exposure scenarios because exposures are very low and although thresholds cannot be reliably identified, the risk of mutagenicity and/or carcinogenicity is considered to be very low.

Combined exposure

Conclusion (iiib) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.

Accurate predictions of the contributions made by individual sources to combined exposure and dose are always imprecise. However, such exposures could occur, comprising the workplace, smoking, the local environment and consumer exposures from polymeric materials, with intermittent exposures derived from filling petrol tanks. In view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. In relation to these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The risks to human health under current environmental exposure levels are uncertain. Setting aside exposure from smoking, the combined exposure is dominated by the occupational exposure. Therefore, the conclusions reached for the occupational setting will apply.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is reached because there are no risks from physicochemical properties arising from the use of 1,3-butadiene

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Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

FIGURES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS no:	106-99-0
EINECS no:	203-450-8
IUPAC name:	1,3-Butadiene
Molecular formula:	C_4H_6
Structural formula:	CH_2=CH-CH=CH_2
Molecular weight:	54.092
Synonyms:	Alpha, gamma-butadiene
	Biethylene
	Bietileno
	Bivinile
	Bivinyl
	Bivinylerythrene
	Butadien
	Butadiene
	Butadiene-1,3
	Buta-1,3-diene
	Diethylene
	Divinilo
	Divinyl
	Eritrene
	Erythrene
	Pyrrolylene
	Trans-butadiene
	Viniletilene
	Viniletileno
	Vinylethylen
	Vinylethylene

1.2 PURITY/IMPURITIES, ADDITIVES

1.2.1 Purity

The purities quoted in the IUCLID data set were all $\geq$ 99% w/w. All but one were quoted to be $\geq$ 99.5% with an upper limit of 99.9%.

The significant impurities (where stated) comprised some or all of the following:

Butenes	0.4% w/w max
1,2-butadiene (CAS No: 590-19-2)	20 ppm
C5s	0.1 % w/w max.
Butadiene dimer	0.05% w/w max.
4-vinylcyclohexene (CAS No: 100-40-3)	0.001 - 0.008% w/w
Peroxides (measured as H_2O_2)	5 ppm
Acetylene (CAS No. 74-86-2)	25 ppm max.

Sulphur	2 ppm
Non-volatile residues (e.g. trimer)	500 ppm max.
Carbinol (as acetaldehyde)	25 ppm max.
Propadiene (CAS No. 463-49-0)	10 ppm max.
Water	trace

The impurities present may vary according to the plant and production method. Other constituents are mainly butenes and saturated hydrocarbons (analysis was by gas chromatography using external standards).

1.2.2 Additives

The stated additive present was:

4-tert-butylpyrocatechol (CAS No: 98-29-3)	0.01 - 0.02% w/w

4-tert-butylpyrocatechol is an inhibitor for 1,3-butadiene, preventing peroxide formation and spontaneous exothermic self-polymerisation (see Sections 1.3.11 and 1.3.15).

1.3 PHYSICOCHEMICAL PROPERTIES

1.3.1 Physical state (at n.t.p.)

1,3-Butadiene is a colourless gas with a mild aromatic odour. The odour threshold limit is between 1.0 and 4.0 mg/m^3.

1.3.2 Melting point

The melting point of 1,3-butadiene has been reported as -108.902°C (Kirk-Othmer 4th Edition, 1991) to -108.966°C (Merck Index 11th Edition, 1989). Values of -108.9°C (CRC Handbook 75th Edition, 1994; Howard, 1990; BASF safety data sheet) and -109°C (Huls safety data sheet) are probably rounded values. None of the handbook values could be traced back to their original source.

The figures quoted in the consolidated IUCLID entry accurately reflect the literature values.

1.3.3 Boiling point

The boiling point of 1,3-butadiene has been reported as between -4.4 and -4.9°C at 101.325 kPa. Values range from -4.411°C (Kirk-Othmer, 1991), -4.5°C (CRC Handbook 75th Edition, 1994; Howard, 1990; Huls safety data sheet) to -4.9°C (BASF safety data sheet). None of the handbook values could be traced back to their original source. However, these values are consistent with what would be expected from vapour pressure studies.

The figures quoted in the consolidated IUCLID entry accurately reflect the measured literature values.

1.3.4 Density

The relative density (D^{20}_4) of 1,3-butadiene is quoted as 0.62 (BASF, Huls, Aver safety data sheets) and 0.6211 (consolidated IUCLID entry). A density of 0.65 g cm^{-3} is quoted at -6°C (Merck Index 11th Edition, 1989 and consolidated IUCLID entry).

1.3.5 Vapour pressure

Values of 244.7 kPa at 21°C and 240.0 kPa at 20°C are quoted in the consolidated IUCLID entry (not to GLP). These values are from the CRC handbook (1988), which cites the DIPPR, American Institute of Chemical Engineers (1987) as an evaluated source of data, although the original reference is not quoted. A further value of 856 mm Hg at -1.5°C (114.1 kPa) is reported in the literature which is quoted from Physical Sciences Data Vol. 17 (Boublik et al., 1984). The original reference is to Heisig (1933), who measured vapour pressure using a mercury manometer.

When log P (kPa) vs 1/T (K) for both the above sets of data are plotted (**Fig. 1**) there is very close agreement. A value of 101.3 kPa is obtained at a temperature of approximately -6°C, which is in close agreement with the quoted boiling point. The vapour concentration could not be calculated at the flashpoint temperature since the vapour pressure was only reported to 66°C and so it was not possible to validate the lower explosive limit in this way.

Since the substance is a gas and the actual vapour pressure exceeds normal atmospheric pressure, in practice the gas will expand until it reaches normal atmospheric pressure. For risk assessment purposes the effective practical vapour pressure will therefore be 101.3 kPa at 20°C.

For environmental modelling purposes, the Henry's Law constant is more important than the vapour pressure of the pure gas. The constant was derived using the ratio of atmospheric pressure (101.3 kPa) to water solubility as explained in Section 3.1.2.2.1.

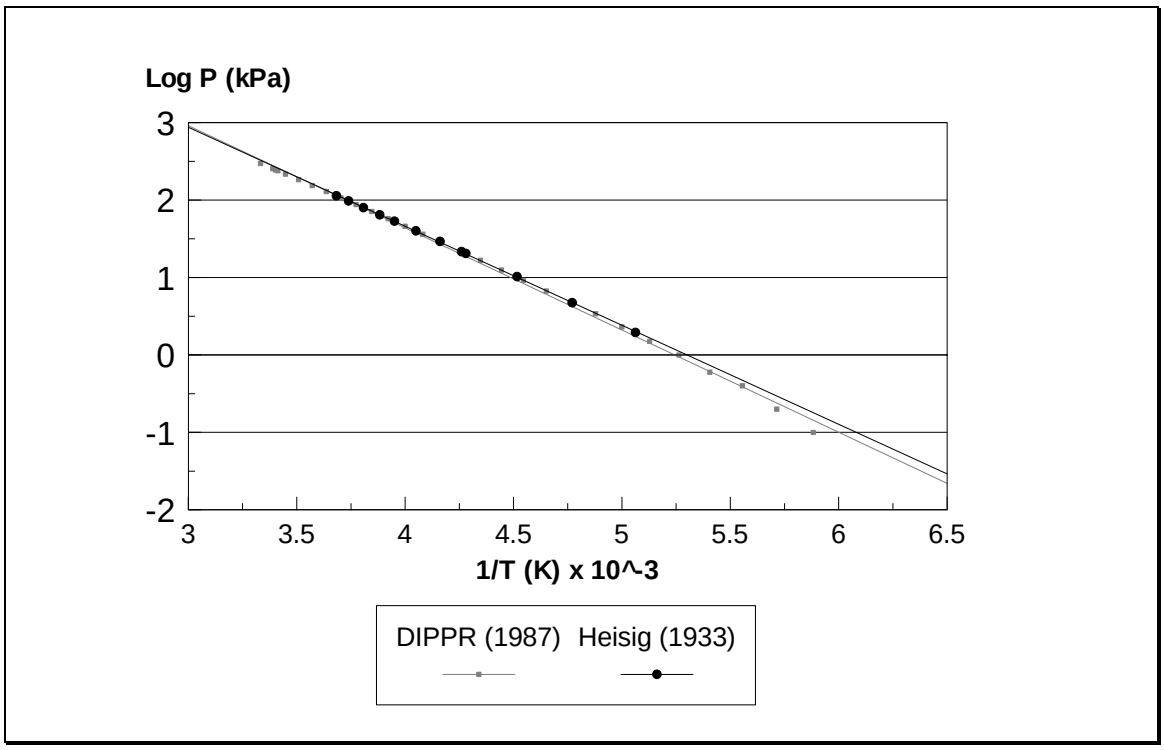

Figure 1 Vapour pressure data for 1,3-butadiene

1.3.6 Solubility

The water solubility of 1,3-butadiene is quoted as ranging from 0.5 g/l to 0.735 g/l at 20°C (consolidated IUCLID entry). No data were submitted to support the value of 0.5 g/l.

The value of 0.735 g/l is taken from McAuliffe (1966) who measured the water solubility of 65 hydrocarbons using gas-liquid chromatography. Gaseous hydrocarbon at atmospheric pressure was shaken vigorously with distilled water for 5 to 10 minutes, then left to stand for 30 minutes before analysis. Aliquots of equilibrated solution were first passed through a fractionator to separate dissolved hydrocarbon from water, then passed through the chromatographic column:

Column:	12' · 0.25" 25% SE 30 gum rubber on 30-60 mesh firebrick
Carrier gas:	Helium
Flow rate:	65 ml/min
Column temperature:	60, 100 and 125°C
Detector:	Flame ionisation detector (limit of detection 0.1 ppm)
Standard:	External, 1,3-butadiene

The purity of 1,3-butadiene used was not reported, although hydrocarbons were used as received. The pH of the solutions was not reported. The method used appears satisfactory, although current Annex V guidelines do not specify a method for volatile substances.

1.3.7 Partition coefficient (Log P_{ow})

Log P	Reference
1.85	Company data unpublished (Huls, 1989)
1.902 (calculated)	Company data unpublished (Huls, 1989)
2.22 (calculated)	Banerjee and Howard (1988)*
1.99	Hansch and Leo (1979)*
1.99 ± 0.1	Sangster (1989)

*Quoted in consolidated IUCLID entry.

The partition coefficient has been assessed both experimentally and theoretically by a number of authors and the values obtained are in reasonably close agreement.

The Huls calculated value was obtained using the Medchem program, as outlined by Hansch and Leo (1979), which has been validated for pure, non-ionic substances (Huls, 1989, unpublished). Banerjee and Howard (1988) utilised the UNIFAC-derived activity coefficients, to which a simple correction regression was applied. The method was validated using experimental data from Hansch and Leo (1979), which showed that compounds on the extreme ends of the K_{ow} scale were most sensitive to errors in estimation. Pending further debate, the measured value of Hansch and Leo (1979) has been used for environmental modelling purposes.

1.3.8 Flash point

The flash point has been reported as -76°C (closed cup) and -85°C (closed cup, DIN 51755) (Huls, 1994; Sax and Lewis, 1987 respectively). Both values were quoted in the consolidated IUCLID entry.

DIN 51755 refers to the use of Abel Pensky apparatus, which is one of the acceptable methods specified in Annex V. Since the original test reports could not be located it is difficult to interpret the difference between these results. However, both values are well below the cut-off point for classification as extremely flammable.

1.3.9 Autoignition

Autoignition occurs between 415°C and 420°C (Auer, 1989; Hommel, 1987). The BASF safety data sheet also quotes 415°C, together with reference to DIN 51794 (one of the test methods specified in Annex V).

1.3.10 Explosivity

Explosive limits in air are in the following ranges:

Lower explosive concentration (% by volume)	Upper explosive concentration (% by volume)	Reference
1.4	16.3	BASF safety data sheet
2	11.5	Lange (1992)
2	12	National Fire Protection Association (1978)

1.3.11 Oxidising properties

Testing for this property is not applicable due to the physical nature of this substance. Pure 1,3-butadiene does not contain functional groups capable of producing an oxidising effect. However, in general olefins with allylic hydrocarbons are prone to peroxide formation, and 1,3-butadiene will readily form butadiene polyperoxide, $(C_4H_6O_2)_x$, in the presence of oxygen. At lower temperatures this is an alternating copolymer of butadiene and oxygen, although at elevated temperatures (>50°C) the proportion of oxygen decreases. Sometimes referred to as "popcorn" polymer, butadiene polyperoxide is nearly insoluble in liquefied butadiene and separates out to form "globules" which settle to form a viscous residue. Butadiene polyperoxide is prone to self-heating and above a critical radius will result in explosive decomposition (Alexander, 1959). Subsequently an inhibitor (4-tert-butylpyrocatechol) is incorporated into commercial products.

1.3.12 Granulometry

Not applicable - the substance is a gas.

1.3.13 Surface tension

No value was reported in the IUCLID entry. Information on this property was available in the literature (Yaws et al., 1991) which quotes a surface tension of 12.49 mN/m at 25°C for the pure liquefied gas. This value is extrapolated from a measured value at -39.8°C of 20.7 mN/m. No experimental detail was given in the reference. The surface tension of liquefied butadiene is extremely low (e.g. compared to water which has a surface tension of 72.75 mN/m at 20°C).

No value could be found for surface tension of an aqueous solution of 1,3-butadiene. As the solubility is greater than 1 mg/l, strictly this is part of the base set requirement, although its relevance is debatable given the volatility of 1,3-butadiene.

1.3.14 Other physicochemical properties

The vapour density of 1,3-butadiene is quoted as 1.9 at 20°C (air = 1), although it is not stated whether this is a measured or calculated value (Kirk-Othmer, 1991).

This can be validated assuming the molar volume of an ideal gas at 25°C is $2.445 \cdot 10^{-2}$ m^3:

$$\frac{RMM\,(g/mol)}{V_{25}\,(m^3/mol)} = \frac{54.092}{2.445x10^{-2}} \sim 220 g/m^3 \text{ at } 25°C \text{ and } 101.325 \text{ kPa}$$

The density of air at 27°C is 1,160 g/m^3:

1,160 : 2,200

Equivalent to:

1 : 1.9

A conversion factor of 1 ppm to 2.21 mg/m^3 (at 25°C, 101.325 kPa) has been used.

1,3-butadiene is a volatile liquefied gas. Spillage of liquefied gas directly on skin will result in volatilisation which can cause freeze burns and frostbite.

1.3.15 Hazardous chemical reactions (particularly with water)

1,3-Butadiene polymerises readily in the presence of oxygen or at elevated temperatures. Polymerisation is exothermic; if this occurs in a container there is the possibility of violent rupture of the container. 1,3-Butadiene can also dimerise to 4-vinylcyclohex-1-ene (Heisig, 1933 - refers to Lebedev and Skrawonskaja, 1912).

In contact with air, 1,3-butadiene can form explosive polymeric peroxides (see Section 1.3.13 above) and 2-propenal (acrolein, CAS no: 107-02-8), which can be exploded by mild heat or shock. Solid butadiene absorbs enough oxygen at sub-atmospheric pressures to make it explode violently when heated to just above its melting point (Hendry et al., 1968).

Technical grades of 1,3-butadiene incorporate 4-tert-butylpyrocatechol as a free radical inhibitor/antioxidant. However, it does not inhibit vapour-phase reactions and a maximum storage time for inhibited product of 12 months is advocated.

1.3.16 Summary of physicochemical properties

The physicochemical properties of 1,3-butadiene are summarised in **Table 1.1**.

Table 1.1 Physicochemical properties

Properties	Value
Molecular weight	54.09
Melting point	-108.9°C
Boiling point	-4.4°C
Relative density	0.62
Vapour pressure	240.0 kPa at 20°C
Water solubility	0.735 g/l at 20°C
Log octanol/water partition coefficient	1.99
Flammability	Flash Point: -85°C
Autoflammability	415°C
Explosive properties	Lower explosive limit: 1.4 % v/v Upper explosive limit: 16.3 % v/v
Vapour density	1.9
Surface tension	20.7 mN/m at -39.8°C
Conversion factor	1 ppm = 2.21mg/m^{3}at 25°C

1.4 CLASSIFICATION

The classification and labelling of 1,3-butadiene is listed in Annex 1 to Directive 67/548/EEC (28th Adaptation to Technical Progress; January 2001), as follows:[4]

Classification: F+; R12
Carc. Cat. 1: R45
Muta. Cat. 2; R46

Labelling: F+; T
R: 45-46-12
S: 53-45

R12 states: *Extremely flammable*

R45 states: *May cause cancer*

Category 1 is for substances known to be carcinogenic to humans. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

[4] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to the technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 225, 21.8.2001, p.1).

R46 states: *May cause heritable genetic damage*

Category 2 is for substances which should be regarded as if they are mutagenic to man. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of:
(a) appropriate animal studies;
(b) other relevant information.

S53 states: *Avoid exposure – Obtain special instructions before use*

S45 states: *In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)*

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION METHODS

The most widely used method of 1,3-butadiene production is recovery from a mixed by-product C_4-hydrocarbon stream during the production of ethylene. The process can use a variety of hydrocarbon feedstocks, the heavier fractions generally giving a higher 1,3-butadiene yield/amount of ethylene produced (Miller, 1978).

In the production process, the hydrocarbon feedstock is pre-heated and cracked in the presence of steam. The product then passes to a pyrolysis/quench system and from there the raw gas is compressed and CO_2 and H_2S are removed. The product then passes through a series of fractionators and a mixed C_4-hydrocarbon stream is obtained. 1,3-Butadiene cannot normally be obtained from the mixed C_4-stream by simple distillation and so an extractive distillation process is often used. In this process, a polar solvent (e.g. furfural, acetonitrile, cuprous ammonium acetate, dimethylformamide, a furfural-methoxypropionitrile system, dimethylacetamide or N-methylpyrrolidone) is added in order to change the relative volatilities of the components of the mixture (Miller, 1978; Peterson et al., 1980; IARC, 1986).

1,3-Butadiene can also be made directly, by dehydrogenation or oxidative dehydrogenation of a C4 fraction from the crude distillation, using chromium-alumina as a catalyst.

In Europe, it is thought that all production of 1,3-butadiene is by the steam cracking of hydrocarbons (Slooff et al., 1994).

2.2 PRODUCTION VOLUMES

There are 22 EU producers of 1,3-butadiene reported in IUCLID. The total production capacity reported is between 1,202,000 and 4,960,000 tonnes/year.

Western European production of 1,3-butadiene has been reported elsewhere and was thought to be 1,778,000 tonnes/year in 1991, 1,853,000 tonnes/year in 1992, and 1,752,000 tonnes/year in 1993 (ECN, 1994). More recent data shows that Western European 1,3-butadiene production was 1,742,000 tonnes/year in 1993 and 1,892,000 tonnes in 1994 (ECN, 1995). Clearly the figure of 1,892,000 tonnes in 1994 is consistent with the range of production figures given in IUCLID.

There are currently two companies reported in IUCLID, which import 1,3-butadiene into the EU. The amounts imported are thought to be small compared with the quantities produced in the EU and so the EU consumption figure will be taken to be 1,892,000 tonnes/year.

2.3 USES

1,3-Butadiene is used in closed systems with a non-dispersive pattern of use. It is used as an intermediate for polymerisation and copolymerisation.

The major uses of 1,3-butadiene world-wide are in the manufacture of synthetic rubber such as styrene-butadiene rubber (SBR) and polybutadiene rubber, thermoplastic resins such as acrylonitrile-butadiene-styrene (ABS), and styrene-butadiene latex. It is also used as a chemical intermediate in the production of neoprene for automotive and industrial rubber goods, in the production of methylmethacrylate-butadiene-styrene (MBS) polymer, which is used as a PVC

reinforcing agent, and for producing adiponitrile, a nylon precursor. The most widespread use of 1,3-butadiene is in the manufacture of SBR and styrene-butadiene latex, the former being used in the production of synthetic rubber products and the latter in paints, carpet backing and paper coating. The other major uses of 1,3-butadiene are in the manufacture of polybutadiene rubber for use in tyres, tyre products and car body sealants and ABS for use in the production of oil resistant gaskets, business equipment and automotive parts. In the UK, transportation of 1,3-butadiene is mainly by road tanker or ship. In mainland Europe it is usually carried by pipeline.

The EU reflects this world-wide use of 1,3-butadiene. Within the EU there are approximately 18 major companies using 1,3-butadiene as feedstock in the production of SBR, styrene-butadiene latex, ABS and other related products such as polybutadiene. These products are sold to a large number of end-user companies.

Table 2.1 summarises the most important uses of 1,3-butadiene world-wide in 1981 (Slooff et al., 1994).

Table 2.1 Applications of 1,3-butadiene world-wide in 1981

Application	Quantity of 1,3-butadiene used (tonnes/year)	Percentage of total use
Styrene-butadiene rubber/latex	2,705,000	56
Polybutadiene rubber	1,080,000	22
Polychloroprene rubber	290,000	6
Nitrile rubber/latex	200,000	4
Acrylonitrile-butadiene-styrene resin	200,000	4
Hexamethylenediamine (used for nylon 6,6)	205,000	4
Other (e.g. 1,4-hexadiene or sulpholane)	180,000	4
Total	4,860,000	100

Assuming that the percentage use figures in **Table 2.1** also apply to the EU, the amounts of 1,3-butadiene used within the EU for the various end-uses can be estimated. The results, assuming a total EU usage of 1,892,000 tonnes, are shown in **Table 2.2.**

Table 2.2 Estimated amounts of 1,3-butadiene used within the EU

Application	Percentage of total*	Estimated amount of 1,3-butadiene used (tonnes/year)
Styrene-butadiene rubber/latex	56	1,059,520
Polybutadiene rubber	22	416,240
Chloroprene rubber	6	113,520
Nitrile-butadiene rubber/latex	4	75,680
Acrylonitrile-butadiene-styrene resin	4	75,680
Hexamethylenediamine	4	75,680
Other uses	4	75,680
Total	100	1,892,000

Note: * percentage of total taken from Slooff et al. (1994) for worldwide use in 1981. It will be assumed that these figures apply to the current situation in the EU.

Table 2.3 shows the largest production sites of several of these compounds and the total capacity in the European Union. These figures are from the Worldwide Rubber Statistics 1994 (IISRP, 1994) and are reasonably consistent with the figures estimated in **Table 2.2**. **Table 2.4** gives a further breakdown of the production capacities within individual member states.

Table 2.3 Largest users of 1,3-butadiene in the EU (IISRP, 1994)

Product	Largest plant capacity (tonnes/year)	Total EU capacity (tonnes/year)
Styrene-butadiene solid rubber (emulsion process)	160,000	779,000
Styrene-butadiene solid rubber (solution process)	50,000	160,000
Styrene-butadiene latex	35,000	188,000
XSBR-PSBR latex	55,000	684,900
Polybutadiene rubber	80,000	456,000c
Polychloroprene rubber*	60,000	133,000
Nitrile solid rubber	35,000	124,000
Nitrile-latex rubber	15,000a	52,000
Acrylonitrile-butadiene-styrene resins	50,000b	/

Notes: a - Estimated capacity - multipurpose plants.
b - No information available in IISRP (1994). This is largest UK capacity (Chem-Intel, 1991).
c - personal communication.
XSBR - Carboxylated styrene-butadiene rubber.
PSBR - Pyridine (vinyl)-styrene-butadiene rubber.
* - emulsion polymerised polychloroprene, both in solid and latex form (reported as dry solid content).

Table 2.4 Synthetic rubber production capacities within the EU (IISRP, 1994)

Country	SBR Solid	SBR Latex	XSBR/ PSBR	BR	NBR solid	NBR latex	Chloroprene
Austria	-	-	6,000	-	-	-	-
Belgium	20,000	-	15,000	20,000	-	-	-
Finland	-	-	89,400	-	-	-	-
France	139,000	48,000	87,000	155,000	44,000	2,000	40,000
Italy	175,000	20,000	65,000	80,000	30,000	10,000	-
Netherlands	150,000	23,000	75,000	-	-	15,000	-
Spain	50,000	-	21,000	20,000	-	-	-
Sweden	-	-	32,000	-	-	-	-
United Kingdom	150,000	35,000	92,500	80,000[a]	10,000	5,000	33,000
Germany	255,000	62,000	202,000	101,000	40,000	20,000	60,000
Total	939,000	188,000	684,900	456,000	124,000	52,000	133,000

Note: [a]personal communication.
SBR solid - emulsion or solution polymerised copolymers of butadiene and styrene in bale or crumb form. Oil content is included but carbon black and other fillers are excluded.
SBR latex - emulsion polymerised styrene-butadiene latex with over 50% butadiene - reported as dry solid content.
XSBR - carboxylated styrene-butadiene rubber; PSBR - pyridine(vinyl)-styrene-butadiene rubber - reported as dry solid content.
BR - solution polymerised polybutadiene. The added oil content is included, but carbon black and other fillers are excluded.
CR - emulsion polymerised polychloroprene, both in solid and latex form - reported as dry solid content.
NBR solid - copolymers of butadiene and acrylonitrile (emulsion polymerised), including carboxylated polymers. Carbon black content is excluded.
NBR latex - copolymers of butadiene and acrylonitrile (emulsion polymerised), including carboxylated polymers - reported as dry solid content.

Estimates for the Western European consumption of various rubber products are also available (IISRP, 1994). These are shown in **Table 2.5**. It should be noted that these figures may include countries other than members of the EU.

Table 2.5 Estimated Western European consumption of synthetic rubber (IISRP, 1994)

Product	Estimated Consumption (tonnes/year)		
	1993	1994	1998
Styrene-butadiene rubber (solid)	542,000	551,000	596,000
Styrene-butadiene rubber (latex)	123,000	121,000	126,000
Carboxylated styrene-butadiene rubber	510,000	520,000	560,000
Polybutadiene rubber	265,000	270,000	292,000
Polychloroprene rubber	61,000	62,000	65,000
Nitrile-butadiene rubber (solid and latex)	80,000	81,000	87,000

2.3.1 Styrene-butadiene rubber (SBR) and styrene-butadiene latex

Styrene-butadiene copolymers can be produced by either solution (monomers dissolved in solvent) or emulsion (monomers dispersed in water) polymerisation. Depending on the relative feed composition of 1,3-butadiene to styrene and the extent of drying in the process, styrene-butadiene copolymers can be prepared as either a solid or an emulsion (latex). Styrene-butadiene polymers with >45% 1,3-butadiene content have rubber-like properties and are known as styrene-butadiene rubber (SBR). A typical ratio of 1,3-butadiene to styrene for SBR formation would be 77:23. When the styrene content is >45 %, the product becomes more plastic and is generally produced in the form of styrene-butadiene latex. However, SBR can also be produced as an emulsion (latex) (Buchanan, 1989; Miller, 1978).

Of the two production methods, emulsion polymerisation is the more common. In a typical process, stored 1,3-butadiene and styrene monomers are washed to remove inhibitors of the polymerisation reaction before being fed into the reactors. After the reaction has proceeded to the required extent, the polymer emulsion is removed from the reactor, along with unreacted monomer. Both 1,3-butadiene and styrene monomers are separated from the emulsion and recycled back to the reactor. The polymer emulsion can then be treated in one of two ways. One route is for it to be blended into an homogeneous emulsion and stored as the finished latex product.

The second route involves coagulation, followed by washing and drying of the solid polymer (Buchanan, 1989).

Ashfords (1994) gives a breakdown of the various types of styrene-butadiene rubbers/latices produced commercially. These are summarised below.

Styrene-butadiene rubber can be produced by either emulsion or solution polymerisation. Styrene contents are typically 23-25%, but may be as high as 40%. The solution polymerisation process allows greater flexibility in the final product (e.g. random, tapered and block copolymer grades can be produced). Styrene-butadiene rubber is used in tyres, cable insulation, conveyor/drive belts, adhesives, hoses and moulded rubber goods. Styrene- butadiene latex is produced by emulsion polymerisation and typically has a solids content of 60-70% and a styrene content of 20-35% (cold polymerisation grades) or 45% (hot polymerisation grades). It is used in floor tile adhesives, roofing felts, paper coating, latex foams (tufted carpet/fabric backing, moulded items) and in non-woven fabric sizing.

Carboxylated styrene-butadiene copolymers (XSBR) are made by the emulsion polymerisation of styrene, butadiene and carboxylic acids (e.g. acrylic/methacrylic/itaconic acids). The product is a latex with a solids content of around 50-55%. The product has a styrene content of around 35-85% and up to 5% carboxylic acid. It is used in bonding agents, adhesives (textile, paper, leather, foil lamination), binders (carpet underlay, carpet backing, paper coatings) and in cement admixtures.

High styrene content styrene-butadiene polymers (high styrene resins) have a styrene content of 80-85% and are usually produced as a latex by emulsion polymerisation. They are used as impregnating resins for thermoformed boards, in shoe soles and as stiffening/reinforcing agents in rubber and styrene-butadiene latex.

Branched styrene-butadiene block copolymers (K-Resin; Philips Petroleum) are produced by solution polymerisation. The styrene content is around 75% and the polymer finds applications in moulded toys/household items and specialist medical/industrial mouldings.

Styrene-butadiene triblock copolymers (SBS) are made by solution polymerisation. The product is a thermoplastic elastomer and has a typical styrene content of around 30%. The product is used as a bitumen modifier, in hot melt adhesives, pressure sensitive adhesives, roller coverings and rubber shoe soling compounds.

2.3.2 Polybutadiene

The polymerisation of 1,3-butadiene leads to the formation of polybutadiene. Several isomeric forms of polybutadiene exist but the commercially significant ones are the cis-1,4-isomer and to a much lesser extent the 1,2-isomer. The majority of polybutadiene is produced by solution polymerisation but emulsion polymerisation can also be used. The relative proportion of the isomers produced depends on the reaction conditions and the catalyst system used. A typical solution polymerisation process involves purification of the 1,3-butadiene and solvent (e.g. hexane or cyclohexane) followed by the polymerisation reaction. The reactor effluent may then be fed to a concentrator, where any unreacted 1,3-butadiene is removed and recycled. After this stage the product stream consists of polybutadiene in solvent (sometimes referred to as "cement"). The solvent can then be removed by steam stripping and the resulting polybutadiene crumb/water stream is dried, compressed and packaged (Buchanan, 1989; Miller, 1978).

Polybutadiene rubber is mainly used in tyres, often in blends with SBR and natural rubber. Ashfords (1994) gives a further breakdown of the various types of polybutadiene rubbers/latices produced commercially. These are summarised below.

Polybutadiene latex is produced by the emulsion polymerisation process. The latex typically contains around 70% trans-1,4-butadiene units, 15% cis-1,4-butadiene and 15% 1,2-butadiene units. It is used in the production of acrylonitrile-butadiene-styrene copolymers, methyl methacrylate-butadiene-styrene copolymers, epoxidised polybutadiene, high impact polystyrene and as a binder in paper sizing.

1,2-Polybutadiene is a thermoplastic obtained by Ziegler polymerisation. Greater than 90% of the monomer units are linked at the 1,2-positions and the resulting polymer is partially crystalline. It is used in bottles and food packaging films.

Epoxidised polybutadiene (polybutadiene oxide) is produced from polybutadiene latex and peracetic acid. It is used as an epoxy resin comonomer in sealants and electronics.

Hydroxyl-terminated polybutadiene (polybutadiene glycol) is used in pipe sealants, as an alkyd resin modifier and in polyurethane adhesives/rocket fuel binders.

Hydrogenated polybutadiene is used as a viscosity modifier in lubricating oils.

2.3.3 Polychloroprene

1,3-Butadiene is used to manufacture chloroprene, which in turn is polymerised to form polychloroprene (also known under the trade name Neoprene). The first stage in the process is the vapour phase chlorination of 1,3-butadiene to form a mixture of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene, along with unreacted 1,3-butadiene. The next stage is isomerisation of 1,4-dichloro-2-butene to 3,4-dichloro-1-butene and removal of unreacted 1,3-butadiene. This stage is performed in a combined reactor distillation column. The recovered 1,3-butadiene is recycled back to the chlorinator and the 1,4-dichloro-2-butene is either recycled or used elsewhere. The final stage in the production of chloroprene is dehydrochlorination of 3,4-

dichloro-1-butene in a solution of sodium hydroxide and water. The chloroprene is then polymerised to form either polychloroprene latex or polychloroprene rubber (Buchanan, 1989; Miller, 1978).

Chloroprene can also be manufactured from acetylene (Miller, 1978).

Polychloroprene rubber has a high chemical, oil and weather resistance and finds use in industrial rubber goods, automotive and transport, construction, adhesives and consumer products (Buchanan, 1989; Miller, 1978).

2.3.4 Nitrile rubber/latex

Nitrile rubber (sometimes known as nitrile-butyl rubber (NBR) or acrylonitrile-butadiene rubber) is a copolymer of acrylonitrile and 1,3-butadiene. The acrylonitrile content of the polymer is usually around 32% but can vary between 18 to 50% for some applications. The main advantage of nitrile rubber is its oil resistance due to the acrylonitrile component. As a result it has extensive applications in petroleum hoses, gaskets and seals. Other uses include moulded goods, adhesives, sealants, sponge, footwear and latex (Buchanan, 1989; Miller, 1978).

The product can be produced in an emulsion polymerisation process, either in batch or continuous operation. The monomers are piped to agitated polymerisation reactors, along with any additives. Water acts as both the reaction medium and heat transfer medium. The reaction takes between 5 and 12 hours and is usually stopped at a pre-determined conversion (typically 75-90% conversion). Antioxidants may then be added to the latex before the unreacted 1,3-butadiene is removed in several vacuum flash steps. The product then undergoes steam stripping to remove the remaining 1,3-butadiene monomer and the unreacted acrylonitrile. The unreacted monomers are collected and recycled. The product can then be either sent to a blending tank where the final latex product is obtained or can undergo coagulation, followed by dewatering and drying, to produce a solid crumb product (Buchanan, 1989; Miller, 1978).

Ashfords (1994) gives a further breakdown of the various types of nitrile rubbers/latices produced commercially. These are summarised below.

Nitrile rubbers have typical acrylonitrile contents of 25-45%. Terpolymers with a small amount of an unsaturated carboxylic acid (such as methacrylic acid) are known as carboxylated nitrile rubber (XNBR).

Carboxyl-terminated acrylonitrile-butadiene (CTBN) polymers are made by solution polymerisation and have a typical acrylonitrile content of 11-26%. They are used as epoxy resin flexibilisers.

Amine-terminated acrylonitrile-butadiene (ATBN) polymers have a typical acrylonitrile content of 10-16% and are produced by solution polymerisation. They are used as flexible epoxy resin curing agents.

2.3.5 Acrylonitrile-butadiene-styrene copolymers

Three processes can be used to produce acrylonitrile-butadiene-styrene (ABS) copolymers. These are emulsion, suspension and continuous mass (bulk) polymerisation. The majority of ABS seems to be produced by emulsion polymerisation, although specialised resins may be produced by suspension polymerisation. Both these processes are based on aqueous phase

reactions. The newest ABS process is based on continuous mass polymerisation. This process does not use water as the reaction medium and so eliminates the need for dewatering and drying of the product, thus reducing the amount of wastewater produced (Buchanan, 1989).

The emulsion process involves three distinct steps. Firstly, 1,3-butadiene is polymerised to form a polybutadiene latex. Secondly, styrene and acrylonitrile are grafted onto the polybutadiene substrate and thirdly, a styrene-acrylonitrile copolymer is formed. In the first stage, around 70-90% of the 1,3-butadiene monomer is converted to polybutadiene. Any unreacted 1,3-butadiene is removed from the latex by flash stripping and is often recovered for reuse. ABS plastic is a blend of ABS rubber and styrene-acrylonitrile (SAN) resin. The mixing of the ABS and SAN can take place at one of two points in the overall process, i.e. a SAN latex is blended with the ABS latex prior to coagulation or solid SAN resin can be mixed with ABS rubber after separation from the ABS latex (Buchanan, 1989).

The suspension process involves dissolving polybutadiene rubber (see Section 2.3.2) in the styrene and acrylamide monomers and a free-radical initiator is added, along with chain transfer agents. After the reaction has proceeded to around 25-35% monomer conversion, the mixture is transferred to a suspension reactor where it is dispersed in water. After the reaction has proceeded to the required monomer conversion, the product is washed/dewatered and then dried (Buchanan, 1989).

The continuous mass process also begins with polybutadiene rubber dissolved in styrene and acrylonitrile monomers, along with initiators and modifiers. The ABS is formed through phase inversion. The reaction begins in a prepolymeriser in which the reaction causes ABS rubber to precipitate. After the reaction has proceeded to around 30% monomer conversion, the mixture is transferred to the bulk polymeriser and the reaction continues to around 50-80% monomer conversion. After reaction the unreacted monomers are removed and recycled and the ABS is extruded, cooled in a water bath and pelletised (Buchanan, 1989).

The composition of ABS can vary widely depending on the required properties of the product. Additions such as methyl styrene or methyl methacrylate are also possible depending on the intended end use. A typical composition of ABS would be 5-30% 1,3-butadiene, 15-25% acrylonitrile and 50-75% styrene.

Acrylonitrile-butadiene-styrene copolymers find applications in automotive applications (e.g. facia panels, door knobs, grilles, fastenings and trims), office machine housings, industrial piping, refrigerator fittings and telephone linings. They also have applications when blended with other polymers, e.g. blends with polyvinyl chloride are used in fire retarded electrical components and housings and blends with polycarbonate or polysulphone are used in electrical components and housings (Ashfords, 1994).

2.3.6 Hexamethylenediamine

1,3-Butadiene can be used to manufacture adiponitrile which is subsequently hydrogenated to hexamethylenediamine, an intermediate in the manufacture of nylon 6,6. Hexamethylene-diamine can also be produced by another route (using acrylonitrile) that does not involve 1,3-butadiene (Buchanan, 1989; Miller, 1978).

Two methods have been used to produce adiponitrile from 1,3-butadiene. The oldest process involves chlorination of 1,3-butadiene to form a mixture of 3,4-dichloro-1-butene and 1,4-dichloro-2-butene. The 3,4-dichloro-1-butene then undergoes cyanation to 3,4-dicyano- 1-butene (the 1,4-dichloro-2-butene can be used in chloroprene synthesis). The 3,4-dicyano- 1-butene then

undergoes an isomerisation reaction to form 1,4-dicyano-2-butene, which is then hydrogenated to form adiponitrile. The new method involves conversion of 1,3-butadiene to 1,4-dicyano-2-butene by reaction with HCN in the presence of a catalyst, followed by hydrogenation to adiponitrile. The hexamethylenediamine is produced by hydrogenation of adiponitrile (Buchanan, 1989; Miller, 1978).

2.3.7 Other uses

1,3-Butadiene has been reported to be used as an intermediate in the production of several other compounds. Examples include, styrene-butadiene-vinylpyridine latex, tetrahydro- phthalic anhydride, butadiene-vinylpyridine latex, methylmethacrylate-butadiene-styrene (MBS) resins, captan, captafol, phygon, cyclooctadiene, cyclododecatriene, 1,4-hexadiene, dodecanedioic acid, butadiene dimer, butadiene cylinders, butadiene-furfural cotrimer, sulfolane, methylmethacrylate-acrylonitrile-butadiene-styrene (MABS) polymer, ethylidene norbornene and nitrile barrier resins (Buchanan, 1989; Miller, 1978).

1,3-Butadiene can also be found from adventitious sources such as the combustion of fossil fuels; for example, it is found in motor vehicle exhausts. It is understood that 1,3-butadiene is also present in motor fuels, although only at very low levels. It was reported by CONCAWE that butadiene is formed as part of the catalytic cracking process and that the levels in finished gasoline would typically be 100 to 200 ppm. It is not present in crude oil fractions. As part of a European gasoline vapour exposure monitoring campaign in 1999-2000 CONCAWE took 24 bulk samples of gasoline in France, Germany, Italy and the UK. 1,3 Butadiene was less than the detection limit of 100 ppm in all but 10 of the samples. The maximum for these 10 samples was 150 ppm.

2.4 LEGISLATIVE CONTROLS

In recognition of the potential for 1,3-butadiene to migrate from food contact materials into food, 1,3-butadiene is included in Directive 90/128/EEC and amendments, relating to plastic materials and articles intended to come into contact with foodstuffs. The maximum permitted quantity of residual 1,3-butadiene monomer in the finished product is 1 mg/kg (1 ppm). Specific Migration Limits (SMLs) into food have also been set for the protection of the consumer. For 1,3-butadiene, the Directive stipulates that there should be no detectable migration into foods or food simulants, using an analytical method with a detection limit of 0.02 mg/kg (20 ppb).

3 ENVIRONMENT

This environmental risk assessment has been carried out using mainly the methods described in the Technical Guidance Document (TGD) for risk assessment of new and existing substances and the associated EUSES program. The EUSES calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it.

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental releases

No information on releases of 1,3-butadiene from production or use was provided in IUCLID. In the absence of information, Appendix 1 of the TGD provides default values for use in release estimates. For 1,3-butadiene, the default release would be 1-25 kg/tonne to air and 3 kg/tonne to wastewater, depending on whether the 1,3-butadiene is isolated in the overall process or not (from Table A2.1 of Appendix 1; vapour pressure >10,000 Pa). The default releases from use of 1,3-butadiene as an intermediate (i.e. monomer) would be expected to be in a similar range (Table A3.3 of Appendix 1 of the TGD).

The US EPA has published a study into the releases of 1,3-butadiene from production and use (Buchanan, 1989). It is based mainly on data submitted by US industry in 1984 to derive emission factors for 1,3-butadiene, and covers five possible types of release: process vent discharges; equipment leaks; emission from secondary sources (e.g. wastewater); storage-related emissions; and emergency or accidental release (the last of these is outside the scope of this analysis). Losses during handling are possible but should be low for safety reasons (due to the explosion hazard) and so will be assumed to be negligible. Equipment leak information is not available as a percentage of plant capacity and so cannot be used in this analysis. Storage-related release is expected to be low because 1,3-butadiene is stored in pressurised containers with no breathing or working losses. The document gives ranges and means for ‘actual emissions’ (in which each facility may control all, some or none of the sources) and ‘uncontrolled emissions’ (incorporating both emissions from existing uncontrolled sources and potential emissions from controlled sources assuming controls had not been in place).

The emission factors in the US EPA report are generally of a similar order of magnitude to the default values given in the TGD. However, they have been derived from specific data for a number of real plants and so they are likely to be more reliable than the default values even though they only represent the US situation. The US EPA report will therefore form the basis of the emission estimates for 1,3-butadiene from production and subsequent use in polymer manufacture within the EU in the following sections. Where actual emissions are listed, the mean value will be used. It should be noted that these data might include plants with no emission control measures in place. Emissions from well-controlled plants are likely to be less than indicated in the following sections. This may be particularly true for some of the emissions to water since some plants reportedly have zero emissions.

Information reported in the US EPA Toxics Release Inventory indicates that emissions of 1,3-butadiene may have reduced substantially over recent years. In 1988, total releases of 1,3-butadiene were reported as 7,534,029 lbs (3,425 tonnes), with 7,002,208 lbs (3,183 tonnes) to air and 522,504 lbs (237 tonnes) to surface water. In 1993 the reported releases had reduced to a total of 3,283,261 lbs (1,492 tonnes) of which 3,274,316 lbs (1,488 tonnes) was released to air and 7,595 lbs (3.45 tonnes) was released to surface water (US EPA, 1993). The 1997 Toxics

Release Inventory indicates that the recorded releases have since fallen further to a total of 2,714,581 lbs (1,234 tonnes), with 2,710,735 lbs (1,232 tonnes) released to air and 2,552 lbs (~1 tonne) to water. It is expected that this trend will also have occurred in the EU. This is indicated in the data available on the UK Environment Agency release inventory, where the reportable air releases of 1,3-butadiene from industrial processes were around 337 tonnes in 1995, 225 tonnes in 1996, 140 tonnes in 1997 and 101 tonnes in 1998.

A further area of uncertainty lies in the estimates of the quantities of various products produced from 1,3-butadiene in the EU. This is because most of the emission factors are given as mass of 1,3-butadiene emitted per tonne of product produced, but the information supplied in Section 2 sometimes gives estimates of the amount of 1,3-butadiene used to make various products, rather than the total amount of product produced.

3.1.1.1 Release from 1,3-butadiene production

Buchanan (1989) gives the following information on emissions from US 1,3-butadiene production plants using the extraction from mixed C_4 stream method (units are kg 1,3-butadiene emitted per tonne 1,3-butadiene produced):

Process vents (air):	actual emission: range: 0.0034-0.0275, mean: 0.0157 uncontrolled emission: range: 0.0161-0.3436, mean: 0.2326
Secondary source (wastewater):	actual emission: range: 0.00034-2.2, mean: 0.468
Secondary source (solid waste):	negligible

Thus from this reference source, the emissions to air are taken as 0.0157 kg 1,3-butadiene per tonne 1,3-butadiene produced (0.0016%) and emissions to water are 0.468 kg 1,3-butadiene/tonne 1,3-butadiene produced (0.0468%).

Concerning releases to the atmosphere, Reinders (1983) estimates an atmospheric emission of all C_4 hydrocarbons of 0.2-2 kg per tonne of 1,3-butadiene. Thus the maximum emission of 1,3-butadiene could be 0.2%.

From the capacity figures given by producing companies, the largest production site in Europe produces 100,000-500,000 tonnes of 1,3-butadiene each year. Obviously this is a very wide range and more accurate figures would aid this analysis enormously. Confidential information provided on the actual amounts manufactured at large sites indicates that this is more generally in the range 100,000-200,000 tonnes/year. Taking these figures, the production at a large site is taken to be 200,000 tonnes/year. Using an emission factor of 0.0468%, release to water is 93.6 tonnes/year and release to the atmosphere is 0.0016%, which is 3.2 tonnes/year. These will be used as releases into the TGD local model for production.

Taking the figure of Western European production of 1,892,000 tonnes/year and emission factors as above, releases to water and air are 885 tonnes/year and 30.3 tonnes/year respectively for the EU as a whole. For the regional model, it is usually assumed that 10% of the total EU production occurs in the ‘region’. Regional emissions of 1,3-butadiene are therefore estimated to be 89 tonnes/year to water and 3 tonnes/year to air.

3.1.1.2 Use in styrene-butadiene rubber/latex

Buchanan (1989) gave emission factors for 1,3-butadiene during the production of styrene-butadiene rubber/latex. No information was given as to which styrene-butadiene polymer products these factors refer to. In the absence of further information, these factors will be used to calculate the emissions from all styrene-butadiene rubber/latex production. The emission factors are as follows (units are kg 1,3-butadiene released per tonne polymer product produced):

Process vents (air):	actual emission: range: 0.00012-47.17, mean: 3.55 uncontrolled emission: range: 0.062-47.17, mean 7.10
Secondary sources (wastewater):	actual emission: range: 0-<5, mean: 0.15
Other liquid waste:	actual emission: <0.01
Solid waste:	actual emission 0-<0.01

Another US EPA document (Pervier et al., 1974) gives information on the release of 1,3-butadiene to air from styrene-butadiene rubber manufacture. Data from three manufacturers showed there were two sources; 1,3-butadiene absorber vents and fugitive emissions. The former arose after polymerisation when unreacted 1,3-butadiene was flashed off, compressed, condensed and recycled. The non-condensable contaminants were vented to the atmosphere. This is mostly air but small amounts of 1,3-butadiene are also lost (approximately 0.1 kg/tonne). Fugitive emissions from the reactor section (0.34 kg/tonne), monomer recovery (0.54 kg/tonne) and storage tanks (0.17 kg/tonne) totalled approximately 0.85 kg/tonne. Thus total release to air was 0.95 kg/tonne.

Further emission factors to air for the production of styrene-butadiene rubber and latex are given in Bouscaren et al. (1986). The factors quoted are 0.3 kg 1,3-butadiene per tonne of product for both the rubber and latex. Slooff et al. (1994) gives a slightly lower emission factor to air of 0.238 kg 1,3-butadiene per tonne product for a styrene-butadiene rubber plant using the emulsion polymerisation process in the Netherlands.

The emission factors that will be used in this assessment are 3.55 kg 1,3-butadiene per tonne polymer product (0.36%) for emissions to air and 0.15 kg 1,3-butadiene per tonne product (0.015%) for emissions to water.

From the capacity figures given in **Table 2.3** it can be seen that the largest styrene-butadiene polymer plant in the EU has a capacity of around 160,000 tonnes/year. Using an emission factor of 0.015%, release to water is estimated to be 24 tonnes/year and release to the atmosphere using an emission factor of 0.36% is estimated to be 576 tonnes/year. These will be used as releases into the local model for this use.

Taking the figure for the amount of 1,3-butadiene used in Western Europe in the production of styrene-butadiene rubber/latex to be 1,059,520 tonnes/year (see **Table 2.2**), the amount of styrene-butadiene rubber produced in Western Europe can be estimated to be 1,376,000 tonnes/year, assuming the weight ratio of 1,3-butadiene to styrene to be 77:23 (see Section 2.3.1). This figure is in good agreement with the 1993 European consumption figure for styrene-butadiene rubber (including both solid and latex and carboxylated styrene-butadiene rubber) of 1,175,000 tonnes/year estimated by IISRP (1994). The total capacity is thought to be 1,811,900 tonnes/year. Using the emission factors above and the estimated production figure of 1,376,000, the estimated releases to water and air are 206 tonnes/year and 4,954 tonnes/year respectively for the EU as a whole from production of styrene-butadiene rubber/latex. For the

regional model, releases are estimated to be 21 tonnes/year to water and 495 tonnes/year to air (10% of the total EU production).

3.1.1.3 Use in polybutadiene rubber production

Buchanan (1989) also gives figures for emissions from polybutadiene production. The emission factors, in units of kg 1,3-butadiene released/tonne polybutadiene produced, are shown below:

Process vents (air):	actual emissions: range: 0.00004-18.03, mean 3.07 uncontrolled emissions: range: 0.0016-18.03, mean 4.48
Secondary sources (wastewater):	facility emissions: range: 0-0.38, mean 0.12 uncontrolled emissions: range: 0-0.38, mean 0.12
Secondary sources (solid waste):	negligible

Bouscaren et al. (1986) gives an emission factor to air of 0.2-1 kg 1,3-butadiene per tonne product for the production of polybutadiene. A lower emission factor to air of 0.145 kg 1,3-butadiene per tonne product has been reported for production of polybutadiene rubber by an emulsion polymerisation process (Slooff et al., 1994).

The emission factors that will be used in this assessment are 3.07 kg 1,3-butadiene per tonne polymer product (0.31%) for emissions to air and 0.12 kg 1,3-butadiene per tonne product (0.012%) for emissions to water.

From the capacity figures given in **Table 2.3** it can be seen that the largest polybutadiene polymer plant in the EU has a capacity of around 80,000 tonnes/year. Using an emission factor of 0.012%, release to water is estimated to be 9.6 tonnes/year and release to the atmosphere using an emission factor of 0.31% is estimated to be 248 tonnes/year. These will be used as releases into the local model from polybutadiene rubber production.

Taking the figure of Western European production of polybutadiene rubber to be 416,240 tonnes/year (see **Table 2.2**; assuming that the quantity of polybutadiene rubber produced is equivalent to the quantity of 1,3-butadiene used) and emission factors as above, releases to water and air are estimated to be 50 tonnes/year and 1,290 tonnes/year respectively for the EU as a whole. Regional releases are estimated to be 5 tonnes/year to water and 129 tonnes/year to air (10% of the total EU production).

3.1.1.4 Use in polychloroprene production

Buchanan (1989) also gives figures for emissions from polychloroprene production. The emission factors, in units of kg 1,3-butadiene released per tonne product produced, are shown below:

Process vents (air):	actual emissions: range: 0.16-3.89, mean 2.02 uncontrolled emissions: range: 0.20-12.09, mean 6.14
Secondary sources (wastewater):	no information

The emission factor that will be used in this assessment is 2.02 kg 1,3-butadiene per tonne polymer product (0.20%) for emissions to air. No information is available on the emissions to

water and so an emission factor of 0.015% will be used since the polymerisation process is similar, in principle, to those used for styrene-butadiene polymers.

Little information appears to be available on the capacities of plants in the EU that produce polychloroprene from 1,3-butadiene. However, it is known that the largest polychloroprene rubber production plant in the EU has a capacity of around 60,000 tonnes/year (see **Table 2.3**). In the absence of other information, this figure will be used here as a worst-case production capacity at one site. Using an emission factor of 0.015%, release to water is estimated to be 9 tonnes/year and release to the atmosphere using an emission factor of 0.2% is estimated to be 120 tonnes/year. These will be used as releases into the local model from polychloroprene production.

Taking the figure of Western European production of polychloroprene to be 133,000 tonnes/year (see **Table 2.3**) and emission factors as above, releases to water and air are 20 tonnes/year and 266 tonnes/year respectively for the EU as a whole. Regional releases are estimated to be 2.0 tonnes/year to water and 26.6 tonnes/year to air (10% of the total EU production). These figures again assume that all the polychloroprene manufactured in the EU uses a method involving 1,3-butadiene. This appears to be a reasonable assumption as, although chloroprene, and hence polychloroprene was also manufactured from acetylene in the past, this processes has now been completely replaced by the process involving 1,3-butadiene (Hort and Taylor, 1991).

3.1.1.5 Use in nitrile-butadiene rubber/latex production

Buchanan (1989) also gives figures for emissions from nitrile-butadiene rubber production. The emission factors, in units of kg 1,3-butadiene released per tonne product produced, are shown below:

Process vents (air):	actual emissions: range: 0.0001-8.9, mean: 2 uncontrolled emissions: range: 0.01<25, mean: 8
Secondary sources:	actual emissions: range: 0.001-0.009, mean: 0.005 The lower end of this range refers to a solid waste stream - the upper end includes solid waste, wastewater and contaminated cooling water.

Bouscaren et al. (1986) gives a similar emission factor to air of 5-15 kg 1,3-butadiene per tonne of product for the production of nitrile-butadiene rubber. The emission factors that will be used in this assessment are 2 kg 1,3-butadiene per tonne polymer product (0.2%) for emissions to air and 0.005 kg 1,3-butadiene per tonne product (0.0005%) for emissions to water.

From the capacity figures given in **Table 2.3** it can be seen that the largest nitrile rubber polymer plant in the EU has a capacity of around 35,000 tonnes/year. Using an emission factor of 0.0005%, release to water is estimated to be 0.18 tonnes/year and release to the atmosphere using an emission factor of 0.2% is estimated to be 70 tonnes/year. These will be used as releases into the local model.

The EU production capacity for nitrile rubber/latex is estimated to be 176,000 tonnes/year (see **Table 2.3**). Using the emission factors above, releases to water and air from nitrile-butadiene rubber/latex production are estimated to be 0.88 tonnes/year and 352 tonnes/year respectively for the EU as a whole. Regional releases are estimated to be 0.09 tonnes/year to water and 35 tonnes/year to air (10% of the total EU production).

3.1.1.6 Use in acrylonitrile-butadiene-styrene resin

Buchanan (1989) also gives figures for emissions from acrylonitrile-butadiene-styrene (ABS) polymer production. The emission factors, in units of kg 1,3-butadiene released per tonne product produced, are shown below:

Process vents (air):	actual emissions: range: 0.08-5.33, mean: 2.11 uncontrolled emissions: range: 3.25-5.64, mean: 4.74
Secondary sources:	no information

The air emission factor that will be used in this assessment is 2.11 kg 1,3-butadiene per tonne polymer product (0.21%). No information is available on the emissions to water and so an emission factor of 0.012% will be used since the polymerisation process is similar, in principle, to that used for polybutadiene.

Since acrylonitrile-butadiene-styrene resins are made using polybutadiene rubber/latex, the following may overestimate the release of 1,3-butadiene from the process. This is because some processes may start with the polybutadiene latex already formed and the emissions from this should have been accounted for in Section 3.1.0.1.3.

From the capacity figures given in **Table 2.3** it can be seen that a typical acrylonitrile-butadiene-styrene polymer plant in the EU has a capacity of around 50,000 tonnes/year. Using an emission factor of 0.012%, release to water is estimated to be 6 tonnes/year and release to the atmosphere using an emission factor of 0.21% is estimated to be 105 tonnes/year. These will be used as releases into the local model.

No information appears to be available on the total EU production capacity for ABS resins. However, it is thought that around 75,680 tonnes/year of 1,3-butadiene are used within the EU to make ABS resins (see **Table 2.2**). Typical compositions of the resins have been given as 5-30% 1,3-butadiene, 50-75% styrene and 15-25% acrylonitrile (see Section 2.3.5). Using a 1,3-butadiene content of 30% by weight, it is possible to estimate the maximum likely EU production of ABS resins as 252,226 tonnes/year. In the absence of any further information this figure will be used here to estimate releases for the regional model and the EU as a whole. Using the emission factors as above, releases to water and air are estimated to be 30.3 tonnes/year and 530 tonnes/year respectively in the EU as a whole. Regional releases are estimated to be 3.0 tonnes/year to water and 53 tonnes/year to air (10% of the total EU production).

3.1.1.7 Use in adiponitrile/hexamethylenediamine production

Buchanan (1989) also gives figures for emissions from adiponitrile production. The emission factors, in units of kg 1,3-butadiene released per tonne adiponitrile produced, are shown below (since adiponitrile and hexamethylenediamine have very similar molecular weights it will be assumed that the same factors apply when considering the amount of hexamethylenediamine produced):

Process vents (air):	actual emissions: 0.06 uncontrolled emissions: range: 2.92-3.15, mean: 3.04
Secondary sources (wastewater):	actual emissions: range: 0.008-0.012, mean: 0.01

The emission factors that will be used in this assessment are 0.06 kg 1,3-butadiene per tonne product (0.006%) for emissions to air and 0.01 kg 1,3-butadiene per tonne product (0.001%) to water.

Little information appears to be available on the capacities of adiponitrile/ hexamethylenediamine plants in the EU. However, from **Table 2.2**, it is estimated that around 75,680 tonnes/year of 1,3-butadiene are used to make hexamethylenediamine/adiponitrile in Western Europe. This is equivalent to the production of around 151,360 tonnes/year of adiponitrile/hexamethylenediamine. Based on this total amount used, it will be assumed that the largest production plant in the EU has a capacity of around 50,000 tonnes (i.e. assuming three plants in the EU). Using an emission factor of 0.001%, release to water is estimated to be 0.5 tonnes/year and release to the atmosphere using an emission factor of 0.006% is estimated to be 3 tonnes/year. These will be used as releases into the local model.

Taking the figure of European production of hexamethylenediamine/adiponitrile from 1,3-butadiene to be 151,306 tonnes/year and emission factors as above, releases to water and air are estimated to be 1.5 tonnes/year and 9.1 tonnes/year respectively for the EU as a whole. Regional releases are estimated to be 0.2 tonnes/year to water and 0.9 tonnes/year to air (10% of the total EU production).

3.1.1.8 Site-specific release information

Information on the release to air and wastewater at several production and use sites in the EU has been obtained. For releases to wastewater, some information was received from eleven 1,3-butadiene production sites and twelve use sites (both production and use occurs on some of these sites although the actual use of 1,3-butadiene at some sites was not stated). The releases were reported to be zero or negligible at six sites, were not detected in influent/effluent of the wastewater treatment plant at five sites and were reported to be in the range <50 kg/year to 60 tonnes/year at six sites.

Information has also been provided by industry on releases to air from 15 production and/or use sites. The releases to air were in the range 0.006-240 tonnes/year, with several plants reporting releases in the 10-100 tonnes/year range and some plants reporting zero emissions.

3.1.1.9 Vehicle exhaust emissions

1,3-Butadiene has been identified as a component of both gasoline and diesel vehicle exhausts. Three-way catalysts and oxidation catalysts have been shown to markedly reduce the amounts of 1,3-butadiene emitted from gasoline-fuelled vehicles. Gasoline or diesel itself has been shown to contain little or no 1,3-butadiene and so evaporative losses of 1,3-butadiene from fuel are likely to be negligible. Indeed, Buchanan (1989) reported that refiners try to minimise the amount of 1,3-butadiene present in fuel since it can readily form a varnish that is harmful to engines.

1,3-Butadiene has also been identified in liquefied petroleum gas (LPG). Some commercial liquefied petroleum gases may contain up to 8% 1,3-butadiene by volume (DoE, 1994). LPG is used in small amounts in Belgium, Italy and the Netherlands (Bouscaren et al., 1986).

A series of emission tests have been carried out in the US using cars from 1984-1987. In the first study (Stump et al., 1989), nine cars with engine capacities between 1.6 and 2.5 litres were used. All the cars were fitted with some sort of emission reduction system (e.g. three-way catalyst, oxidation catalyst or both). Emission test were carried out at three temperatures, -6.7^{o}C, 4.4^{o}C

and 21.1°C using either summer grade or winter grade unleaded gasoline as appropriate. The cars were tested using the Urban Dynamometer Driving Schedule (UDDS) of the Federal Test Procedure (FTP) and a modified version of the Federal Test Procedure (MFTP), which included a 5 minute idling time to simulate warming up the engine and defrosting of the car (as may occur in winter). 1,3-Butadiene was detected in the exhaust emissions only in the cold start samples. Little or no 1,3-butadiene was detected in the exhaust samples once the engine (and hence catalyst system) had warmed up. The emissions of 1,3-butadiene over the whole test cycle were found to account for 0.07-0.13% by weight of the total hydrocarbon emissions under all conditions studied. In the second study (Stump et al., 1990a), eleven cars with engine capacities between 1.5 and 5.0 litres (again all fitted with emission reduction systems) were tested under the same conditions as above. Similar results were obtained, with 1,3-butadiene accounting for 0.06-0.55% of the total hydrocarbon emissions over the whole test cycle.

Stump et al. (1990b) investigated the effect of blending oxygen-containing organic chemicals into unleaded gasoline on the exhaust emissions of 1,3-butadiene. The car used was a 2.0 litre, 1988 model, equipped with a three-way catalyst. Four fuels were tested (two unleaded gasolines and blends with ethanol or methyl tertiarybutyl ether (blends had an oxygen content of 3.0%)) at three temperatures. No emissions of 1,3-butadiene were detected in diurnal tests and hot-soak tests, indicating that 1,3-butadiene is not present in significant amounts in the gasoline. Exhaust emissions were determined using the UDDS. Emission factors for 1,3-butadiene were determined as 0.2-1.10 mg/mile at 4.4°C, 0.2-0.6 mg/mile at 23.9°C and 0.2-0.5 mg/mile at 32.2°C over the whole test cycle. Very similar results were obtained in another study using a 1987 2.0 litre car fitted with a three-way catalyst (Stump et al., 1990c). Here the 1,3-butadiene emission factors were found to be 0.5-1.25 mg/mile at 4.4°C, 0.35-0.90 mg/mile at 23.9°C, 0.35-1.1 mg/mile at 32.2°C and 0.7-1.0 mg/mile at 40.6°C over the whole test cycle.

In a further study by Stump et al. (1992), tailpipe emissions of 1,3-butadiene from seven cars (model years 1987-1990; engine capacities 2.8-5.0 litres) were determined at three temperatures (23.9, 32.2 or 40.6°C) using the UDDS and summer grade gasoline. All cars were fitted with some sort of emission control device (e.g. oxidation/reduction catalyst, three-way catalyst or oxidation catalyst), six of the cars had port fuel injection (PFI) systems and the other car was carburetted. In all cases, 1,3-butadiene was formed mainly in the first 2 minutes of vehicle start up when the fuel:air mixture was rich and the emission control system was inactive. Emissions of 1,3-butadiene from the carburetted car were higher than those found in the PFI cars. The 1,3-butadiene emission rates determined over the whole test cycle were found to be 1.75-2.05 mg/mile in PFI cars and 4.85-5.93 mg/mile in the carburetted car.

Warner-Selph (1989) determined exhaust emissions of 1,3-butadiene from two cars (2.5 litre fitted with three-way catalyst and oxidation catalyst; 2.0 litre fitted with three-way catalyst) using the FTP (average speed 19.5 miles/hour), Highway Fuel Economy Test (HFET; average speed 48.2 miles/hour) and New York City Cycle (NYCC; average speed 7.1 miles/hour) using an unleaded gasoline. The FTP is a cold start test, whereas the HFET and NYCC are hot start tests. 1,3-Butadiene was detected in exhaust emissions only in the FTP test (the experimental detection limit was equivalent to a 1,3-butadiene emission rate of 0.4 mg/mile). The 1,3-butadiene emission factors determined over the whole test cycle were 0.77-0.88 mg/mile (0.26-0.49% of the total hydrocarbon emissions). However, 1,3-butadiene was again shown to be emitted only in the cold start portion of the test. Once the engine had warmed up the emission of 1,3-butadiene was <0.4 mg/mile. This was attributed to the fact that the catalyst was effective at removing 1,3-butadiene from the exhaust gases only after a warm up period. The emission rates of 1,3-butadiene during the early stages of the test (cold start part) were 3.81-4.47 mg/mile.

Further studies on exhaust emissions of 1,3-butadiene from gasoline-powered cars have been carried out by Hoekman (1992). These studies used the Federal Test Procedure at 23.9°C with two fuels, a typical Los Angeles premium gasoline and a reformulated gasoline containing around 11% by volume of methyl tertiarybutyl ether. The tests were carried out with nineteen vehicles (model years 1970-1989; engine size 1.4-5.7 litres) fitted with either no catalyst, oxidation catalyst, three-way catalyst or three-way catalyst with adaptive learning. The average 1,3-butadiene emission factors over the whole test cycle were found to be 1.81-2.96 mg/mile for vehicles with no catalyst, 0.02-0.33 mg/mile for vehicles fitted with an oxidation catalyst, 0.05-0.07 mg/mile for vehicles fitted with a three-way catalyst and 0.00-0.14 mg/mile for vehicles fitted with a three-way catalyst with adaptive learning.

Smith (1989) carried out similar tests to those above with two diesel-powered cars (3.0 litre fitted with a catalysed particle trap system; 1.6 litre fitted with an additive regenerated trap system). Two diesel fuels were used, one with an aromatics content of 36.2% and one with an aromatics content of 16.2%. The cars were tested both with and without the particulate traps fitted using the FTP, HFET and NYCC procedures. The exhaust emissions of 1,3-butadiene were found to be similar for both vehicles and were in the range 3.0-4.4 mg/mile (1.3-1.8% of the total hydrocarbons emitted) during the FTP. The emissions were found to occur during all phases of the FTP (not just the cold start phase as seen with catalyst equipped gasoline vehicles).

Buchanan (1989) reported that a figure of 0.35% weight was representative of the amount of 1,3-butadiene found in the total hydrocarbons emitted from light-duty, three-way catalyst equipped vehicles and that emissions could be higher from non-catalyst equipped vehicles. This figure was used to derive typical 1,3-butadiene emission factors for the US fleet. These factors are shown in **Table 3.1**, along with the other factors reported above.

Table 3.1 1,3-Butadiene emission factors determined in the USA

Vehicle type	Year	Emission factor (mg/mile)	Reference
Light-duty gasoline (car)	1980	12.7	Buchanan, 1989
	1995[a]	4.1	Buchanan, 1989
	1995[b]	2.8	Buchanan, 1989
	1987	0.35-1.25	Stump et al., 1990c
	1988	0.2-1.1	Stump et al., 1990b
	1984-7	1.75-5.93	Stump et al., 1992
	1986	0.88	Warner-Selph, 1989
	1987	0.77	Warner-Selph, 1989
	1970-1989	0.00-2.96	Hoekman, 1992
Light-duty gasoline (truck)	1980	20.5	Buchanan, 1989
	1995[a]	8.7	Buchanan, 1989
	1995[b]	5.5	Buchanan, 1989
Heavy-duty gasoline vehicle	1980	32.8	Buchanan, 1989
	1995[a]	8.9	Buchanan, 1989
	1995[b]	8.9	Buchanan, 1989
Light-duty diesel (car)	1986	3.0-4.4	Smith, 1989
Heavy-duty diesel	1980	15.9	Buchanan, 1989
	1995[a]	8.6	Buchanan, 1989
	1995[b]	8.6	Buchanan, 1989

Notes: a - estimated for 1995 fleet assuming no regular inspection and maintenance program
b - estimated for 1995 fleet assuming a regular inspection and maintenance program

It is very difficult to choose a representative emission factor for 1,3-butadiene from gasoline vehicle exhausts. This is due to the changing proportion of catalyst-equipped cars on the road over time and across the EU, and also to the variation of 1,3-butadiene emissions during the course of a journey. The results generally show that the 1,3-butadiene emissions are initially quite high but are then much reduced as the engine warms up. Many of the emission factors reported are average concentrations obtained over the test cycle and since the test cycles are usually over a fixed time (and hence distance), the 1,3-butadiene emission figures obtained may underestimate the emissions during short journeys and overestimate the emissions over longer journeys. In addition, more and more cars are currently being fitted with three-way catalysts, whilst many non-catalyst equipped vehicles are still on the road in Europe. It might be expected that these would have significantly higher overall emissions of 1,3-butadiene than catalyst-equipped vehicles. Bearing this in mind, an estimate of the likely maximum total emissions of 1,3-butadiene in Western Europe can be made by using an emission factor of 4 mg 1,3-butadiene/mile for light-duty vehicles. This figure is in line with the emissions found from non-catalyst gasoline and diesel cars. A figure of 8 mg 1,3-butadiene/mile will be used for heavy-duty vehicles.

IISRP (1994) provides an estimate of the total number of passenger cars (152,610,000) and commercial and other vehicles (41,950,000) thought to be in use in Western Europe in 1992. The same report also estimates total traffic volume to be 2,200,413 million vehicle kilometres (1,364,256 million vehicle miles). Therefore, assuming that this mileage is distributed evenly among the entire Western European fleet, it can be estimated that the light-duty and heavy-duty vehicle activity is around 1,070,100 million vehicle miles and 294,150 million vehicle miles respectively. Thus the estimated Western European emission of 1,3-butadiene from vehicle exhaust can tentatively be estimated as 6,633 tonnes/year. The increasing use of catalyst-equipped vehicles will reduce this figure.

Bouscaren et al. (1986) reports an earlier literature survey of the components of exhaust from gasoline-powered vehicles without emission control. The results show a concentration of 1,3-butadiene ranging from 1.3 to 4.3% with an average of 2.5% weight based on the total unsaturated hydrocarbons emitted. The concentration of 1,3-butadiene was then estimated for all road traffic exhaust (assumed 86% gasoline vehicle exhaust, 11% diesel vehicle exhaust and 3% LPG vehicle exhaust) as 0.5% weight of total hydrocarbons emitted. Using these data, estimates for the amount of 1,3-butadiene emitted in gasoline vehicle exhausts were reported for several countries for the year 1985. These are shown in **Table 3.2**.

Table 3.2 Estimated 1,3-butadiene emissions from gasoline vehicle exhausts for 1985 (Bouscaren et al., 1986)

Country	Amount of 1,3-butadiene in gasoline vehicle exhaust emissions (tonnes/year)
Belgium	400
Denmark	150
Germany	2,300
France	2,400
Greece	200
Ireland	100
Italy	2,400
Luxembourg	20
Netherlands	450 (400-1,400[a])
Portugal	90
Spain	800
United Kingdom	2,800
Total	12,110

Notes: a) Estimated by Slooff et al. (1994) for 1988.

It should be noted that these emissions are based on there being no emission reduction systems (e.g. three-way catalysts) fitted. It would be expected that present emissions of 1,3-butadiene would be lower than these estimates for some countries where such technology is relatively common.

For the purposes of this assessment, it will be assumed that the total release of 1,3-butadiene in the EU from vehicle exhaust is 6,633 tonnes/year and the amount released in the regional model is 10% of this value, i.e. 663 tonnes/year.

3.1.1.10 Cigarette smoke

1,3-Butadiene has been detected in cigarette smoke. The average airborne yield of 1,3-butadiene has been reported as 400 µg/cigarette (Löfroth et al., 1989). Figures are available for the amount of cigarettes produced in various countries. These are shown in **Table 3.3**, along with the estimated 1,3-butadiene emissions.

Table 3.3 Estimated amounts of 1,3-butadiene released from smoking cigarettes

Country	Year	Number of cigarettes produced[a] (million)	Estimated amount of 1,3-butadiene released (tonnes/year)
Austria	1990	14,961	6.00
Belgium	1990	25,600	10.20
Denmark	1990	11,170	4.50
Finland	1990	8,974	3.60
France	1990	53,000	21.20
Germany	1990	206,205	82.50
Greece	1990	28,450	11.40
Ireland	1990	7,850	3.10
Italy	1990	65,000	26.00
Luxembourg			
Netherlands	1990 1988	78,052 33,100[c]	31.2 13.2
Portugal	1990	15,220	6.10
Spain	1990	79,500	31.80
Sweden	1990	9,970	4.00
United Kingdom	1990 1993	112,000 95,200[b]	44.8 38.1
Total (1990)		715,952	286.40

Notes: a) Data on cigarette production; United Nations (1993)
b) Data on cigarette consumption; CSO (1995)
c) Data on cigarette consumption; Slooff et al. (1994)

For the purposes of the assessment, it will be assumed that the release of 1,3-butadiene from cigarette smoke in the EU is 286.4 tonnes/year and the release in the regional model will be one tenth of this value, i.e. 28.6 tonnes/year.

3.1.1.11 Release from polymer products

There is the possibility of unreacted 1,3-butadiene monomer being present in the polymer product. This may then be released during the use of the polymer. Little is known about the significance of this exposure route. Some data are available from studies examining the migration of residual 1,3-butadiene from food packaging materials:

- In the United Kingdom, ABS is used for the manufacture of tubs for foods such as soft margarines. Startin and Gilbert (1984) took five major brands of margarine from a supermarket and tested them for residual 1,3-butadiene. They found that 1,3-butadiene levels ranged from <5 to 310 µg/kg in the tubs but none was detected in the margarine (detection limit 0.2 µg/kg).
- McNeal and Breder (1987) analysed several 1,3-butadiene copolymers used for food packaging by dissolving them in dichloromethane and analysing for residual 1,3-butadiene by headspace gas chromatography. The results are shown in **Table 3.4** below.

Table 3.4 Residual 1,3-butadiene in polymers for food contact (McNeal and Breder, 1987)

Product	Residual 1,3-butadiene (µg/kg polymer)
9.4% Styrene/SBR resin	48-57
2.2% Styrene/SBR resin	40
Olive oil bottles (butadiene rubber modified acrylonitrile-acrylic)	4,600-6,600
Vegetable oil bottle (rubber modified PVC)	Not detected[a]
Potato salad tub	77
Potato salad lid	1,700
Cottage cheese tub	100
Chewing gum (5 brands, 1,3-butadiene rubber base)	Not detected[b]
Yoghurt tub lid (rubber modified polystyrene)	21

Notes: a - detection limit 5 µg/kg
b - detection limit 0.5 µg/kg

Olive oil, vegetable oil and yoghurt were tested for the presence 1,3-butadiene, and only olive oil contained any measurable quantity (8-9 µg/kg). The detection limit for 1,3-butadiene in vegetable oil and yoghurt was 1 µg/kg (McNeal and Breder, 1987).

These studies show that despite the presence of free 1,3-butadiene in the polymer, there is generally little or no migration into food. Note that Directive 90/128/EEC restricts the amount of residual 1,3-butadiene monomer in food contact materials to 1 mg/kg within the EU.

As a worst-case approach to estimating the release of 1,3-butadiene from polymers, the following gross assumptions can be made. The maximum residual concentration of 1,3-butadiene in all polymers is 6,600 µg/kg (6.6 g/tonne) and all this 1,3-butadiene is released from polymers during the first year of use.

Figures for the amounts of different polymers produced in the EU have been generated in Sections 3.1.0.1.2 to 3.1.0.1.6 and these, along with the estimated release of residual 1,3-butadiene are shown in **Table 3.5**. Obviously, this approach may grossly overestimate the actual residual release but, even so, it can be seen that the estimated 1,3-butadiene release from this source are insignificant compared to those from other sources.

Table 3.5 Estimated release of residual 1,3-butadiene from polymers

Polymer	Estimated EU production (tonnes/year)	Amount of residual 1,3-butadiene released (tonnes/year)
SBR (solid, latex, XSBR)	1,175,000	7.8
Polybutadiene	265,000	1.7
Polychloroprene	61,000	0.4
Nitrile rubber	80,000	0.5
ABS	252,226	1.7
	1,833,226	12.10

3.1.1.12 Polymer disposal

Rutkowski and Levin (1986) undertook a literature survey of the pyrolysis products of ABS copolymers. Of the three main studies investigating thermooxidative degradation products of ABS, none identified 1,3-butadiene.

Adams (1977) studied the composition of the combustion gases from heating samples of hemlock wood, wool carpet, PVC flooring, brominated polyester and rubber foam. The samples were heated by radiant heaters (2.5 watts/cm^2) until around 10 g weight loss had occurred. Only compounds present in the combustion gases at concentrations of 1 ppm (≡2.2 mg/m^3 for 1,3-butadiene) or greater were reported. 1,3-Butadiene was detected only during the experiments with rubber foam and was estimated to be emitted at a rate of 0.69 mg 1,3-butadiene per gram of sample weight loss. This result shows that 1,3-butadiene may be liberated from certain polymers on heating. However, complete destruction of 1,3-butadiene would be expected on incineration.

1,3-Butadiene is mainly incorporated into polymer products and hence is not released as such when polymer products are disposed of. Combustion studies with polymeric materials have shown that generally 1,3-butadiene will not be released during combustion processes. Controlled incineration of polymer material would not be expected to release significant amounts of 1,3-butadiene.

3.1.1.13 Natural sources

1,3-Butadiene has been reported to be produced during forest fires (Howard, 1990), but is not known to occur as a natural product. It has been estimated that the total global emission of 1,3-butadiene is around 770,000 tonnes/year from burning of biomass (Ward and Hao, 1992, cited in Environment Canada/Health Canada, 2000). For Canada, it has been estimated that the 1,3-butadiene emitted from forest fires may account for around 28-65% of the total 1,3-butadiene emissions for that country (CPPI, 1997, cited in Environment Canada/Health Canada, 2000). No information appears to be available on the emissions from this forest fires/biomass combustion in the EU, but it is likely to be a significant source of 1,3-butadiene. However, the available information does not allow this source to be quantified for the EU, and so it is not included in the summary of emissions.

3.1.1.14 Summary of releases

In the previous sections, the release of 1,3-butadiene from several sources has been estimated. These releases are summarised in **Table 3.6** and will form the basis for the estimation of predicted environmental concentrations (PECs) of 1,3-butadiene.

It should be noted that the actual emissions from many industrial processes might be lower than those given here, because the figures represent a worst-case situation. This is illustrated by the data for actual sites (Section 3.1.1.8), where although the highest values reported are generally lower than, but in reasonable agreement with, the estimates given in **Table 3.6**, some sites have actual releases that are considerably lower. The worst-case assessment may therefore overestimate the actual risks associated with such sites.

Table 3.6 Summary of estimated releases of 1,3-butadiene

Source	Route of release	Amount released/site (local model) (tonnes/year)	Amount released in regional model (tonnes/year)	Amount released in continental model (=total EU release-regional release) (tonnes/year)
1,3-Butadiene production	wastewater	93.6	89	797
	air	3.2	3	27.3
Styrene-butadiene rubber/latex production	wastewater	24	21	185
	air	576	495	4,459
Polybutadiene rubber production	wastewater	9.6	5	45
	air	248	129	1,161
Polychloroprene production	wastewater	9	2	18
	air	120	26.6	239
Nitrile-butadiene rubber/latex production	wastewater	0.18	0.09	0.79
	air	70	35	317
Acrylonitrile-butadiene-styrene resin production	wastewater	6	3	27.3
	air	105	53	477
Adiponitrile/ hexamethylene diamine production	wastewater	0.5	0.15	1.4
	air	3	0.9	8.2
Vehicle exhaust emissions	air	/	663	5,970
Cigarette smoke	air	/	28.6	257
Polymers (residual 1,3-butadiene)	air	/	1.2	10.9
Total	wastewater		120	1,074
	air		1,435	12,926

The estimated amounts released in the regional model are based on an assumption that 10% of the total EU production and use occurs in a region (as defined in the TGD). However, some of the plants that produce and use 1,3-butadiene account for more than 10% of the EU total. If it is assumed that the regional model contains the largest plant for production and each use, then the total estimated releases in the regional model could be 143 tonnes/year to wastewater and 1,818 tonnes/year to air (the corresponding continental releases are 1,050 tonnes/year to wastewater and 12,544 tonnes/year). These figures, along with those in **Table 3.6** assuming 10% activity in the regional model, will be used later to generate a $PEC_{regional}$ using EUSES. In the model, a 70% connection rate to wastewater treatment plants will be assumed (as indicated in the TGD).

3.1.2 Environmental fate

3.1.2.1 Degradation

3.1.2.1.1 Abiotic degradation

Hydrolysis

On the basis of a lack of hydrolysable functional groups, 1,3-butadiene is not expected to hydrolyse appreciably in the environment (Howard, 1990).

Photolysis

No information on direct photolysis of 1,3-butadiene under environmental conditions has been found. It is assumed to be an insignificant process compared to the photooxidation reactions below.

Photooxidation

1,3-Butadiene has been shown to react rapidly with hydroxyl radicals in the vapour phase. Several laboratories have measured second order reaction rate constants for reactions in air and the results are shown in **Table 3.7**.

Table 3.7 Rate constants for the reaction of 1,3-butadiene with hydroxyl radicals

Second order reaction rate constant k_{OH} ($cm^3 molecule^{-1} s^{-1}$)	Temp (K)	Comments	Reference
6.79×10^{-11}	305	relative to n-butane ($k = 2.69\cdot10^{-12}$ cm^3 $molecule^{-1}$ s^{-1})	Lloyd et al., 1976
6.85×10^{-11}	299.5	absolute rate method	Atkinson et al., 1977
6.51×10^{-11}	~300	relative to ethene ($k = 8.45\cdot10^{-12}$ cm^3 $molecule^{-1}$ s^{-1})	Barnes et al., 1982; Atkinson, 1985
$6.16\text{-}6.88\times10^{-11}$	297	relative to propene ($k = 2.65\cdot10^{-11}$ cm^3 $molecule^{-1}$ s^{-1}) and 2-methyl-2-butene ($k = 8.72\cdot10^{-11}$ cm^3 $molecule^{-1}$ s^{-1})	Ohta, 1983; Atkinson, 1985
6.65×10^{-11}	295	relative to propene ($k = 2.68\cdot10^{-11}$ cm^3 $molecule^{-1}$ s^{-1})	Atkinson and Aschmann, 1984
$6.1\text{-}6.8\times10^{-11}$	295		Becker et al., 1984
6.85×10^{-11}			Funcke, 1979

Atkinson (1985) reviewed the available rate constant data for reaction of 1,3-butadiene with hydroxyl radicals and recommended a value for k_{OH} of $6.68\cdot10^{-11}$ cm^3 $molecule^{-1}$ s^{-1} at 25°C. Howard et al. (1991) gives values for atmospheric hydroxyl radical concentrations of $3\cdot10^5$ and $3\cdot10^6$ molecule cm^{-3} as being representative of relatively clean and polluted air respectively. The atmospheric half-life of 1,3-butadiene for reaction with hydroxyl radicals is therefore likely to be in the range 0.96-9.6 hours (0.04-0.4 days). The TGD recommends a value of $5\cdot10^5$ for the

atmospheric hydroxyl radical concentration, which corresponds to an atmospheric half-life of 5.8 hours (0.24 days).

1,3-Butadiene is also reactive with ozone in the atmosphere. Atkinson and Carter (1984) report literature values for the second order rate constants for the reaction of $8.1 \cdot 10^{-18}$ and $8.4 \cdot 10^{-18}$ cm^3 molecule s^{-1}, recommending the former value. Howard et al. (1991) gives values for the atmospheric ozone concentrations of $5.0 \cdot 10^{11}$ and $3.0 \cdot 10^{12}$ molecule cm^{-3} as being representative of relatively clean and polluted air respectively. The atmospheric half-life of 1,3-butadiene for reaction with tropospheric ozone can therefore be estimated at between 7.9-47.5 hours (0.33-2.0 days). Klöpffer et al. (1988) estimated a similar half-life for reaction with atmospheric ozone of 1.9 days based on a second order reaction rate constant of $6.1 \cdot 10^{-18}$ cm^3 $molecule^{-1}$ sec^{-1}. Thus, reaction with ozone is rapid, but less important than reaction with hydroxyl radicals. However, at night, when the concentration of hydroxyl radicals falls to negligible levels, this removal mechanism will become more important.

The photooxidation of a 1,3-butadiene-NO-air system at 298±2 K was investigated in an environmental chamber under simulated atmospheric conditions. The initial concentrations of 1,3-butadiene were 0.5, 1.0 and 2.0 ppm (1.1, 2.2 and 4.4 mg/m^3) and NO was present at 0.11-2.4 ppm. Acrolein and NO_2 were identified as the primary stable photoproducts from the reaction, but acrolein undergoes further reaction under the conditions used (Maldotti et al., 1980).

1,3-Butadiene will also react with NO_3 radicals in the atmosphere. Atkinson and Carter (1984) measured a second order rate constant for the reaction of $5.34 \cdot 10^{-13}$ cm^3 $molecule^{-1}$ s^{-1} at 295 K. This may be another important removal mechanism for 1,3-butadiene, particularly at night, where typical levels of NO_3 radicals are 10 ppt (approx. $2.5 \cdot 10^7$ molecules/cm^3) in a "clean" atmosphere and 100 ppt (approx. $2.5 \cdot 10^8$ molecules/cm^3) in a moderately polluted atmosphere. Using these values for the NO_3 radical concentration, the estimated half-life for the reaction with 1,3-butadiene is around 14 hours in "clean air" and around 1.4 hours in moderately polluted air.

Kopczynski et al. (1972) sampled downtown Los Angeles air in morning traffic and found a concentration of 11 ppb (~10.3 $\mu g/m^3$) of 1,3-butadiene. After six hours irradiation in natural sunlight all the 1,3-butadiene had been degraded.

Given the high reactivity of 1,3-butadiene to radical species in the atmosphere, it is likely that similar reactions will also occur in surface water, where radical species such as hydroxyl radicals also exist. Insufficient information is available to assess the significance of these reactions.

As most 1,3-butadiene will distribute to the atmosphere (section 3.1.2.2), the most dominant environmental fate process will be photooxidation.

3.1.2.1.2 Biodegradation

No standard biodegradation tests are available for 1,3-butadiene. Given its high volatility, it would be very difficult to carry out such tests meaningfully. There are indications from other sources that 1,3-butadiene may biodegrade but it is considered that volatilisation and subsequent photodegradation in the atmosphere is likely to be the most important removal mechanism for 1,3-butadiene from soil and surface water.

Watkinson and Somerville (1975) isolated a species of *Nocardia* from soil that was capable of growing on 1,3-butadiene as sole source of carbon and energy. Cultures were grown at 25°C with 1,3-butadiene present in the headspace at 10-15% by volume. The 1,3-butadiene was thought to

degrade by several steps to give carbon dioxide and acetate. The stepwise intermediates were thought to be the monoepoxide, β,γ-unsaturated α-keto acid, acrylate, lactate and pyruvate.

Several strains of bacteria have been shown to oxidise 1,3-butadiene. Hou et al. (1979) demonstrated that three strains of methane-utilising bacteria (*Methylosinus trichosporium*, *Methylococcus capsulatus* and *Methylobacterium organophilum*) could degrade 1,3-butadiene to 1,2-epoxybutene in resting cell suspensions. The 1,2-epoxybutene accumulated and was not metabolised further. The bacteria were grown in a 50% methane/50% air atmosphere and were then incubated in a 50% 1,3-butadiene/50% oxygen atmosphere at 30°C. Subsequent work (Hou et al., 1983) showed that 27 strains of propane-utilising bacteria also degraded 1,3-butadiene to 1,2-epoxybutene when incubated in a 50% 1,3-butadiene/50% oxygen atmosphere at 30°C. The 1,2-epoxybutene was then metabolised further.

1,3-Butadiene was listed in a group of chemicals that should be biodegraded during biological sewage treatment as long as suitable acclimation is achieved (Thom and Agg, 1975). The available experimental evidence suggests that 1,3-butadiene may biodegrade under certain conditions to give relatively harmless products. However, there are insufficient data available to classify it as readily or inherently biodegradable. Thus, a biodegradation rate of 0 h^{-1} will be assumed for environmental modelling purposes as a worst-case approach.

3.1.2.2 Environmental distribution

A level I fugacity model was used to assess the distribution of 1,3-butadiene when released into the environment (Exxon Biomedical Sciences: US EPA, 1991). This type of modelling assumes equilibrium partitioning and no advection. The results showed that the vast majority (99.97%) would be found in the air compartment.

3.1.2.2.1 Volatilisation

1,3-Butadiene has a very high vapour pressure (measured at 2,351-2,500 hPa at 20°C, which is greater than atmospheric pressure) and so would be expected to volatilise very rapidly from land and surface water. The rate of volatilisation has been shown to be dependent on the Henry's law constant. It is possible to estimate this constant from the ratio of vapour pressure to water solubility. For gaseous substances a vapour pressure of 1 atmosphere (101,325 Pa) is usually used. Using the solubility of 1,3-butadiene of 0.735 g/l (735 g/m^3) at 20°C the Henry's law constant can be estimated to be 0.073 atm m^3 mol^{-1}. This is in good agreement with values for the Henry's law constant estimated from the chemical structure using the EPI estimation program (Syracuse Research Corporation) of 0.078 atm m^3 mol^{-1} (bond contribution method) and 0.071 atm m^3 mol^{-1} (group contribution method). Using these values, it is possible to estimate the half-life for volatilisation from surface water at a depth of 1 metre to be around 3.8 hours (Lyman et al., 1982).

The TGD gives the following equation for estimating the rate constant for volatilisation from soil (k_{volat}):

$$\frac{1}{k_{volat}} = \left(\frac{1}{kasl_{air} \times K_{air-water}} + \frac{1}{kasl_{soil-air} \times K_{air-water} + Kasl_{soil-water}} \right) \times K_{soil-water} \times DEPTH_{soil}$$

where $kasl_{air}$ = partial mass transfer coefficient at air side of the air-soil interface = 120 m/d.
$kasl_{soil-air}$ = partial mass transfer coefficient at soil-air side of the air-soil interface = 0.48 m/d.
$kasl_{soil-water}$ = partial mass transfer coefficient at soil-water side of the air-soil interface = $4.8 \cdot 10^{-5}$ m/d.
$K_{air-water}$ = air-water equilibrium distribution constant = 3.15 m^3/m^3 (based on a Henrys Law constant of 0.073 atm m^3/mole for 1,3-butadiene).
$K_{soil-water}$ = soil-water partition coefficient = 2.38 m^3/m^3 (based on a Koc value of 51.6 l/kg for 1,3-butadiene).
$DEPTH_{soil}$ = depth of soil = 0.1 m for grassland and 0.2 m for agricultural soil.

Thus for 1,3-butadiene k_{volat} can be estimated at 6.33 d^{-1} for grassland and 3.16 d^{-1} for agricultural soil. The half-life for volatilisation from soil can be estimated at 0.11 days (2.6 hours) for grassland and 0.22 days (5.3 hours) for agricultural soil.

3.1.2.2.2 Adsorption

1,3-Butadiene has a log Kow value of 1.99. According to the TGD, the following partition coefficients can be estimated from this, assuming the fraction of organic carbon in soil, sediment and suspended sediment is 0.02, 0.05 and 0.1 respectively (default values):

soil organic carbon - water partition coefficient (Koc):	51.6 l/kg
soil-water partition coefficient:	1.03 l/kg
sediment-water partition coefficient:	2.58 l/kg
suspended sediment-water partition coefficient:	5.16 l/kg

The equivalent values for the dimensionless forms of the partition coefficients are $K_{soil-water}$= 2.38 m^3/m^3, $K_{sed-water}$= 2.09 m^3/m^3 and $K_{susp-water}$= 2.19 m^3/m^3. These indicate that adsorption onto soil and sediment is not likely to be important for 1,3-butadiene.

3.1.2.3 Accumulation

No measured bioconcentration factors (BCF) are available for 1,3-butadiene. Estimated bioconcentration factors for fish have been reported in IUCLID. For *Pimephales promelas* (fathead minnow) exposed for a 304-day period, the estimated BCF is 13 (US EPA, 1991). Another estimation method gave a BCF for fish of 19.1 (Hansch and Leo, 1982).

Using the equation log BCF = 0.85×log Kow – 0.70 as recommended in the TGD, a BCF of 9.8 can be estimated for 1,3-butadiene (log Kow = 1.99).

The low estimated BCF values indicate that 1,3-butadiene is unlikely to bioconcentrate or bioaccumulate in the food chain.

3.1.3 Aquatic Compartment (incl. sediment)

3.1.3.1 Calculation of PEC

3.1.3.1.1 Calculation of PEC for surface water

The TGD includes the model for estimating the PEC after treatment of aqueous emissions from a wastewater treatment plant (WWTP). The PEC_{local} calculates the concentration of the chemical after release to a typical WWTP (as defined in the TGD), taking into account the effects of biodegradation through the plant, dilution in the receiving stream and initial adsorption to sediments and suspended matter. It may be calculated from:

$$PEC_{local} = \frac{C_{eff}}{(1+K_{p(susp)}.c_{susp})\cdot D} \text{ mg/l} + PEC_{regional}$$

where: C_{eff} = concentration of the chemical in the WWTP effluent (mg/l)

$K_{p(susp)}$ = suspended matter - water adsorption coefficient. This is estimated as 5.16 l/kg for 1,3-butadiene

c_{susp} = concentration of suspended matter in the river (kg/l). This varies between wide ranges. A typical default of 15 mg/l (1.5×10^{-5} kg/l) is used in the absence of other information

D = dilution factor of wastewater stream into receiving stream. In the absence of specific data, a dilution factor of 10 is used

$PEC_{regional}$ = 7.3×10^{-5} mg/l (see below)

The concentration of the chemical in WWTP effluent is given by:

$$C_{eff} = \frac{W\,(100-P)}{Q\cdot 100} \text{ g/l}$$

where: W = emission rate (g/d)

Q = volume of wastewater into which the emission occurs. For the standard environment, Q should be based on the average sewage flow of a 10,000 population, who produce 200 l/day giving a volume of 2,000,000 l/day

P = percentage removal of 1,3-butadiene through a typical wastewater treatment plant

Local releases to the water compartment were estimated in Section 3.1.1 and summarised in **Table 3.6**. These values are estimates of the amounts released per year. In order to convert them into amounts released per day, it will be assumed that release occurs over 300 days. For 1,3-butadiene the percentage removal in the wastewater treatment plant is estimated from the Simpletreat model given in the TGD. This requires the values for log Kow and log Henry's law

constant and knowledge of whether the compound is non-, readily or inherently biodegradable. As a conservative approach, it is assumed that no biodegradation occurs during wastewater treatment. Using this method, the percentage removal of 1,3-butadiene is estimated to be approximately 94.6%, of which ~94.1% volatilises and ~0.5% goes to sludge. The remaining 5.42% is released to surface water.

The values of PEC_{local} estimated by this method are shown below:

1,3-Butadiene production	PEC_{local} = 0.85 mg/l
Styrene-butadiene rubber/latex production	PEC_{local} = 0.22 mg/l
Polybutadiene production	PEC_{local} = 0.087 mg/l
Polychloroprene production	PEC_{local} = 0.081 mg/l
Nitrile-butadiene rubber/latex production	PEC_{local} = 0.0017 mg/l
ABS production	PEC_{local} = 0.054 mg/l
Adiponitrile/hexamethylene diamine production	PEC_{local} = 0.0046 mg/l

Later in Section 3.1.3.3, the results of PEC calculations for specific production and processing sites based on actual emission and dilution information where available are presented.

The $PEC_{regional}$ and $PEC_{continental}$ can be estimated using EUSES (printout attached as an Appendix). The amounts of 1,3-butadiene released into the regional model were 120 tonnes/year to wastewater (a 70% connection rate to wastewater treatment plants was assumed) and 1,435 tonnes/year to air (see Section 3.1.1 for how these values were derived). In addition, the model was run assuming that the region contained the largest plant for production and each use. In this case the amounts released were 143 tonnes/year to wastewater and 1,818 tonnes/year to air. It is assumed that 1,3-butadiene is not readily biodegradable and the atmospheric half-life is 0.4 days. The results from the model for surface water were $PEC_{regional}$ = 0.073 µg/l (assuming 10% of the total EU release occurs in the region) and $PEC_{regional}$ = 0.087 µg/l (assuming the region contains the largest plant for production and each use). The $PEC_{continental}$ was 7.6-7.8 ng/l. These very low values reflect the volatility of 1,3-butadiene and its removal in the atmosphere.

3.1.3.1.2 Calculation of PEC for sediment

The concentration in sediment (bulk) can be derived from the corresponding water body concentration, assuming a thermodynamic partition equilibrium:

$$PEC_{local(sed)} = \frac{K_{susp\text{-}water} \cdot PEC_{local(water)} \cdot 1{,}000}{RHO_{susp}}$$

where: $K_{susp\text{-}water}$ = sediment matter - water partition coefficient. This is estimated at 2.19 m^3/m^3 for 1,3-butadiene

RHO_{susp} = bulk density of suspended matter = 1,150 kg/m^3

This method gives the following estimated values of $PEC_{local(sed)}$:

1,3-Butadiene production	$PEC_{local(sed)}$ = 1.61mg/kg wet wt.
Styrene-butadiene rubber/latex production	$PEC_{local(sed)}$ = 0.41 mg/kg wet wt.
Polybutadiene production	$PEC_{local(sed)}$ = 0.17 mg/kg wet wt.
Polychloroprene production	$PEC_{local(sed)}$ = 0.16 mg/kg wet wt.
Nitrile-butadiene rubber/latex production	$PEC_{local(sed)}$ = 0.0032 mg/kg wet wt.
ABS production	$PEC_{local(sed)}$ = 0.10 mg/kg wet wt.
Adiponitrile/hexamethylene diamine production	$PEC_{local(sed)}$ = 0.0088 mg/kg wet wt.

Using a similar method and the $PEC_{regional}$ estimated in Section 3.1.3.1.1 for surface water, the $PEC_{regional(sed)}$ can be estimated using EUSES (see Appendix) as 0.12 µg/kg wet wt. (assuming 10% of the total EU release occurs in the region) and 0.14 µg/kg wet wt. (assuming the region contains the largest plant for production and each use).

3.1.3.2 Measured exposure data

There are two reports of levels of 1,3-butadiene in surface waters. In US drinking water, 1,3-butadiene was detected but not quantified (US EPA, 1981).

Also in the US, 204 water samples were collected from sites at 20 heavily industrialised river basins, estuaries, canals and lakes during 1975-76. Only compounds present at concentrations greater that 1 µg/l were tabulated and 1,3-butadiene was reported only once at a concentration of approximately 2 µg/l in the Carquinez Straight in the San Francisco Bay area (Ewing et al., 1977).

Information on the levels of 1,3-butadiene in effluent streams from a production plant in Canada have recently become available (Environment Canada/Health Canada, 2000). Composite samples of aqueous effluents were collected at 4-hour intervals during 1996 and 1,3-butadiene was detected in only 2 out of 2,103 samples collected. The levels found in the two samples were 2 and 5 µg/l, and would have been further diluted in the receiving water.

No measured levels of 1,3-butadiene in the sediment compartment were found.

3.1.3.3 Comparison of measured and modelled values of exposure for the aquatic compartment

Clearly there is a discrepancy between the predicted concentrations of 1,3-butadiene and the measured levels found in the environment. Although the monitoring data for the aquatic compartment is fairly limited, it is clear from a large survey of industrial areas in the US that 1,3-butadiene is present in surface waters at only low concentrations (2 µg/l or less), if it is present at all. A similar situation was found in the recent effluent monitoring data at a production site in Canada. Although it is not known if any of the measurements from the US survey were taken just downstream of a 1,3-butadiene production or use site and so are directly comparable with the scenarios that the PEC_{local}s represent, it is possible that the PEC_{local}s estimated here are likely to grossly overestimate the actual situation.

There are several reasons why the calculated PEC_{local} probably overestimates the actual situation. Firstly a wide range of emission factors have been quoted for release to water and it is possible that the factors at the high end of this range represent older plants that at the time had poor

emission control technology. Information reported in the US EPA Toxic Release Inventory indicates that, in the US, the total emission of 1,3-butadiene to wastewater from production and use had reduced from 237 tonnes/year in 1988 to 3.45 tonnes/year in 1993 (US EPA, 1993), with a further reduction to around 1 tonne/year in 1997. The 1993 production of 1,3-butadiene in the US was around 1,405,000 tonnes/year, and so the overall emission factor in 1993 for release of 1,3-butadiene to water can be estimated as $2.45 \cdot 10^{-3}$ kg/tonne produced/used, which is considerably lower than the values used in this assessment.

Secondly, most of the plants considered in the local scenario are very large (this is particularly true for 1,3-butadiene production) and it is likely that the default river flow is not appropriate for such plants. The standard river in the TGD, which produces a 10-fold dilution of the standard wastewater treatment plant effluent, has a flow of 0.23 m^3/sec. The TGD (Chapter 7) indicates that a more typical value for a river receiving effluent from a plant producing and using chemicals as intermediates would be 60 m^3/sec. Using this flow rate would produce a PEC for production of 3.3 μg/l.

Information has been received from a number of EU sites (see Section 3.1.1.8). The actual PECs at these sites are generally low (<1 μg/l), as a result of higher dilution and lower releases than used in the worst-case assessment here (releases to wastewater were reported to be zero or negligible at six sites, were not detected in influent/effluent of the wastewater treatment plant at five sites, were in the range <50 kg/year to 60 tonnes/year at six sites, with the higher release values being associated with higher dilution, with no data available for five sites). Concentrations in water have been calculated from the data provided for actual production and processing sites. For some of the sites, information on both releases and receiving water flow rates was available. For other sites, information on the actual flows and the capacity of the plants was available but nothing on releases, and for a last group of sites only the capacity was available. The gaps in the data set were filled by using the emission factors selected in Section 3.1.1 and the TGD receiving water flow for chemical production sites as appropriate. These calculations cover all of the known production and processing sites. The values for the production sites fall in to the following ranges: <0.1 μg/l, 2 sites; 0.1-1.0 μg/l, 9 sites; 1.0-10 μg/l, 10 sites; >10 μg/l, 3 sites. The highest concentration calculated is 25 μg/l. These sites include some where processing also occurs; in these cases the emissions were combined. Many of the processing sites use butadiene in more than one type of process on site. In each case, the emissions from all of the processes using butadiene have been combined for that site. For the 37 processing sites, the concentrations fall into the following ranges: <0.1 μg/l, 3 sites; 0.1-1.0 μg/l, 32 sites; 1.0-10 μg/l, 1 site; >10 μg/l, 1 site. The maximum concentration is 16 μg/l.

Thirdly, volatilisation from the receiving water is likely to be rapid for 1,3-butadiene and this is not taken into account when considering the PEC_{local}. So, even if relatively high concentrations are found in the vicinity of a production or use site, the concentration will decrease rapidly downstream of the site. An estimate of the significance of the effect of volatilisation on the concentration 1 km downstream of a point of release can be obtained by using the SAMS river model. The model was run for two rivers, one of 0.23 m^3/s flow rate, 10 m width and 0.5 m depth and one of 60 m^3/s flow rate, 40 m width and 0.5 m depth. The predicted loss from the river due to volatilisation 1 km downstream from the source of discharge was estimated to be 15-17%.

Based on the discussion above, the PEC values calculated in Section 3.1.4.1 are not considered to be representative of production and use sites. Instead, the highest calculated values based on at least some data from actual sites will be used. These are 25 μg/l for production and 16 μg/l for

processing. This latter value will be used to represent all processing activities. The limited measurements of 1,3-butadiene in water are all below this value.

Using these values of PEC_{local} for surface water, the corresponding $PEC_{local(sed)}$ can be estimated as 48 µg/kg wet wt for production and 30 µg/kg wet wt for processing . No measured data are available for sediment, but given the properties of 1,3-butadiene, the concentration would be expected to be low.

Very low concentrations were predicted for surface water (0.073 µg/l) and sediment (0.12 µg/kg) in the regional scenario. The value for surface water is consistent with the many "not detected" values reported for 1,3-butadiene in the survey of surface waters in industrial areas of the USA. The main sources of direct release to surface water and hence sediment have been assumed to be from 1,3-butadiene production and its subsequent use in polymers. It is possible that the actual amounts released to surface water from these processes are much lower than those estimated in this assessment (see the discussion above) and so these $PEC_{regional}$ values might actually be lower still.

3.1.4 Terrestrial Compartment

3.1.4.1 Calculation of PEC

1,3-Butadiene is not applied directly to the soil or crops, but it may occur in sewage sludge in very small amounts and may thus be applied to soil. It is also released to the air and may undergo deposition to land.

The concentrations in soil can be estimated using EUSES (see Appendix). No biodegradation was assumed in the model. The concentrations estimated in agricultural soil, averaged over 30 days, are shown below:

1,3-Butadiene production	$PEC_{local(soil)}$ = 29 µg/kg wet wt.
Styrene-butadiene rubber/latex production	$PEC_{local(soil)}$ = 7.8 µg/kg wet wt.
Polybutadiene production	$PEC_{local(soil)}$ = 3.1 µg/kg wet wt.
Polychloroprene production	$PEC_{local(soil)}$ = 2.8 µg/kg wet wt.
Nitrile-butadiene rubber/latex production	$PEC_{local(soil)}$ = 0.11 µg/kg wet wt.
ABS production	$PEC_{local(soil)}$ = 1.9 µg/kg wet wt.
Adiponitrile/hexamethylene diamine production	$PEC_{local(soil)}$ = 0.16 µg/kg wet wt.

The estimated concentrations of 1,3-butadiene in the soil in the regional and continental scenarios have also been estimated using EUSES. The results from the model for agricultural soil were $PEC_{regional}$ = 0.10 ng/kg wet wt. (assuming 10% of the total EU release occurs in the region) and $PEC_{regional}$ = 0.12 ng/kg wet wt. (assuming the region contains the largest plant for production and each use). Lower levels (0.01 ng/kg wet wt.) were predicted in industrial and natural soil in the regional scenario.

3.1.4.2 Measured exposure data

No measured levels of 1,3-butadiene in the soil compartment were found.

3.1.5 Atmosphere

3.1.5.1 Calculation of PEC

Clearly release to the air is very important for 1,3-butadiene as it is such a volatile chemical. From the WWTP model, an estimated 94.1% of 1,3-butadiene input to the WWTP will be emitted to air. Thus, when calculating the PEC, this "indirect" release to the atmosphere should be compared to the direct release to the atmosphere from the site, and the highest value used in the PEC calculation.

According to the TGD, the concentration of a gaseous substance in air can be calculated from the relationship:

$$C_{local\ (air)} = Emission \cdot Cstd_{air}\ (mg/m^3)$$

$$PEC_{local\ (air,\ ann)} = C_{local\ (air)} \cdot \frac{Temission}{356} + PEC_{regional\ (air)}$$

where:
- Emission = emission rate to air (kg/s) (either direct or from WWTP)
- $Cstd_{air}$ = standard concentration in air, where a source strength of 1 kg/d leads to a concentration of 2.78×10^{-4} mg/m^3
- $C_{local\ (air)}$ = concentration in air at 100 m from a point source during an emission episode
- Temission = number of days/year that emission takes place (300 days/year)
- $PEC_{regional\ (air)}$ = 2.57×10^{-5} mg/m^3

Using this relationship and the release rates estimated in Section 3.1.1 (assuming that 94.1% of the release to wastewater treatment), the following $PEC_{local(air,\ ann)}$ can be estimated assuming that release occurs over 300 days:

	Direct emission	Emission via wwtp	$PEC_{local(air,\ ann)}$
1,3-Butadiene production	10.7 kg/day	294 kg/day	67 µg/m^3
Styrene-butadiene rubber/latex production	1,920 kg/day	32 kg/day	439 µg/m^3
Polybutadiene production	30.1 kg/day	827 kg/day	189 µg/m^3
Polychloroprene production	28.2 kg/day	400 kg/day	91.4 µg/m^3
Nitrile-butadiene rubber/latex production	0.56 kg/day	233 kg/day	53.3 µg/m^3
ABS production	18.8 kg/day	350 kg/day	80.0 µg/m^3
Adiponitrile/ hexamethylene diamine production	1.57 kg/day	10 kg/day	2.3 µg/m^3

Vehicle exhausts are also a significant source of release of 1,3-butadiene to air. Strictly speaking these are diffuse sources but it is possible to estimate a "local" concentration if some gross assumptions are made. For example, if it is assumed that 1,000 cars/second are in a "local environment", each travelling at 30 mile/hour and emitting 4 mg 1,3-butadiene/mile (see Section 3.1.1.8), then the total emission of 1,3-butadiene would be $3.3 \cdot 10^{-5}$ kg/s or 2.85 kg/day. Using the modelling approach above, this would give a $PEC_{local(air, ann)}$ of around 0.8 µg/m^3.

The $PEC_{regional}$ and $PEC_{continental}$ can be estimated using EUSES (printout attached as an Appendix). The amounts of 1,3-butadiene released into the regional model were 120 tonnes/year to wastewater (a 70% connection rate to wastewater treatment plants was assumed) and 1,435 tonnes/year to air (see Section 3.1.1 for how these values were derived). In addition, the model was run assuming that the region contained the largest plant for production and each use. In this case the amounts released were 143 tonnes/year to wastewater and 1,818 tonnes/year to air. It was assumed that 1,3-butadiene was not readily biodegradable and the atmospheric half-life was 0.4 days. The results from the model for air were $PEC_{regional}$ = 25.7 ng/m^3 (assuming 10% of the total EU release occurs in the region) and $PEC_{regional}$ = 32.1 ng/m^3 (assuming the region contains the largest plant for production and each use). These very low values are a result of the reactivity of 1,3-butadiene in the atmosphere.

3.1.5.2 Measured exposure data

Table 3.8 below shows the levels of 1,3-butadiene measured in air at different locations.

In the United Kingdom, continuous routine monitoring for 1,3-butadiene is carried out at several locations (see **Table 3.8**, reference A). Typically, average urban levels are up to 1.5 µg/m^3, with average rural levels being lower at up to around 0.09 µg/m^3. Higher levels have been noted under certain conditions. For instance, in London in December 1991 heavy traffic and very cold weather produced a pollution episode where the hourly average concentration of 1,3-butadiene was around 22 µg/m^3. The large difference in concentrations between rural and urban locations indicates that road traffic emissions are a significant source in urban areas and that 1,3-butadiene in the atmosphere degrades rapidly and so is not transported over significant distances from release (DoE, 1994).

Table 3.8 1,3-Butadiene levels in air

Location	Sample type	Comments	Level (µg/m^3)	Ref.
London, UK	urban roadside	July-December 1991 average January-June 1992 average February-December 1993 average	2.4 1.4 0.71	A
London, UK	urban	August 1992-March 1994 average	0.46	A
Middlesbrough, UK	urban	January-December 1992 average January-December 1993 average	0.77 0.99	A
Belfast, UK	urban	August 1993-March 1994 average	1.4	A
Birmingham, UK	urban	August 1993-March 1994 average	0.91	A
Cardiff, UK	urban	November 1993-March 1994 average	1.3	A

Table 3.8 continued overleaf

Table 3.8 continued. 1,3-Butadiene levels in air

Location	Sample type	Comments	Level (μg/m³)	Ref.
Edinburgh, UK	urban	October 1993-March 1994 average	0.53	A
West Beckham, UK	rural	January 1990-March 1991 average	0.088	A
Great Dun Fell, UK	remote rural	January 1990-March 1991 average	0.022	A
Bilthoven, the Netherlands	rural	average or median value	0.07	J
Houtakker, the Netherlands	rural	average or median value	0.12 summer 0.73 winter 0.43 year	J
Eastern United States	urban	24-hour samples collected every 12 days at 12 sites during 1990; detected in 30.4% of samples (detection limit 0.066 μg/m³)	315 max 2.2 mean 0.69 median	K
United States	urban	3-hour samples collected between 6 and 9 am at 7 sites during 1990; detected in 54% of samples (detection limit 0.22 μg/m³)	15.1 max 4.4 mean	L
Eastern United States	urban	24-hour samples collected every 12 days at 14 sites during 1989; detected in 40.3% of samples (detection limit 0.088 μg/m³)	10.6 max 0.40-0.46 mean 0.60 median	I
Eastern United States	urban	24-hour samples collected every 12 days at 19 sites from October 1987-1988; detected in 31.8% of samples (detection limit 0.22 μg/m³)	6.9 max 0.44-0.50 mean	C
Windsor, Ontario	urban	13 Month average, 1987-1988	0.5	B
Los Angeles	suburban/ urban	Central business district, Aug-Nov 1960; samples collected over 1 hour between 7 and 9 am on days where smog formation was expected; 13/16 samples positive.	<1.1-19.9	D
Los Angeles	urban	Average (Sept-Nov 1967)	4.4	E
Azusa (California)	urban	Average (Sept-Nov 1967)	2.2 2.2-4.4	E
United States	urban suburban rural	382 samples 196 samples 2 samples	0.64 0.71 0.22	F
United States	suburban/ urban	Literature survey. 498 samples, 1970-1980.	3.3 median 2.7-4.9 Interquartile range	G
United States	source dominated	Literature survey. 9 samples, 1970-1980.	4.2 median 1.3-18.4 Interquartile range	G
Houston	source dominated/ urban	1973-1974, 16 out of 21 grab samples positive.	1.3-125	H

References:

A - DoE, 1994
B - Dann et al., 1989
C - McAllister et al., 1989
D - Neligan, 1962
E - Altshuller et al., 1971
F - Shah and Heyerdahl, 1988
G - Brodzinsky and Singh, 1983
H - Lonneman et al., 1979
I - McAllister et al., 1990
J - Slooff et al., 1994
K - McAllister et al., 1991a
L - McAllister et al., 1991b

Stephens and Burleson (1969) took air samples at various localities in southern California. 1,3-Butadiene was detected at a level of 79.2 µg/m^3 in air from an industrial area of Los Angeles County. Samples taken from Riverside indicated that the air levels of 1,3-butadiene were much higher in the morning (approximately 8.0 µg/m^3 at 07:30) compared with late afternoon (0.64 µg/m^3 at 16:10). These latter results are consistent with vehicle exhaust emissions being a major source of atmospheric 1,3-butadiene and that it is rapidly degraded in the atmosphere.

ATSDR (1992) reports a personal communication with the Texas Air Control Board (TACB). On a monitoring trip in 1986, the TACB measured ambient air concentrations within a mile of a petrochemical complex suspected of exceeding air quality limits. The average concentration of 1,3-butadiene was 221 µg/m^3 with a highest daily and hourly average of 316 µg/m^3 and 2,000 µg/m^3. A 1989 monitoring trip to another complex had maximum 12 hour and 1 hour average concentrations of 530 µg/m^3 and 1,419 µg/m^3 within one mile of the complex.

3.1.5.3 Comparison of measured and modelled PEC

There appear to have been very few measurements of 1,3-butadiene taken near to point sources but the calculated $PEC_{local(air)}$s are in reasonable agreement with levels found near to refineries in the US.

Information provided by industry on release from fifteen production and/or use plants gives releases to air in the range 0.006-240 tonnes/year, with some plants reporting zero emissions. Based on these data, the estimated $PEC_{local(air, ann)}$ are in the range 0.005-183 µg/m^3, with several sites in the 10-100 µg/m^3 range. Therefore, the estimated releases to air are in reasonable agreement with the actual releases from some plants. However, it should be noted that the releases reported for individual sites cover a wide range and so local concentrations associated with some sites will be much less than the worst-case figures given here.

Long-term monitoring programs for 1,3-butadiene are carried out in some countries. Typical levels of 1,3-butadiene measured in urban areas are around 1.5 µg/m^3 and vehicle emissions are thought to contribute significantly to these levels. This value is in good agreement with the "$PEC_{local(air, ann)}$" of 0.8 µg/m^3 estimated for traffic. The calculated $PEC_{regional}$ is slightly lower than these urban levels and is more consistent with levels found in rural areas. For this reason a figure of 1.5 µg/m^3 will be used as a realistic worst-case estimate for the $PEC_{regional}$ in the rest of this assessment. This figure also represents the likely "local" exposure to 1,3-butadiene as a result of vehicle emissions.

3.1.6 Secondary poisoning

1,3-Butadiene is not bioaccumulative and is highly volatile and so the major route of exposure to organisms higher up the food chain is likely to be directly from air.

3.1.7 Summary of PECs

Table 3.9 summarises the PECs derived for use in the environmental risk assessment. The PECs are based on estimated releases, site-specific information on releases and likely dilution, knowledge of the likely environmental behaviour of the substance and monitoring data. Further information, particularly on direct releases to water from production processes and use in

polymer manufacture would add confidence to the assessment. The $PEC_{regional}$ for air is based on extensive air monitoring surveys.

Table 3.9 Summary of PECs that will be used in the environmental risk characterisation

Source (PEC type)	Surface water (mg/l)	Sediment (µg/kg)	Soil (µg/kg)	Air (µg/m³)
1,3-Butadiene production (local)	0.025	48	29	67
Styrene-butadiene rubber/latex production (local)	0.016	30	7.8	439
Polybutadiene production (local)	0.016	30	3.1	189
Polychloroprene production (local)	0.016	30	2.8	91.4
Nitrile-butadiene rubber/latex production (local)	0.016	30	0.11	53.3
ABS production (local)	0.016	30	1.9	80.0
Adiponitrile production (local)	0.016	30	0.16	2.3
All known sources (regional) [a)]	7.3×10^{-5}	0.12	0.0001	0.03

[a)]: excludes biomass burning

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Aquatic toxicity

No valid aquatic toxicity tests appear to have been carried out using 1,3-butadiene. A 24-hour Median Tolerance Limit (LC_{50}) of 71.5 mg/l for pin perch (*Lagodon rhomboides*) is frequently quoted for 1,3-butadiene but the actual chemical tested was cyano-1,3-butadiene (Daugherty and Garrett, 1951) and so the result is not relevant to this assessment.

No data are available on the toxicity of 1,3-butadiene to microorganisms.

The lack of experimental aquatic toxicity results for 1,3-butadiene is not surprising in view of the physical nature of the substance. Indeed, due to its high vapour pressure and flammable nature it would be very difficult to test meaningfully.

In the absence experimental toxicity data, two approaches can be taken. Firstly, the toxicity of 1,3-butadiene can be estimated using suitable quantitative structure-activity relationships (QSAR); and secondly, toxicity data from structurally similar substances can be used to assess the likely toxicity of 1,3-butadiene. The two approaches should be seen as complementary.

3.2.1.1.1 QSAR Estimations

The TGD gives equations for estimating toxicity endpoints for various species. The following toxicity data has been derived for 1,3-butadiene using a log Kow value of 1.99 and a molecular weight of 54.09 g/mole. The equations used are thought to be suitable for non-polar narcotic chemicals and it is thought that 1,3-butadiene is a member of this class of chemical (Bol et al., 1993).

72h-EC_{50} for algae	= 32.6 mg/l
48h-EC_{50} for freshwater invertebrates (*Daphnia magna*)	= 33.3 mg/l
96h-LC_{50} for freshwater fish (fathead minnow (*Pimephales promelas*))	= 44.8 mg/l
16-day NOEC for fresh water invertebrates (*Daphnia magna*) reproduction/growth	= 6.2 mg/l
28-day NOEC for freshwater fish (zebra fish (*Brachydanio rerio*) and fathead minnow (*Pimephales promelas*))	= 4.4 mg/l

3.2.1.1.2 Toxicity of structurally similar chemicals

A limited amount of information is available for two structurally similar chemicals, isoprene (2-methyl-1,3-butadiene) and 1,3-pentadiene. Both these substances are highly volatile (although not as volatile as 1,3-butadiene) and so are likely to be difficult to test.

The data for 1,3-pentadiene have been reviewed as part of the OECD HPV program. The following results are taken from the OECD assessment. Short-term tests were carried out with fish (fathead minnow (*Pimephales promelas*)), *Daphnia magna* and algae (*Selenastrum capricornutum*). The tests were carried out to GLP using OECD test guidelines. The fish and *Daphnia* tests used a 24-hour static renewal procedure and the concentration of the test substance was measured at the beginning and end of every 24-hour period. The concentration of 1,3-pentadiene was found to decrease over the 24-hour period in both tests but it was thought that this decrease would not affect the results significantly. In the algal study, no renewal of the test solution was carried out over the test period. It was again reported that the concentrations were measured at the beginning and end of the test and that losses occurred during the test. The results of the tests were 96-h LC_{50} to fish = 139.9 mg/l, 48-h EC_{50} to *Daphnia* = 221.5 mg/l and 96-h EC_{50} for algae = 174.6 mg/l based on growth rate and 245.8 mg/l based on growth inhibition. The NOEC for algae was 40.9 mg/l. Given the inherent difficulties in testing the substance, the results (particularly for fish and *Daphnia*) can be considered as being reasonably reliable.

Toxicity information has been reported for isoprene with several fish species (Pickering and Henderson, 1966). The tests were carried out using a static system and no attempt was made to limit volatilisation or monitor the concentration. The 96-h LC_{50}s reported were 74.8 mg/l and 86.5 mg/l with fathead minnow (*Pimephales promelas*) in hard and soft water respectively, 42.5 mg/l with bluegill sunfish (*Lepomis macrochirus*) in soft water, 180 mg/l with goldfish (*Carassius auratus*) in soft water and 240 mg/l with guppy (*Lebistes reticulata*) in soft water. LC_{50}s were also reported after 24 and 48 hours but these were identical to the 96-h LC_{50}. Given that isoprene is likely to be quite volatile these results are probably not reliable over the 96-hour exposure period but may give an indication of the toxicity seen over a shorter exposure period (e.g. 24 hours).

Toxicity data has also been generated for isoprene with *Daphnia magna* and algae (*Scenedesmus quadricauda*). These tests are reported in IUCLID for isoprene but the experimental details are not published in the open literature and so it is not currently possible to comment on the validity of the results. The results reported for *Daphnia* were 24-h EC_{50} = 260 mg/l and 48-h EC_{50} = 140 mg/l. The 96-h EC_{50} for algae was >1,000 mg/l.

Since values for the log Kow are available for both isoprene and 1,3-pentadiene, it is possible to estimate the toxicity of these substances using the QSARs given in Chapter 4 of the TGD and compare the estimated results with the measured data. The results of such an analysis are shown below in **Table 3.10**. As can be seen from **Table 3.10,** the QSAR estimates are generally in agreement to within a factor of 10 of the measured data, and the QSAR data are almost always lower than the measured data.

Table 3.10 Comparison of QSAR estimates and measured aquatic toxicity data for 1,3-pentadiene and isoprene

Endpoint	QSAR estimate	Measured data
1,3-pentadiene (log Kow = 2.3 (calculated; from IUCLID) or 1.5 (estimated; OECD assessment))		
Fish 96h-LC_{50}	30.8 mg/l or 147 mg/l	139.9 mg/l
Daphnia 48h-EC_{50}	21.3 or 123 mg/l	221.5 mg/l
Algae 72h-EC_{50}	20.1 or 127 mg/l	174.6 mg/l
Isoprene (log Kow =2.3 (calculated ClogP (Bol et al., 1993))		
Fish 96h-LC_{50}	30.8 mg/l	42.5-240 mg/l
Daphnia 48h-EC_{50}	21.3 mg/l	140 mg/l
Algae 72h-EC_{50}	20.1 mg/l	>1,000 mg/l

3.2.1.2 Derivation of the PNEC for the aquatic compartment

From the aquatic toxicity results reported above it can be seen that data from structurally similar compounds suggest that 1,3-butadiene may be slightly less toxic than might be expected from QSAR predictions. Therefore, in the absence of experimental data for 1,3-butadiene it is proposed to estimate the PNEC based on both the acute $L(E)C_{50}$ QSAR predictions with an assessment factor of 1,000 and the long-term NOEC QSAR predictions with an assessment factor of 100. This approach gives a $PNEC_{water}$ of 32.6 µg/l from the acute QSAR data and 44 µg/l from the long-term NOEC QSAR data. As a conservative approach, the lower $PNEC_{water}$ of 32.6 µg/l will be used in the assessment.

No experimental or predicted toxicity data are available for the sediment compartment. It is possible to estimate a tentative PNEC for sediment based on the PNEC for surface water by using the equilibrium partitioning method (as described in the TGD).

$$PNEC_{sediment} = \frac{K_{susp\text{-}water} \cdot PNEC_{water} \cdot 1{,}000}{RHO_{susp}}$$

where $K_{susp\text{-}water}$ = suspended sediment-water partition coefficient = 2.19 m^3/m^3
RHO_{susp} = bulk density of suspended sediment = 1,150 kg/m^3

Thus, the tentative PNEC for sediment is 62.1 µg/kg wet wt.

3.2.2 Terrestrial compartment

There are no toxicity data available for terrestrial organisms exposed via soil. Exposure of plants to 1,3-butadiene vapour is covered in Section 3.2.3.1.

In the absence of experimental data for effects in soil-dwelling organisms, the equilibrium partitioning approach can be used as a screening tool. This approach compares the estimated soil pore water concentration with the PNEC derived for aquatic organisms. This approach will be used here, but it should be noted that there are many uncertainties associated with the derivation of the PNEC for aquatic organisms and so the PNEC for soil organisms should be regarded as tentative.

$$PNEC_{soil} = \frac{K_{soil\text{-}water} \cdot PNEC_{water} \cdot 1{,}000}{RHO_{soil}}$$

Where $K_{soil\text{-}water}$ = soil-water partition coefficient = 2.38 m^3/m^3
RHO_{susp} = bulk density of suspended sediment = 1,700 kg/m^3

Taking the PNEC for aquatic organisms to be 32.6 µg/l, then the PNEC for soil organisms can be estimated as 45.6 µg/kg, using the soil-water partition coefficient of 1.03 l/kg ($K_{soil\text{-}water}$ = 2.38 m^3/m^3) (see Section 3.1.2.2.2).

3.2.3 Atmosphere

3.2.3.1 Plants

The toxicity of 1,3-butadiene to several species of plant has been determined. All the experiments have been carried out by exposing the plant to 1,3-butadiene vapour, since this is the most likely route of exposure to plants.

Burg and Burg (1967) studied the effect of 1,3-butadiene on growth and tropistic behaviour of etiolated pea stem sections (*Pisum sativum*). After germination, the peas were developed in darkness at 23°C for 7 days. After this time, 10 mm long sections were taken from the 3rd internode and were exposed to 1,3-butadiene in the gas phase in the dark at 23°C. After 3 hours exposure, the sections were visibly inspected for curvature and 15 hours later the section was dried, weighed and measured. The concentration of 1,3-butadiene that was required to produce half-maximum activity in the pea straight growth test was found to be 500,000 ppm (1,110 g/m^3). The small effects seen may have been due to the presence of trace amounts of ethylene in the 1,3-butadiene (around 0.2 ppm), since the half-maximum activity value for ethylene in the same test is around 0.1 ppm.

The effect of 1,3-butadiene on the abscission-regulating activity of the red kidney bean (*Phaseolus vulgaris*) has been studied (Abeles and Gahagan, 1968). 1,3-Butadiene was added to the gas-phase above bean explants aged 21 hours at 25°C and the abscission after 4 hours was measured. The concentration of 1,3-butadiene that was required for half-maximum stimulation of abscission was found to be 100,000 times greater than that of ethylene. Since the half-maximum stimulation concentration of ethylene was found to be around 0.1 ppm, the half-maximum stimulation concentration of 1,3-butadiene was around 10,000 ppm (22.2 g/m^3). Again, any effect seen with 1,3-butadiene could be due to trace amounts of ethylene present in the sample tested.

Further tests on plants have been carried out by Heck and Pires (1962). The effects of 1,3-butadiene on growth and development of various plants including cotton (*Gossypium hirsutum*), cowpea (*Vigna sinensis*), tomato (*Lycopersicum esculentum*), coleus (*Coleus* sp.), sorghum (*Sorghum* sp.) and soybean (*Glycine soja*) was determined. When plants were exposed

to 1,000 ppm (2,210 mg/m^3) of 1,3-butadiene for 7 days, no injury was reported for coleus, sorghum and soybean and only slight injury was reported in cotton, cowpea and tomato. When exposed for 21 days to 1,3-butadiene, no injury was seen in coleus, cotton and tomato exposed to 10 ppm (22.1 mg/m^3) and no significant (<5%) injury was seen in cotton and tomato exposed to 100 ppm (221 mg/m^3). The authors summarised the results as 0% injury occurred on exposure to 22.1 mg/m^3 and only slight (<5%) injury occurred on exposure to both 221 and 2,210 mg/m^3. The nature of the injury was not stated. The 1,3-butadiene tested was >99% purity with impurities including t-butyl catechol, n-butane, butenes and acetylenes.

3.2.3.2 Mammals

From the human health assessment (Section 4), it can be seen that 1,3-butadiene shows low acute toxicity in mammalian system via inhalation. Mice appear to be much more sensitive to 1,3-butadiene than other species tested in studies involving repeated exposure. Ovarian atrophy is seen at 6.25 ppm (13.8 mg/m^3) at the end of a two year study. At 9 and 15 months NOAELs of 62.5 ppm (138 mg/m^3) and 6.25 ppm were seen. Other severe effects, including marked mortality and/or tumour development at 20 ppm (44.2 mg/m^3) and above and tumour development in females at 6.25 ppm (males at 20 ppm) were seen at the end of the study.

3.2.3.3 Other effects

1,3-Butadiene reacts rapidly in the atmosphere with hydroxyl radicals and other atmospheric oxidants (see Section 3.1.2.1.1). Little is known about the oxidation products formed during the reactions of 1,3-butadiene, however, it would be expected that the mechanisms involved and products formed would be similar to those of other simple alkenes.

Alkenes as a group are thought to be important precursors for ozone formation close to the ground during photochemical episodes. Such episodes are observed throughout the EU during most summers. The cause of such photochemical ozone episodes is not straightforward but is thought to involve hydrocarbons, oxides of nitrogen, and sunlight. At a simple level, the ozone is thought to be produced by the reaction of radical species such as peroxy radicals in the presence of nitrogen oxides. The peroxy radicals, and other radical species are thought to be produced from reaction of hydrocarbons with hydroxyl radicals. The region of photochemical ozone production is thought to be governed by the availability of nitric oxide and nitrogen dioxide. The reactivity of the hydrocarbon is thought to relate to the spatial distribution of the photochemical ozone formed within this region. For instance, close to sources of release, photochemical ozone production is driven largely by the oxidation of highly reactive hydrocarbons, however, for photochemical ozone production over longer timescales/distances, hydrocarbons of medium and low reactivity are also needed, along with replenishment of nitric oxide and nitrogen dioxide. Other reactions can also occur during photochemical pollution episodes, such as formation of PAN (peroxyacetylnitrate) and the oxidation of sulphur dioxide and nitrogen oxides to form visibility-reducing aerosols (Derwent and Jenkin, 1990 and 1991).

The formation of photochemical ozone episodes has been modelled (Derwent and Jenkin, 1990 and 1991). The model includes 684 reactions, involving 384 chemical species. The model was originally run using 69 hydrocarbon species, but was later extended to include over 150 hydrocarbon species, including 1,3-butadiene. Alkenes, as a group, were found to be important contributors to photochemical ozone formation, since as well as producing peroxy radicals during their degradation with hydroxyl radicals, they are also thought to form aldehydes, and ketones. The species formed, particularly formaldehyde and acetaldehyde, can undergo direct

photolysis in the atmosphere forming further radical species (such as HO_2) which can oxidise nitric oxide to nitrogen dioxide, subsequently producing ozone. A photochemical ozone creation potential (POCP) of 105 has been determined for 1,3-butadiene using the model. The POCP value reflects the ability of a substance to form low-level ozone as a result of its atmospheric degradation reactions, the POCP value being calculated relative to ethylene (a chemical that is thought to be important in low-level ozone formation and is given a POCP of 100) on a unit mass emission basis. Thus, 1,3-butadiene is likely to play an important role in photochemical smog and low-level ozone formation near to sources of release.

Low-level ozone formation is of concern with respect to effects on human health, as well as possible effects on crops, plants and trees. Organic compounds, which as a class are involved in photochemical ozone formation, fall within the scope of the Geneva Protocol to the UNECE International Convention on Long Range Transboundary Air Pollution (UNECE, 1991) (Derwent 1995).

3.2.3.4 Calculation of PNEC for the atmospheric compartment

The toxicity of 1,3-butadiene to several species of plants has been determined. Low toxicity is generally shown, with any effects seen being possibly due to the presence of trace amounts of ethylene. The lowest concentration reported to show no effects was 22.1 mg/m^3 over a 21-day exposure period. Since several plant species have been tested and little or no effects were seen in plants exposed to 100 times this concentration it is proposed that an assessment factor of 10 is applied to this NOEC. Thus the PNEC for plants exposed to 1,3-butadiene in the atmosphere is 2.2 mg/m^3.

From the mammalian data, a NOAEL/LOAEL of around 13.8 mg/m^3 was seen in a long-term study. Based on these data, a PNEC of around 1.38 mg/m^3 is appropriate using an assessment factor of 10. This is similar to the PNEC obtained based on the plant data.

Given the complexity of the reactions involved, it is not possible to derive a PNEC for other possible atmospheric effects of 1,3-butadiene, such as photochemical ozone formation.

3.2.4 Secondary poisoning

For secondary poisoning to be a possibility and therefore to require assessment, three criteria have to be met. The first is whether indirect exposure to ecosystems can occur. As the bulk of 1,3-butadiene is released to air and its subsequent distribution includes movement to soil and water then this is possible. The second criterion is an indication of bioaccumulation potential. The log Kow for 1,3-butadiene of 1.99 indicates a low potential for bioaccumulation and so indicates that there is no need to carry out an assessment of secondary poisoning. The third criterion is that the chemical be classified on the basis of its mammalian toxicology. 1,3-Butadiene is classified as toxic and so would meet this criterion. Thus, although 1,3-butadiene meets some of the criteria for carrying out an assessment of secondary poisoning, the low bioaccumulation potential indicates that this is not necessary, and so the substance is not a cause for concern with regard to secondary poisoning. The main source of exposure of higher animals to 1,3-butadiene is likely to be via inhalation and this is considered in Section 3.3.3.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

For surface water, a PNEC of 32.6 µg/l has been estimated for 1,3-butadiene based on QSAR and data from structurally similar substances.

The PEC/PNEC ratios obtained, based on the estimated PECs given in **Table 3.9** are:

1,3-butadiene production	PEC/PNEC = 0.77
Styrene-butadiene rubber/latex production	PEC/PNEC = 0.49
Polybutadiene production	PEC/PNEC = 0.49
Polychloroprene production	PEC/PNEC = 0.49
Nitrile-butadiene rubber/latex production	PEC/PNEC = 0.49
ABS production	PEC/PNEC = 0.49
Adiponitrile/hexamethylene diamine production	PEC/PNEC = 0.49

The estimated $PEC_{regional}$ is 0.073 µg/l giving a PEC/PNEC ratio of 0.002, again indicating low concern.

No information (measured or modelled) is available on the toxicity of 1,3-butadiene to sediment dwelling organisms. A tentative PNEC of 62.1 µg/kg wet wt. Has been estimated for the sediment compartment using the equilibrium partitioning method. The PEC/PNEC ratios obtained, based on the estimated PECs given in **Table 3.9** are:

1,3-butadiene production	PEC/PNEC = 0.77
Styrene-butadiene rubber/latex production	PEC/PNEC = 0.49
Polybutadiene production	PEC/PNEC = 0.49
Polychloroprene production	PEC/PNEC = 0.49
Nitrile-butadiene rubber/latex production	PEC/PNEC = 0.49
ABS production	PEC/PNEC = 0.49
Adiponitrile/hexamethylene diamine production	PEC/PNEC = 0.49

The estimated $PEC_{regional}$ for sediment is 0.12 µg/kg giving a PEC/PNEC ratio of 0.002, again indicating low concern.

It is expected that any 1,3-butadiene present in surface water will volatilise rapidly. Therefore, even if 1,3-butadiene were released to surface water from point sources, the concentration would be expected to decrease markedly with increasing distance from the source. Thus any potential problems are likely to be associated with the area immediately downstream of a point source discharge.

It is not possible to carry out a risk characterisation for microorganisms in a wastewater treatment plant, due to the absence of toxicity data and the difficulty in obtaining any.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

3.3.2 Terrestrial compartment

There is no toxicity information available for terrestrial organisms exposed via soil. Given the physical properties of 1,3-butadiene, soil is not thought to be a significant route of exposure, because any 1,3-butadiene deposited onto soil during "rain-out" will rapidly re-volatilise.

A tentative PNEC for soil organisms of 45.6 µg/kg has been derived. The PEC/PNEC ratios estimated using the PECs from **Table 3.9** are:

1,3-butadiene production	PEC/PNEC = 0.63
Styrene-butadiene rubber/latex production	PEC/PNEC = 0.17
Polybutadiene production	PEC/PNEC = 0.07
Polychloroprene production	PEC/PNEC = 0.06
Nitrile-butadiene rubber/latex production	PEC/PNEC = 0.002
ABS production	PEC/PNEC = 0.04
Adiponitrile/hexamethylene diamine production	PEC/PNEC = 0.003

On a regional basis, the PEC/PNEC ratio is 2×10^{-6}, indicating low concern.

Based on the available information, 1,3-butadiene is unlikely to present a risk to the terrestrial environment.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

3.3.3 Atmosphere

3.3.3.1 Plants

A PNEC of 2.2 mg/m^3 has been derived for plants exposed to 1,3-butadiene in air. Using the PECs derived for the local scenario (see **Table 3.9**), the following PEC/PNEC ratios can be estimated (similar ratios would be obtained from the mammalian data):

1,3-butadiene production	PEC/PNEC = 0.03
Styrene-butadiene rubber/latex production	PEC/PNEC = 0.20
Polybutadiene production	PEC/PNEC = 0.09
Polychloroprene production	PEC/PNEC = 0.04
Nitrile-butadiene rubber/latex production	PEC/PNEC = 0.02
ABS production	PEC/PNEC = 0.04
Adiponitrile/hexamethylene diamine production	PEC/PNEC = 0.001

Vehicle exhaust emissions are likely to be an important source of 1,3-butadiene in the regional scenario, for which a $PEC_{regional}$ of 1.5 µg/m^3 gives a PEC/PNEC ratio of 0.0007. Clearly the risk to organisms exposed to 1,3-butadiene via the atmosphere is small. In addition, measures to protect human health from air exposures would also be expected to be protective of higher organisms in the environment.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

3.3.3.2 Other effects

1,3-Butadiene may play a role in photochemical smog and low-level ozone formation. The major source of atmospheric 1,3-butadiene is from vehicle exhausts. However, vehicles fitted with catalysts have been demonstrated to emit much less 1,3-butadiene than non-catalyst vehicles. Therefore, the increasing use of catalyst-equipped vehicles in future will reduce the potential for these effects.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

3.3.4 Secondary poisoning

Although 1,3-butadiene meets some of the criteria given in the TGD for carrying out an assessment of secondary poisoning (see Section 3.2.4), the low bioaccumulation potential indicates that this is not necessary, and so the substance is not a cause for concern with regard to secondary poisoning. The main source of exposure of higher animals to 1,3-butadiene is likely to be via inhalation and this is considered in Section 3.3.3.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General introduction

Definitions and limitations

In this document, unless otherwise stated, the term exposure is used to denote personal exposure as measured or otherwise assessed without taking into account the attenuating effect of any respiratory protective equipment (RPE) which might have been worn. The effect of RPE is dealt with separately. This definition permits the effects of controls, other than RPE, to be assessed and avoids the considerable uncertainty associated with attempting to precisely quantify the attenuation of exposure brought about by the proper use of RPE.

The section entitled general discussion summarises the more important issues arising from the exposure assessments and bring together measured exposure data with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data is limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

EASE predicts exposures as ranges in the form of conventional eight-hour time weighted averages (TWAs). It does not directly predict short-term exposures. However, because these exposures are process specific, they can be thought of as those experienced for that process either over the whole eight hours or over any shorter period. These shorter periods can be further time weighted to construct other eight-hour time weighted averages. Although this device allows short-term exposures to be dealt with by EASE, such constructs should be regarded with caution. Dermal exposure is assessed by EASE as potential exposure rate predominantly to the hands and forearms (approximately 2,000 cm^2).

Overview of exposure

Occupational exposure to butadiene may occur during:

a. catalytic steam cracking of petroleum streams and subsequent extraction of butadiene;
b. the production of butadiene polymers;
c. the use of the polymers; and
d. during the production and handling of motor fuels.

The largest industry sector where workers are exposed to butadiene are those involved with its manufacture and those in the working on polymer production plants. The number of workers exposed to butadiene polymers (for example, in the rubber industry) is clearly greater than those exposed in the monomer and polymer production industries, however, their exposure is very low when compared to these industries. Fajen et al. (1990) measured exposure to butadiene during the use of polymers at two rubber plants and found all results to be lower than the detection limit of 0.3 μg/sample.

To establish occupational exposure during the manufacture of butadiene monomer and polymers about 5,000 results were collated from various sources and presented in this risk assessment. This occupational exposure data was obtained from HSE's National Exposure Database (NEDB), from industry via trade European associations and from published review articles. These showed that over 90% of exposures were less than 5 ppm 8-hour TWA, with the majority of these less than 1 ppm 8-hour TWA. It was concluded that higher results, although on occasion significantly higher than 5 ppm, were as a result of one-off identifiable occurrences and not representative of an individuals workers routine exposure.

Occupational Exposure Limits

Table 4.1 details the occupational exposure limits for EU member states.

Table 4.1 Occupational exposure limits in the EU for butadiene

Country	8-hour TWA		Source of information (these are assumed to be the current limits)
	ppm	mgm^{-3}	
Belgium	10	22	A
Denmark	10	22	A
Finland	1	2	
Germany	15	34	B :processing after polymerisation, loading
	5	11	B :others
Sweden	10	20	A
	20	40	
Switzerland	5	11	A
United Kingdom	10	22	EH40/97 Occupational Exposure Limits 1997. Table 1 Maximum Exposure Limits

A: Occupational exposure limits for airborne toxic substances –ILO, 1991
B : Deutsche Forschungsgemeinschaft, List of MAK and BAT values 1995; Report No.31.

These limits are provided for information and not as an indication of the level of control of exposure achieved in practice in workplaces in these countries.

4.1.1.1.2 Occupational exposure during the production of butadiene and its use in the production of polymers

Occupational exposure during the production of butadiene and its use to manufacture polymers may occur during:

a. the steam cracking of petroleum fractions (butadiene containing product streams);
b. the solvent extraction of the butadiene from the crude C_4 fraction; and
c. the use of butadiene monomer to manufacture polymers.

The steam cracking of the petroleum fraction and the butadiene extraction may be carried out on the same site, although on different plants, with the crude C_4 transferred by pipeline to the solvent extraction plant. There are estimated to be several thousand workers exposed to butadiene during its manufacture and during its use throughout the EU.

The steam cracking of petroleum, the extraction of the butadiene, and the use of butadiene on polymer plants are carried out in closed systems. Occupational exposure for workers on these closed plants will be intermittent and as a result of tasks where the system is breached. Consequently 8-hour TWA exposure arises from a series of short-term exposures. The nature of these tasks and the approach of companies to controlling emissions are likely to be similar for both producers and users of butadiene. Clearly systems are adopted that minimise the potential for the release of butadiene gas during breaches of the plant. Occupational exposure may also occur from fugitive emissions, for example, leaks from pump seals. Occupational exposure during production and use as a chemical intermediate, for example in the production of styrene butadiene rubber, can therefore be considered together. The tasks that give rise to this occupational exposure may include the following.

(a) Material sampling. During use in polymer manufacture, exposure will be progressively more to the reaction products and not butadiene. Therefore the actual exposure may be significantly less than during production. This exposure is likely to very short (less than 1 minute) and dependent on how the emission is controlled. The butadiene monomer manufacturing industry is understood to use “sample bombs”. These “sample bombs” are connected to the system, filled and removed (i.e. the system is closed to the external environment during sampling).

(b) Filling road tankers and ships. Although this work may take about 60 minutes, the actual exposure time will again be very short and primarily when the delivery line is uncoupled. Exposure, however, may be for the duration of the filling if contaminated air displaced from the road or rail tanker, or storage vessel is not controlled. Exposure during coupling is likely to be negligible. The significance of the release during uncoupling will depend on how this is carried out and controlled. The butadiene monomer manufacturing industry is understood (personal communication) to use dry break coupling systems to minimise releases.

(c) Periodic and unplanned maintenance. During planned and unplanned maintenance the potential for exposure exists for the duration of the time taken to carry out the work. The significance of exposure will depend on the steps taken to ensure the system is uncontaminated prior to breaching.

(d) Fugitive emissions. In addition to the above tasks, exposure may also arise from process leaks, which will depend on the integrity of the equipment and again the industry's approach to monitoring and controlling such leaks.

The nature of the above tasks and the potential for exposure are similar for all chemical manufacturing processes. The significance of the resulting exposure will depend on the industries and the individual companies' approach to controlling or preventing emissions.

Occupational exposure data from a number of sources is presented below, namely:

a. butadiene production – HSE exposure data;
b. butadiene production – industry exposure data;
c. butadiene polymer production – HSE exposure data;
d. butadiene polymer production – industry exposure data;
e. butadiene polymer production – published exposure data;
f. butadiene monomer and polymer production – modelled exposure data;
g. butadiene monomer and polymer production – modelled dermal exposure data.

Butadiene monomer production – HSE exposure data

In 1984, HSE conducted a survey of 7 companies, 2 producing butadiene and 5 using this substance as a chemical feed-stock in polymer production. The results for butadiene production are reproduced here, and for polymer production are reported in – polymer production – HSE exposure data.

The exposure data for the two production plants comprised ten personal 8-hour TWAs samples, of which 9 were below 1 ppm and 1 was above 10 ppm (**Table 4.2**). The high personal exposure level of 17 ppm was reported to be due to the draining of pumps and filters for routine cleaning or from collecting samples for quality control analysis.

Table 4.2 Personal exposures during monomer production – 8-hour TWA

Process & operations	Number of samples in given range (ppm)				No of samples	Range (ppm)	Mean (ppm)
	1	1.1 to 10	10.1 to 20	>20			
1,3-butadiene manufacture (2 factories)	9	-	1	-	10	< 0.3 – 17	2

Butadiene monomer production – industry exposure data

In 1993 and then in 1995 CEFIC collated occupational exposure data from EU companies operating petroleum crackers and butadiene extraction plants (data reproduced from ECOTOC special report, 1997). The 1993 exposure data is detailed in **Tables 4.3 and 4.4** for petroleum crackers and butadiene extraction plants respectively and relates to measurements taken between 1986 and 1993.

Table 4.3 Occupational exposure to butadiene at petroleum crackers – 8-hour TWA (streams containing 1,3-butadiene)

Job category	Year of sampling	Number of samples	no of results in specified range (ppm)					
			< 1	1.01 to 3	3.01 to 5	5.01 to 10	10 to 25	> 25
unloading / loading / storage	1986 to 92	92	82	6	3	0	1	0
distillation section	1986 to 93	392	382	3	3	0	2	2
laboratory sampling	1986 to 93	184	178	3	3	0	0	0
maintenance	1986 to 92	371	364	5	1	0	1	0
other	1990 to 92	509	487	20	2	0	0	0
total	1986 to 93	1,548	1,493	37	12	0	4	2

Of the 1,548 personal air sampling results taken for operators working on petroleum crackers 1,493 (96.4%) were less than 1 ppm 8-hour TWA, with 99.6% of results below 5 ppm 8-hour TWA. From the measurements taken on monomer extraction plants 843 (81.4%) of the 1035 results were less than 1 ppm 8-hour TWA, and 92.5% of results were less than 5 ppm 8-hour TWA.

Table 4.4 Occupational exposure to butadiene at EU extraction plants*

Job category	Year of sampling	Number of samples	No of results in specified range (ppm)					
			< 1	1.01 to 3	3.01 to 5	5.01 to 10	10 to 25	> 25
unloading / loading / storage	1986 to 93	224	178	17	9	11	2	7
distillation section	1985 to 93	626	535	39	17	8	12	15
laboratory sampling	1985 to 93	48	29	6	4	3	5	1
maintenance	1986 to 93	127	93	17	3	3	4	7
other	1984 to 92	10	8	2	0	0	0	0
total	1984 to 93	1035	843	81	33	25	23	30

*Butadiene monomer extraction plant (i.e. isolation from C_4 stream)

In 1995, CEFIC repeated the exercise with occupational exposure data collated from 15 of the 16 EU producers of butadiene through a questionnaire sent by their Lower Olefins Sector group. The 15 companies responding covered 18 sites, 15 of which were butadiene extraction plants. Two of the remaining sites were integrated derivatisation units. These results were sent to HSE and are reproduced in ECOTOC's special report on butadiene (1997). Representative 8-hour TWAs and ranges were only provided for the data. Without the number of samples and distribution of the data it was only possible to carry out a limited analysis of the results. In addition, information on the methods used to control exposure were also not provided. Air sampling was carried out by a number of methods, which were generally based on collection on charcoal tubes, solvent desorbtion and analysis by gas chromatography. **Table 4.5** summarises the exposure data.

The results in **Table 4.5** show that measured exposure ranged from 0 to 60 ppm 8-hour TWA. Although it was not possible to determine the number of results below any given value, the data

does suggest that the majority of exposures were less than 5 ppm 8-hour TWA. The activities giving the highest exposures appear to be centred around tasks such as sampling and pipeline coupling. This is particularly evident with the short-term exposure results which were for production, transport and laboratory technicians. These were the only job classifications where short-term exposure were measured, presumably as they involved tasks such as sampling and pipeline uncoupling. These short-term results ranged from 0 to 177 ppm, although the sampling duration was not reported.

Table 4.5 Occupational exposure to butadiene at EU extraction plants

Activity	8-hour TWAs (ppm)			Short term	
	No of* responding sites	range (all samples from all sites)	range of "representative results"**	No of responding sites	range (all samples from all sites)
butadiene extraction plants (15 in total)					
production	13	0 to 14	< 0.01 to 2	5	0 to 100
transport	3	< 0.1 to 1.2	<0.1 to 1	1	27 to 101
storage / filling	10	0 to 18.1	< 0.02 to 5	-	-
laboratory	7	0 to 13.1	0.03 to 1	1	0.1 to 24.6
integrated monomer extraction and SBR production plants (2 in total)					
production	2	0.07 to 60	1.4 & 3.4	2	0 to 177
transport	1	0.02 to 12	0.7	1	0 to 114
storage / filling	-	-	-	-	-
laboratory	1	0.07	0.07	-	-

*No of samples for each site not reported.
** Reported as "representative 8-hour TWA of shift". It is not known whether these are means, medians etc.
< denotes less than.
NB Where "0" is reported in the table, the company did not report the detection limit.

A UK manufacturer of butadiene has also supplied airborne exposure data independently from CEFIC's surveys, although this data may have been collated by CEFIC and thus included in tables 4.3 and 4.4 above. This exposure data represents personal sampling undertaken between 1988 and 1993 and between 1990 and 1994. In these surveys 268 results were obtained. The production of butadiene is within an enclosed system but there is the potential for exposure during routine maintenance of the plant and during the loading and unloading of road tankers or ships. The sampling of personal exposure was carried out for periods of 5 – 8 hours and results were presumed equivalent to an 8-hour TWA. The exposures were measured by a method in which the contaminated air was drawn through a tube packed with Tenax and the butadiene was thermally desorbed and analysed by GC. The recorded exposures are given in **Table 4.6**.

Table 4.6 Personal exposures at UK production plant

Year	No of Results	Mean (ppm)	Max (ppm)
1988 – 1993*	43	0.12	0.72
1990 – 1994*	225	0.44	3.9

*Assumed to be different areas of plant.

All the exposures recorded were below 5 ppm 8-hour TWA with a maximum of 3.9 ppm. There is no indication from which specific locations the samples were taken nor the work activities of those exposed.

Butadiene monomer manufacture – published exposure data

Sorsa et al. (1996) reported the results of personal air sampling carried out at three different butadiene manufacturing plants. These plants were in Finland, Portugal and the Czech Republic. The authors reported that 70% of the results were less than 0.2 ppm 8-hour TWA for the Portuguese and Finnish plants. The results for the sampling at the plant in the Czech republic were reported to be typically between 0.2 and 2 ppm 8-hour TWA, with about 10% of these samples exceeding 10 ppm 8-hour TWA. A few very high exposures of up to 500 ppm were recorded. The reference period for these higher results was not reported.

The authors also reported the results of measurements taken in the polymer production industry (see butadiene polymer manufacture – published exposure data). The authors concluded, in respect of the chemical manufacturing industry, that their measurements indicated that full-shift exposures are mainly less than 1 ppm and seldom in excess of 3 ppm. They also concluded that higher exposures resulted from operators carrying out repairs, maintenance, cylinder sampling and bomb voiding. Short-term exposures were of up to 100 ppm were also measured in this study.

Butadiene polymer manufacture – HSE exposure data

In 1984, HSE conducted a survey of 5 companies using butadiene as a chemical feed-stock in polymer production. Of the 135 personal 8-hour TWA samples obtained, 97% were below 10 ppm, 93.3% were below 5 ppm and 72.6% were less than 1 ppm (**Table 4.7**). The highest levels of exposure were found in laboratory workers and this was probably due to the fact that some of the butadiene analysis work was performed on the open bench or inadequate local exhaust ventilation (LEV) was provided.

Table 4.7 Occupational exposure to butadiene during the manufacture of butadiene polymers

Process & operations	Number of samples in given range (8-hour TWA) (ppm)					Total number of samples	Range (ppm)	Mean (ppm)
	1	1.1-5	5.1-10	10.1-20	>20			
Butadiene use- Manufacture of various butadiene rubbers								
reactor operators	51	16	2	1	-	70	< 0.3 to 20	1.3
finishing / packing operators	29	4	-	-	-	33	<0.3 to 4.2	0.7
ancillary workers	8	5	2	-	-	15	<0.5 to 7	1.9
laboratory workers	10	3	1	1	2	17	<0.3 to 37.5	5.9

Exposures of up to 20 ppm 8-hour TWA were measured for reactor operators handling butadiene. Exposure may have occurred during the discharge of contaminated process waste, the release of residual monomer during finishing operations, the filling of road and rail tankers or during the discharge of road tankers to bulk storage tanks.

Butadiene polymer production – industry exposure data

In 1994 the European Section of the Institute of Synthetic Rubber Producers collated data on occupational exposure to butadiene in the synthetic rubber and rubber latex producing industries. The data covered 1062 workers from 13 of 27 sites, operated by 26 European producers over the years 1984 to 1993. Companies generally carried out air sampling by pumping air through charcoal tubes with analysis by gas chromatography or by using charcoal diffusion badges. These results are reported in **Table 4.8**.

Table 4.8 IISRP survey of occupational exposure to butadiene at European Synthetic rubber plants (1984-1993) – 8-hour TWAs

Job category	Number of samples	No of results in specified range (ppm)						
		< 0.5	0.5 to 1	1.01 to 3	3.01 to 5	5.01 to 10	10 to 25	> 25
unloading / loading / storage	77	47	1	14	3	5	5	2
polymerisation	147	61	23	43	10	7	3	0
recovery	165	113	9	23	11	5	4	0
finishing	120	90	16	7	6	1	0	0
laboratory sampling	113	68	13	18	6	3	5	0
maintenance	39	28	1	3	3	1	2	1
total	661	407	63	108	39	22	19	3
percentile*	-	61.6	71.1	87.4	93.3	96.6	99.5	100

* Results below higher figure of quoted range.

Of the 661 results reported in **Table 4.8**, 93.3% (617 results) were less than 5 ppm 8-hour TWA, with 71.1% of results less than 1 ppm 8-hour TWA. Relatively high exposures were also found for most job categories. The tasks giving the highest exposures were unloading / loading / storage and maintenance.

One UK company which manufactures acrylonitrile-butadiene rubber within an enclosed system has monitored personal exposure using charcoal tubes which were subsequently thermally desorbed for GC analysis. The exposure results represent a full working day shift including the loading/unloading of road tankers, the taking of samples for analysis and during routine operations on the site. The company states that most airborne exposures to butadiene are less than 2.0 ppm 8-hr TWA with greater than 95% of these results below 1 ppm 8-hour TWA.

A UK company using butadiene to produce SBR for use in tyres and tyre products and styrene-butadiene latex for use in carpet backing and paper coating provided some occupational exposure data. The reaction process in which styrene and butadiene are co-polymerised to produce SBR is carried out within an enclosed system. Any un-reacted monomers are recovered from the styrene-butadiene latex in the monomer recovery area. The stripped latex is passed to storage where it can be converted into solid rubber or used as a feed-stock to produce high solid lattices. In 1993/94 66 personal samples were collected using charcoal tubes and charcoal badge, with analysis by thermal desorption and gas chromatography. The personal 8-hour TWA exposures to butadiene are given in **Table 4.9**.

The highest personal workplace exposure was 14.6 ppm 8-hour TWA, although the company reported that exposures of up to 41 ppm 8-hour TWA have been recorded during unloading / loading operations. The exposures which exceeded the present UK Maximum Exposure Limit of 10 ppm 8-hr TWA, were reported to be the result of control system failures which have since been rectified.

Table 4.9 Personal exposures during SBR production

Site	Year	No of Samples	Exposures 8-hr TWA (ppm)	
			Range	Arithmetic Mean
Reaction Area (SBR)	1993	5	0 to 2.0	1.6
	1994	6	2 to 4	2.4
Recovery Area (SBR)	1993	19	0 to 4.0	2.1
	1994	13	0 to 12	3
Storage (butadiene)	1993	4	0 to 1.5	0.4
	1994	4	0 to 3	1.1
Latex Plant – Reaction & Recovery	1993	8	0 to 1.3	0.2
	1994	4	0 to 7.3	2.8
Tanker Loading of Latex	1993	2	0-2.0	1
	1994	1	0	0

A further UK company uses butadiene to manufacture a range of synthetic lattices within enclosed plant by co-polymerisation with styrene and uses acrylates as minor co-monomers. The polymerisation reactions are carried out in a range of glass lined reactors by the continuous addition of monomer or by a batch reaction technique. The batch is transferred to bulk storage tanks following steam stripping to remove un-reacted monomer and filtration to remove fine coagulum. This company also manufactures polybutadiene by batch process in which several stages are run concurrently. Limited occupational exposure data has been provided by the firm for workers potentially exposed to butadiene during the manufacturing processes. The results are for a full working shift and taken during various operations such as road tanker loading/unloading, routine maintenance and recovery. There are 9 employees per shift and monitoring is performed routinely by the company using activated charcoal badges which are subsequently thermally desorbed and analysed using GC. The company indicates that most of the results obtained are less than 3.0 ppm 8-hr TWA with many less than 1.0 ppm 8-hr TWA.

Butadiene polymer production – published exposure data

Fajen et al. (1990) carried out surveys to measure 8-hour TWA and short-term exposure to butadiene at five USA polymer plants. These results are reproduced in **Tables 4.10 and 4.11** Full-shift exposures of up to 42.9 ppm were measured, with this result for an operator working on a butadiene compressor. During the surveys 132 samples from fixed locations were also taken, which ranged from less than 0.006 to 9.01 ppm 8-hour TWA. The authors reported that of the total 584 samples collected 3.3% were above 10 ppm, 7.7% were between 2 and 10 ppm, 3.3% were between 1 and 2 ppm with the remaining 85.8% less than 1 ppm.

Table 4.10 Occupational exposure to butadiene during the manufacture of butadiene polymers – full shift (Fajen et al., 1990)

Job	No of samples	Range	Arithmetic mean		Geometric Mean	
			mean	standard deviation	mean	standard deviation
laboratory technician	49	< 0.006 to 37.9	3.09	6.91	0.33	12.1
tank farm operator	23	0.009 to 24.0	1.97	5.01	0.26	9.59
front end (reaction)	108	< 0.006 to 24.7	1.8	4.02	0.15	12.1
maintenance	42	0.012 to 42.9	1.84	6.85	0.14	7.44
back end (finishing)	79	<0.005 to 7.12	0.35	1.07	0.04	7.13
other	137	< 0.005 to 0.167	0.04	0.03	0.02	3.03
Total	438	< 0.005 to 42.9	1.14	4.02	0.07	9.27

Short-term exposures (**Table 4.11**) were between 0.087 and 280 ppm, although the means suggest that most of the exposures were towards the lower end of the range. The highest short-term exposure of 280 ppm was for an operator taken a sample from a barge. Details were not provided on how quality control sampling and maintenance were carried out.

Table 4.11 Occupational exposure to butadiene during the manufacture of butadiene polymers – short term (Fajen et al., 1990)

Job	No of samples	Range	Arithmetic mean		Geometric Mean	
			mean	standard deviation	mean	standard deviation
quality control sampling	10	< 0.1 to 280	48.7	86.4	9.37	11.8
maintenance	4	0.087 to 14.4	4.5	6.77	1.05	9.95
Total	14	0.087 to 280	36.1	74.9	5.02	12.8

Sorsa et al. (1996) reported the results of personal air sampling carried out at two different butadiene polymer manufacturing plants in the EU. The majority of exposures were between 5 and 10 ppm 8-hour TWA, with 40% in excess of 10 ppm 8-hour TWA. An explanation for these higher results was not given by the authors.

Modelled exposure data

Only limited short-term exposure data was received for this risk assessment. To further determine short-term exposure during tasks such as sampling, and loading and unloading of road tankers, modelling was carried out using the EASE model. During these tasks there will be brief periods of exposure followed by longer periods of no exposure, during the 15-minute reference period. For these predictions it is assumed that exposure during these periods of "no exposure" is negligible.

During sampling the operator will only be exposed for the short time to take the sample, which is likely to be about 30 seconds. The EASE scenario that best describes this short-term exposure is non-dispersive without ventilation (assuming some of these tasks may be inside with no ventilation). This results in an EASE prediction of greater than 1,000 ppm for the period of the

task. This can be converted to provide a short-term (15 minute reference period) exposure prediction. In this 15-minute reference period there will be 14½ minutes of no exposure and 30 seconds at greater than 1,000 ppm, which results in a calculated short-term exposure of greater than 33 ppm.

During the period of filling / emptying of road and ship storage tankers releases are unlikely to be significant as vapour returns are understood to be in use. Releases are therefore only likely to occur during uncoupling. During coupling the line is likely to be free of butadiene. The exposure during uncoupling is likely to last about 1 minute. The EASE scenario that best describes this is non-dispersive with dilution ventilation (i.e. natural ventilation). This results in an EASE prediction of 500 to 1,000 ppm for the period of the task. This can be converted to provide a short-term (15-minute reference period) exposure prediction. In this 15-minute reference period there will be 14 minutes of no exposure and 1 minute at 500 to 1,000 ppm, which results in a calculated 15-minute TWA of 33 to 67 ppm.

These EASE predictions do not take any account of the control measures employed during uncoupling and during sampling. This modelling indicates that activities in which the system is breached provide the opportunity for the operator to be exposed to high levels for a brief period of time (i.e. 1/2 minutes or less). The 15-minute TWA modelled exposures are comparable with those measured by CEFIC in 1995 (monomer plants), and Fajen et al., 1990 (polymer plants).

Butadiene monomer and polymer manufacture – modelled dermal exposure data

Dermal contact with butadiene is unlikely as it exists as a gas at ambient temperature. The EASE model was used to confirm this and predicted exposure to be very low. Although dermal exposure is unlikely to be significant operators of monomer and polymer plants are understood to issue workers with personal protective equipment.

4.1.1.1.3 Occupational exposure to residual butadiene during the use of butadiene polymers

The concentrations of residual butadiene monomer in SBR, styrene-butadiene latex, crumb and other related products are low. Most of the butadiene is reacted during the production of these products but some polymers may contain residual traces of the butadiene (figures of 0.04 to 0.2 ng/mg were received from a manufacturer of butadiene). Airborne exposure during handling of these products by end-users such as rubber tyre and plastics manufacturers is thus expected to be minimal.

Fajen et al. (1990) carried out a study at a USA rubber tyre plant and an USA industrial hose plant, to determine exposure to butadiene during the use of styrene-butadiene, polybutadiene and acrylonitrile rubber. A total of 124 personal samples were collected covering operators potentially exposed to residual monomer. All samples were lower than the limit of detection (0.3 μg/sample).

Occupational exposures to 1,3 butadiene during the use of these polymers is therefore likely to be negligible and will not be taken forward to the risk characterisation.

4.1.1.1.4 Occupational exposure during the production and handling of motor fuels

It is understood that 1,3-butadiene occurs at very low levels in motor fuels (100 to 200 ppm and in many cases lower). It is not added to motor fuels and is understood to be formed during cracking, therefore it is not intentionally supplied for use. As a consequence, this source of potential exposure is not subject to consideration under EEC/793/93. However, an assessment of the potential exposure to 1,3-butadiene arising from this source has been included in this instance, to provide a relevant context within which to consider the other sources of exposure included in this assessment. It is presented only for information, and exposures arising from this adventitious source will not be included in the risk characterisation.

Table 4.12 details the results of measurements to determine exposure to butadiene during the handling and distribution of motor fuels.

Table 4.12 Personal exposures associated with gasoline production and handling (after CONCAWE, 1987 as quoted in IARC, 1989)

Location	Concentration 8-hour TWA (ppm)	
	mean	range
production on-site (refining)	0.13	nd to 5.07
production off-site (refining)	0.04	nd to 0.71
Loading ships (closed systems)	2.85	nd to 9.35
Loading ships (open systems)	0.49	nd to 1.87
loading barges	1.16	nd to 6.76
Jettyman	1.16	nd to 7.08
bulk loading road tankers – top loading < 1 hour	0.62	nd to 14.37
- top loading > 1 hour	0.18	nd to 2.09
- bottom loading < 1 hour	0.09	nd to 1.34
- bottom loading > 1 hour	0.18	nd to 6.27
road tanker delivery	nd	-
rail car top loading	0.27	nd to 2.76
Drumming	nd	-
service station – dispensing fuel	0.13	nd to 0.49
service station – self service	0.71	nd to 4.72*

* 2-minute sample

The numbers of samples and distribution of results were not provided, although the means and ranges suggest that the majority of exposures are less than 5 ppm 8-hour TWA. These results are likely to represent exposure during any situation where petroleum streams containing butadiene are used.

The table above shows two results for occupational exposure to 1,3 butadiene at service stations. The exact nature of these activities and the concentration of the 1,3 butadiene in the fuel are not known. The highest result of 4.72 ppm was measured over a 2-minute period and presumably represents the attendant's exposure during filling. Although it is not possible to draw any

meaningful conclusions from only two results, as indicated above, it is understood that 1,3-butadiene levels in motor fuels are extremely low, therefore occupational exposures are likely to be very low. CONCAWE have completed and published and update of this survey (Report 2/00, A Review of European Gasoline Exposure Data for the Period 1993 – 1998). 150 measurements were reported by member companies, with almost all of them non-detectable or close to the detection limit (0.01 mgm^{-3} for a full-shift sample). Only for refinery laboratory technicians were higher values reported (up to 6.2 mgm^{-3} for a full-shift sample). It was reported that these higher values were from operators carrying out activities where they were not just exposed to gasoline streams. It was therefore felt that they didn't accurately represent exposure to butadiene from gasoline.

4.1.1.1.5 Occupational exposure (general discussion)

Occupational exposure may occur during the:

a. the production of butadiene (i.e. steam cracking of petroleum and monomer extraction plants);
b. the production of butadiene polymers;
c. the use of butadiene polymers; and
d. during the production and handling of motor fuels.

The occupational exposure data used in this risk assessment is summarised below in **Tables 4.13 and 4.14** for 8-hour TWA and short-term exposure respectively. The use of butadiene polymers gives rise to exposure as a result of residual monomer and thus is not likely to give rise to significant exposure. Fajen et al. (1990) confirmed this by carrying out measurements in a rubber tyre plant and industrial hose plant. All 124 personal air samples collected were below the detection limit of 0.3 μg/sample. Occupational exposures to 1,3 butadiene during the use of these polymers is therefore likely to be negligible and will not be taken forward to the risk characterisation. Occupational exposure may also occur during the handling and distribution of petrol. CONCAWE reported data that showed most exposures were less than 5 ppm 8-hour TWA. Exposures during tanker off loading and motor vehicle refuelling are likely to be negligible due to the low level of 1,3 butadiene in motor fuels and the infrequent nature of the activities. Occupational exposures from adventitious sources of exposure will not be taken forward to the risk characterisation.

The largest exposed population are those involved in the manufacture of butadiene and polymer derivatives. The manufacture of the monomer and the polymer are carried out in closed plant with exposure predominantly during tasks where the system is breached. These tasks, which may give rise to relatively high short-term exposures, include sampling, coupling of delivery lines, and planned and unplanned maintenance. The significance of these exposures depends on how these tasks are carried out and what measures are taken to reduce the exposure. For example, the use of closed loop / enclosed sampling points and dry break coupling systems will reduce exposure. The extent of the use of such systems was not established. It is therefore the extent to which these short-term exposures are controlled that will dictate the significance of the 8-hour time weighted average exposure. Conversely 8-hour TWAs that appear to be relatively low, may actually be masking high short-term exposures. An operator who only carries out an activity once or twice a day may receive a high short-term exposure, which may not be apparent if exposure was measured for the full shift. His / her exposure may have only been for a few minutes in the shift. Control can therefore only be achieved by fully addressing these short-term exposures.

Table 4.13 Summary of 8-hour TWA exposure data used in this document

Industry	Source	No of Samples	Arithmetic Mean (ppm)	Range (ppm)	Percent less than		
					1 ppm	5 ppm	10 ppm
Monomer production							
cracker / extraction	HSE 1984	10	2	< 0.3 to 17	90	90	100
petroleum cracker	CEFIC 1986 to 93	1548	nk	nk	96.4	99.6	99.6
extraction plants		1035	nk	nk	81.4	92.5	97.1
extraction plants	CEFIC 1995	nk	< 0.01 to 5*	0 to 18.1	nk	nk	nk
integrated extraction/ SBR production plant		nk	0.07 to 3.4	0.02 to 60	nk	nk	nk
cracker / extraction plants	UK industry 1988 – 94	268	0.39	max = 3.9	nk	100	-
monomer	Sorsa et al. (1996)	70% < 0.2 ppm (2 plants) & 0.2 to 2 ppm for 3rd plant, with 10% > 10 ppm.					
Polymer production							
various butadiene polymers	HSE 1984	135	1.8	< 0.3 to 37.5	72.6	93.3	97
synthetic rubber / latex	IISRP 1994	661	nk	nk	71.1	93.3	99.5
SBR / ABS / SB latex	UK industry 1993/94	66	1.9	0 to 12	nk	nk	nk
various polymers	UK industry, no date.	Two plants : first; 95% < 1 ppm; and second with most < 3 ppm					
not specified	Fajen et al. (1990)	438	1.14	< 0.005 to 42.9	nk	nk	nk
not specified	Sorsa et al. (1996)	two plants : majority between 5 and 10 ppm, with 40% > than 10 ppm					
During the use of butadiene polymers							
rubber tyre plant	Fajen et al. (1990)	124	nk	nd*	100	-	-
During the production and handling of motor fuels							
various	CONCAWE 1987	nk	nk	nd to 14.37	nk	nk	nk

* reported as representative 8-hour TWAs
nd. Non detected. Limit of detection was 0.3 μg / sample

Occupational exposure data was received from manufacturers and users of butadiene from plants operating in a number of EU member states. This data was received from the Olefins sector group of CEFIC for manufacturing plants and represents the majority of EU manufacturers. Data was also received from IISRP, which represented most 13 EU sites using butadiene to produce synthetic rubber or latex rubber. Occupational exposure data from published review articles was also used and data received direct from UK companies. HSE's NEDB was also accessed to provide data. In total it was estimated that about 5,000 measurements have been collated and presented in this risk assessment. This comprises over 2,800 results for monomer production and 1,300 results for polymer production. The exact number of samples collated was not known as some sources did not report the number of samples taken. Although there is considerably more exposure data available, the addition of further results in the risk assessment is unlikely to change any resulting conclusions.

Table 4.14 Summary of short-term exposure data used in this document

Industry	Source	No of Samples	Arithmetic Mean (ppm)	Range (ppm)
monomer production				
extraction plants	CEFIC 1995	nk	nk	0 to 100
integrated extraction/ SBR production plant		nk	nk	0 to 177
monomer	Sorsa et al. (1996)	nk	nk	up to 100*
polymer production				
not specified	Fajen et al. (1993)	14	36.1	0.087 to 280
during the production and handling of motor fuels				
self service station – filling tank	CONCAWE 1987	nk	0.71	nd to 4.72
modelled data for monomer / polymer industries				
monomer / polymer	EASE	33 ppm for sampling and 33 to 76 ppm for loading / unloading		

* Results with unspecified reference periods also reported of up to 500 ppm.

The majority of exposure data received was collated and anonymised by the relevant European trade associations before forwarding to HSE. Some details, such as sample numbers, means and ranges were not always provided. Therefore, it was not possible to calculate overall percentiles. It is, however, clear from the results that:

a. the majority of results are less than 1 ppm 8-hour TWA (about 70% for polymer production and 90% for monomer production);

b. over 90% of results were less than 5 ppm 8-hour TWA;

c. that approaching 100% of results were less than 10 ppm 8-hour TWA; and

d. that short-term exposures may be on occasion in excess of 100 ppm. Exposures of 33 to 67 ppm for sampling and loading / unloading were predicted using EASE. Peak exposures are likely to be higher than this, possibly several hundred ppm. These peaks may only last a few seconds.

As stated some statistical details were not provided. The information, however, was sufficient to have a sufficient degree of confidence in the above picture. It is also worth noting that the exposures for polymer production appear to be higher than the monomer production plants although no explanation was established.

It is reasonable to conclude from the above that occupational exposure does not frequently exceed 5 ppm 8-hour TWA and that it is usually less than 1 ppm 8-hour TWA. Exposures above 10 ppm 8-hour TWA are likely to be rare and as a result of identifiable unplanned releases. Where exposures are higher than 5 ppm 8-hour TWA, resulting from high short-term exposures, it was assumed that these exposures were mitigated by the use of respiratory protective equipment. These particular activities may include maintenance and unloading / loading where

higher exposures may be expected and additional control measures are needed. These short-term exposures may contain relatively high peak exposures of several hundred ppm.

Dermal exposure to a gas is only likely to occur if it condenses on to the operator's skin. The EASE model predicts dermal exposure to gases to be very low.

Table 4.15 Summary of 8-hour TWA exposure data used in the risk characterisation

Industry	8-hour TWA (ppm)
Monomer production	1 ppm
Polymer production	5 ppm

4.1.1.2 Consumer exposure

4.1.1.2.1 Introduction

Of the 1,892,000 tonnes of 1,3-butadiene consumed within the EU per annum, virtually all is used either as a monomer in the manufacture of a variety of synthetic rubber and plastics, or as an intermediate. Butadiene is present as a minor impurity in liquefied propane gas and petrol; it is also released as a component of cigarette smoke. The latter is not a product of the butadiene industry but does help to set the other exposures into context. Butadiene as such is not added to consumer products.

Consumers will be exposed to items manufactured from synthetic polymers, which may contain residual free monomer.

Styrene: butadiene rubber (SBR)	Used to make belting, hoses, moulded goods, floor coverings, 'rubber' soled shoes, fabric coatings and electrical insulation.
	Also used in latex paints and adhesives and as a component of chewing gum base.
Cis-1,4-polybutadiene	Blended together with styrene-butadiene copolymer to manufacture tyres for the automotive industry.
Neoprene (or polychloroprene)	An elastomer widely used in consumer products. Has good chemical and oil resistance.
Acrylonitrile-butadiene rubber	Used for items that must be oil resistant e.g. petrol tanks/pipes and gaskets, oil resistant paper, textiles and leather, and creamery equipment.
Acrylonitrile-butadiene-styrene (ABS) resins	Used for high impact resistant items such as piping, appliances, automotive components, business machines and telephones, luggage and recreational vehicles. They are also used in food packaging e.g. yoghurt pots and margarine containers.

Butadiene is also used as a chemical intermediate in the production of impact modifiers and in the synthesis of hexamethylenediamine and cyclododecatriene (precursors in the manufacture of various nylon fibres) and also has minor uses in the manufacture of other resins, chemical intermediates, pesticides and fungicides. Use of butadiene as an intermediate is not expected to result in consumer exposure.

4.1.1.2.2 Release of free monomer from polymeric consumer products

Butadiene polymers/copolymers are likely to contain small amounts of free butadiene. Consumers could be exposed via the inhalation route when using products manufactured from any of the synthetic rubbers/plastics mentioned above e.g. carpet backings, floor coverings, latex paints and fabric coatings. Additionally, some chewing gum may contain a small amount of food grade SBR (<3%) and some food packaging materials incorporate butadiene copolymers (ABS), so there is also a potential for exposure via the oral route.

Industry data suggests that 62% of analysed SBR samples contained free butadiene monomer at below 1 ppm, the limit of detection of the analytical method used (BP, 1994, personal communication). The results ranged from below detection levels to 3 ppm. Just over 3% of samples contained 3 ppm butadiene.

More recent data confirm that most SBR contains < 1 ppm, with 1.4 ppm being the highest level reported (IISRP, 2000). In addition, this industry data indicates that monomer levels in butadiene rubber, acrylonitrile-butadiene rubber and styrene-butadiene-styrene thermoplastic elastomer are generally $\leq$ 1 ppm. These data are based on measurements from about 20 plants, with up to 200 samples analysed per year over a 3-year period (1998-2000). Analyses were conducted using head space (FID) gas chromatography with limits of detection between 0.1 and 1 ppm.

Carpet backings

Information from industry indicates that the amount of free monomer in SBR dispersions used for carpet backing is < 1 ppm, based on an analytical method with a detection limit of 0.1 ppm (actual data not supplied). Before application to the carpet, filler (chalk) and water is added to the SBR. The total amount of SBR applied per carpet is reported by industry to be 0.2-0.3 $kg.m^{-2}$.

Industry has undertaken analysis of emissions from carpets during the drying stage of the production process, which takes place at temperatures between 120 and 150 C. According to industry information, no butadiene emissions have been detected during carpet production (actual data not supplied; detection limit reported to be 1 ppm). In addition, since 1991, industry has regularly undertaken analyses of carpet samples for emissions. It is reported that no butadiene has ever been detected in these analyses (industry information, actual data not supplied). This is to be expected, given the very low levels reported above for the presence of free monomer in polymers and also in view of the high temperature process involved in the production of carpet backings, during which any free monomer would be expected to be released.

Data for the co-monomer – styrene – suggests that the bulk of residual styrene monomer is released relatively quickly following manufacture of floor tiles (Gadaline et al., 1969). While this study is poorly reported, a second study carried out for the US Environmental Protection Agency came to the conclusion that the exposure to styrene following laying of a new carpet peaked in the first 24 hours and fell rapidly thereafter (RTI, 1992). It seems likely that this would also occur with the butadiene copolymer. However, while the concentration of free butadiene

monomer is much less than that for styrene monomer (<1 ppm for butadiene, compared with up to 200 ppm for styrene), there are uncertainties about the relative amounts of material that can diffuse from the matrix and the rates at which they do so.

The information from industry suggests that emissions of butadiene from carpet backing are below the limit of detection of 1 ppm. Therefore no value for this scenario will be carried forward to the risk characterisation.

Indoor air

Information on levels of butadiene in indoor air is limited. Two published references are available. Indoor air levels of butadiene are reported to be generally less than 2.2 µg/m^3, with background levels at 0 – 1 µg/m^3, based on measured data (Slooff et al., 1994). Indoor air levels of up to 19 µg/m^3 butadiene have been reported in tobacco-smoke filled taverns (Löfroth et al., 1989). However, given that butadiene is emitted from tobacco smoke as a product of combustion, this latter value is inappropriate for use in determining consumer exposure arising from release of free monomer from polymeric products.

For risk assessment purposes, emissions from polymeric products will be assumed to lead to a maximum background level in indoor air of 2.2 µg/m^3. Assuming an ambient level of indoor exposure of 2.2 µg/m^3 and an adult inhalation rate of 11.5 l/minute (CONSEXPO default) for a 24-hour exposure, daily exposure will be in the region of 36 µg/day (0.036 mg/day). For a toddler (aged 1.4-4.5 years), assuming an inhalation rate of about 3.5 l/minute for a 24-hour exposure, daily exposure will be about 11 µg/day (0.01 mg/day).

Chewing gum

Some brands of chewing gum contain food-grade SBR as a base, reported to be present at no more than 2.4% by weight. Food-grade SBR is reported by the European Association of the Chewing Gum Industry (EACGI) to contain no more than 300 ppb butadiene monomer. However, the finished product may contain less than this, as a result of losses of free monomer during the chewing gum production process. A study by McNeal and Breder (1987) investigated the release of residual butadiene from five different brands of chewing gum with a butadiene rubber base. The chewing gum samples were placed in an oven at 90°C for 1 hour in a sealed vial and the headspace gas analysed for butadiene. No butadiene was detected from any of the five product samples (limit of detection 2 ppb). This information suggests that residual butadiene monomer in chewing gum is below the limit of detection and therefore no value for this scenario will be taken forward to the risk characterisation.

4.1.1.2.3 Leaching of free monomer from food packaging into foodstuffs

There is the possibility of some exposure to butadiene due to leaching from food packaging composed of ABS copolymers into foodstuffs, particularly foods containing significant amounts of oil or fat e.g. margarine, dairy products, olive oil.

Butadiene was not detected in margarine where the plastic tubs contained < 5 – 310 µg/kg butadiene (Startin and Gilbert, 1984). The limit of detection was 0.2 µg/kg. It is assumed the residual butadiene in the plastic was present as an impurity/additive contained within the polymer matrix.

Further work was carried out by McNeal and Breder (1987), reported in the environmental section and repeated here in the context of individual uptake. Several butadiene-based polymers used for food packaging were analysed for free butadiene content. In addition, analyses were conducted on some foodstuffs contained in the butadiene-based food packaging. Although several of the packages clearly contained monomeric butadiene, when three of the contained foods – olive oil, vegetable oil and yoghurt – were analysed, only olive oil contained a measurable quantity of butadiene (8-9 µg/kg). The detection limit in vegetable oil and yoghurt is quoted as 1 µg/kg.

Residual butadiene in copolymer was also determined to be 3.9 ± 2.4 mg/kg (Association of Plastics Manufacturers in Europe, 1988, personal communication). This study aimed to evaluate the precision of the analytical method used and so did not make clear whether the samples were representative of food packaging materials (this figure is comparable with levels quoted for residual monomer in SBR generally).

An estimate of intake of butadiene as a consequence of its migration from food packaging into foodstuffs can be derived, based on the following assumptions:

i. The maximum concentration of 1,3-butadiene in foodstuffs packed in butadiene-based polymers is < 0.02 mg/kg (as stipulated by Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs);

ii. The only potential for migration is into foodstuffs containing significant amounts of oil or fat;

iii. The daily consumption of foods containing $\geq$ 5% fat (dairy products and vegetable oils) is 0.73 kg (adults) or 0.86 kg (toddler, aged 1.5-4.5 years) (UK data for the 97.5th percentile consumer; HMSO (1990, 1995)).

Based on the above, eating packaged oily/fatty foodstuffs gives a worst-case oral exposure of < 0.015 mg/day for an adult and < 0.017 mg/day) for a toddler.

4.1.1.2.4 Thermal degradation of polymer leading to release of free monomer

Where polymers are heated during normal use, it is possible that release of free monomer may occur. This could be due either to thermal degradation of polymer/copolymer or increased rate of release of free monomer. Generally polymers with unsaturation in their structure are sensitive to thermal, oxidative and UV degradation. However, polybutadiene and SBR are considered thermally stable due to the inclusion of antioxidants during manufacture. Polybutadiene may release 14% free monomer and SBR may release 12% butadiene on thermal decomposition (Billmeyer, 1984), although specific conditions were not specified e.g. whether this was for pure polymer/copolymer, or commercial grade material containing antioxidants, and under what conditions the polymer degraded. It is not clear how this relates to the reported free monomer level in SBR of less than 3 ppm.

No decomposition temperature has been quoted for either polymer, although an upper use temperature of 100°C is quoted for cis-1,4-polybutadiene (commercial grade polybutadiene consists primarily of the cis isomer). Some heating may occur during normal use of items such as tyres and electrical insulation. Temperatures reached in normal use are not known, however, they are likely to be well below the upper use temperature.

The only foreseeable consumer exposure is to monomer accumulating in enclosed spaces such as around electrical inspection hatches. Such exposure is likely to be infrequent and result in exposures in the order of µg/m^3. However, no measured data are available to confirm this.

For the purposes of risk assessment, no additional uptake will be added to take account of this very minor potential source of exposure.

4.1.1.2.5 Liquid Propane Gas

Butadiene is present in liquid propane gas (LPG), presumably as an impurity, although this is not confirmed. Manufacturers claim that they have reduced this to a maximum level of 1% (LPG Association, 1995, personal communication). Analytical data were not provided to substantiate this claim.

Any potential exposure to butadiene from this source arises as a consequence of its presence as a natural component (impurity) of LPG, rather than as a result of its supply and use. As a consequence, this source of potential exposure is not subject to consideration under EEC/793/93 and therefore is not covered in this assessment.

4.1.1.2.6 Vapour from motor fuels

It is understood that 1,3-butadiene occurs at very low levels in motor fuels (typically < 0.1%). It is not added to motor fuels and is understood to be present only as an impurity from the addition of butane, therefore it is not intentionally supplied for use. As a consequence, this source of potential exposure is not subject to consideration under EEC/793/93. However, an assessment of the potential exposure to 1,3-butadiene arising from this source has been included in this instance, to provide a relevant context within which to consider the other sources of exposure included in this assessment. It is presented only for information, and exposures arising from this adventitious source will not be included in the risk characterisation.

1,3-Butadiene has been detected in petrol vapour (2 µg/m^3) (IARC, 1986, no reference cited). However, a later volume of IARC (IARC, 1989) suggests a higher exposure is likely. For the period of filling a maximal value of 1.6 mg/m^3 is possible.

Inhalation of petrol vapours during refilling car fuel tanks may contribute to exposure, although the significance of butadiene exposure must be weighed against the overall effect of exposure to other components of petrol vapour. 1,3-butadiene produced as a result of combustion of petrol is considered in the context of exposure via environmental routes.

Assuming:

i. the concentration in petrol vapour is maximal at 1.6 mg/m^3;
ii. an approximate average lung ventilation rate of 1.3 m^3/hour;
iii. the average time taken to fill a petrol tank is 2 minutes.

Exposure during filling:

$$\frac{2(\min)x1.6(mg.m^{-3}x1.3(m^3.hour^{-1})}{60x10^3} \cong 69\mu g / event$$

For the purposes of risk assessment an exposure of 69 µg/event will be assumed.

4.1.1.2.7 Smoking cigarettes

1,3-Butadiene is produced as a consequence of combustion of tobacco and therefore occurs in tobacco smoke. It is not supplied for use in tobacco. As a consequence, this source of potential exposure is not subject to consideration under EEC/793/93. However, an assessment of the potential exposure to 1,3-butadiene arising from this source has been included in this instance, to provide a relevant context within which to consider the other sources of exposure included in this assessment. It is presented only for information, and exposures arising from this adventitious source will not be included in the risk characterisation.

The total airborne yield of 1,3-butadiene from 1 cigarette is 0.4 mg (Löfroth et al., 1989). A person who smokes 10 – 15 cigarettes per day will potentially inhale 4 – 6 mg of 1,3- butadiene, a heavy smoker, say 60-80 cigarettes per day, will potentially inhale 24 – 32 mg. This represents by far the greatest potential for consumer exposure. The potential for passive smoking is not clear, but people exposed to air concentrations of up to 19 µg/m^3 (Löfroth et al., 1989) in a smoke filled room would inhale approximately 13 µg/hour of 1,3-butadiene. If the exposure is for 12 hours, the amount inhaled will be 156 µg/day.

4.1.1.2.8 Summary

Consumer exposure to butadiene may arise from long-term low level emissions arising from the consumer use of polymeric products. Other exposures can arise from adventitious sources, namely from filling fuel tanks, smoking, and use of liquid propane gas (LPG).

An attempt has been made to quantify potential exposures arising from the use of polymeric products indoors, eating chewing gum, transfer into food from food packaging, filling a car with motor fuel and smoking. Estimated exposures arising from the latter two sources have been derived for information only and to place the other exposures into context; these adventitious exposures will not be carried forward to the risk characterisation.

Exposure scenario	**Estimated intake (mg/day)**
Release of free monomer from polymeric consumer products (indoor air) (inhalation – adult)	0.036
Release of free monomer from polymeric consumer products (indoor air) (inhalation – toddler)	0.01
Chewing gum	not detectable
Leaching of free monomer from food packaging into foodstuffs (oral – adult)	0.015
Leaching of free monomer from food packaging into foodstuffs (oral – toddler)	0.017

Exposures arising from adventitious sources:

Exposure scenario	**Estimated intake (mg/day)**
Heavy smoker (inhalation)	
80/day	32
40/day	16
Passive smoking (inhalation)	0.156
Petrol filling (inhalation)	0.069 per event

The available data suggest that the most likely route of exposure is inhalation of 1,3-butadiene present in cigarette smoke. Compared with these exposures, other potential sources of exposure result in very low levels of 1,3-butadiene intake. Some oral exposure from packaged food may occur and as a result of the use of 1,3-butadiene as a monomer/ co-monomer in polymeric products. Its presence as an impurity in petrochemicals may also result in very low exposures. Use of 1,3-butadiene as an intermediate is not expected to result in consumer exposure.

The values for exposure as a result of release of free monomer from polymeric consumer products into indoor air and as a result of leaching of free monomer from food packaging into foodstuffs will be carried forward to the risk characterisation.

4.1.1.3 Humans exposed via the environment

Section 3.1.7 (**Table 3.9**) summarises the predicted environmental exposures to butadiene at the local and regional level. While there are predicted levels of contamination for water, soil, sediment and air, the volatility of butadiene suggests that as far as indirect exposure to humans is concerned, the greatest predicted exposures to butadiene via the environment are from butadiene in air. Therefore, only airborne exposure estimates are considered in this part of the risk assessment.

The maximum local predicted environmental concentration ($PEC_{local(air)}$) is 439 µg/m^3 (0.2 ppm), due to release from a styrene – butadiene rubber/latex production plant. Predicted local emissions from polybutadiene, polychloroprene and ABS production plant are approximately one half, one fifth and one fifth, respectively, of the predicted local emissions from styrene – butadiene rubber/latex production plant.

The predicted regional environmental concentration ($PEC_{regional}$) in air from all known sources is considerably lower, 1.5 µg/m^3 (0.00068 ppm).

The available real data in Europe is much closer to the "regional" than the "local" predictions. However, there are some American data which are clearly consistent with the higher figures (Section 3.1.5.2). Industry information on release from production and/or use plants gives releases to air in the range of 0.006 – 240 tonnes/year. Estimated $PEClocals_{(air)}$ based on these data are in the range 0.006 – 222 µg/m^3 (0.000003 – 0.1 ppm), showing that the estimated and actual releases to air are in good agreement.

The measured urban levels in the UK are up to 1.5 µg/m^3 but higher levels have been noted under certain conditions, for example, heavy traffic and cold weather combined producing an

episodic concentration of 22 µg/m^3 (0.01 ppm) (Section 3.1.5.2). These data are consistent with the non industrial (ie general urban and suburban) data from the United States.

For the purposes of risk assessment for the EU, the concentrations calculated from industry release information will be used, that is 222 µg/m^3 (0.1 ppm) for emissions from local industry dominated sources and 1.5 µg/m^3 (0.00068 ppm) for a regional background level.

4.1.1.4 Combined exposure

Exposure to butadiene may reasonably be predicted to arise as a result of combined exposure from workplace, consumer and environmental sources. As a reasonable worst-case, someone who works in and lives locally to a butadiene plant, is a smoker and is exposed via carpet backing and monomer leaching from packaging into foodstuffs, could have a combined exposure largely comprising the contributions from the workplace, cigarettes and local emissions. Assuming an inhalation rate of 11.5 l/minute, an 8-hour working day and then 16 hours living in the locality of the factory, the main contributions comprise the workplace (2.2 – 11 mg/m^3 leading to inhalation of approximately 12 – 60 mg/day), smoking (16 mg/day for 40 cigarettes), and local environmental exposure (approximately 0.2 mg/m^3 for a local source, leading to inhalation of 2.2 mg/day). These figures are clearly very approximate.

4.1.2 Effects assessment:Hazard identification and dose (concentration) – response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

The toxicokinetics of butadiene in different species has been extensively studied and modelled. The data are summarised in a number of recent reviews, ECETOC (1992, 1997), IARC (1992, 1993), Himmelstein et al. (1997) and DECOS (1990). Birnbaum (1993) provides a useful overview of the toxicokinetics of butadiene while Henderson et al. (1993) provide an assessment of species differences in metabolism. Only the more important studies are individually summarised below.

4.1.2.1.1 Studies in animals

In vivo studies

The uptake and metabolism of butadiene in male Sprague-Dawley rats and male B6C3F1 mice in a closed chamber system has been investigated in a number of studies, providing similar results (Bolt et al., 1983, 1984; Filser and Bolt, 1984; Kreiling et al., 1986b). In these studies, rats or mice were placed in an airtight chamber filled with a known concentration of butadiene for a period of a few hours. The disappearance of butadiene from the chamber, due to uptake and metabolism by the animals, was monitored. These experiments demonstrated that butadiene is readily taken up and metabolised in both species. Uptake and metabolism obey simple first order kinetics. In both rats and mice, the disappearance of butadiene from the closed chamber was linear with exposure concentrations up to around 1,000 ppm. Saturation of this process begins at about 1,500 ppm in both species. In the rat, approximately 50% of the initial chamber concentration of butadiene disappeared in 2 hours, at concentrations below about 1,500 ppm (Kreiling et al., 1986b). Uptake and metabolism of butadiene is approximately 2-fold faster in the mouse compared with the rat. At butadiene concentrations up to 1,000 ppm, the maximum metabolic elimination rate in mice was measured as 400 µmol/hour/kg bodyweight in mice and 220 µmol/hour/kg in rats (Bolt et al., 1984; Kreiling et al., 1986b).

The metabolism of butadiene to the highly reactive metabolite, 1,2-epoxy-3-butene (epoxybutene), was demonstrated (Bolt et al., 1983; Bolt et al., 1984; Filser and Bolt, 1984). This metabolite can be detected in the exhaled air of both rats and mice exposed to butadiene. Metabolism to epoxybutene is via cytochrome P450-catalysed epoxidation of one of the double bonds.

Bond et al. (1986) also studied the uptake and metabolism of butadiene in male Sprague- Dawley rats and male B6C3F1 mice. The animals were exposed nose-only to 0.08-1,000 ppm ^{14}C-butadiene, with rats exposed additionally to 7,100 ppm, for 6 hours. At the end of the exposure period, 4-6 rats or mice per group were sacrificed for measurement of the total ^{14}C retained per animal. An additional 4 rats from the 70, 1,000 and 7,100 ppm exposure groups and 4 mice from the 7, 70 and 1,000 ppm groups were maintained in metabolism cages for measurement of metabolites excreted in air, urine and faeces, at intervals from 1-65 hours post-exposure. Further groups of three rats and mice per exposure concentration were sacrificed at 2, 4 or 6 hours from the start of exposure and blood analysed for butadiene and the potential metabolites, epoxybutene, diepoxybutane, butenediol and CO_2.

Respiratory measurements made during the exposure were used to calculate the amount of butadiene inhaled per animal. There was a concentration-related reduction in the percentage of inhaled butadiene absorbed and retained after the 6-hour exposure, in both species. In the rat, the percentage of ^{14}C retained per animal decreased from 17% at the lowest exposure concentration, 0.08 ppm, to 1.5% at 7,100 ppm. In the mouse, 16% was retained at 0.08 ppm, falling to 4% at 1,000 ppm. These data are indicative of saturable metabolism. At each exposure concentration except 0.8 ppm, the amount of ^{14}C retained per kg bodyweight was statistically significantly, 4-7 fold higher in the mouse compared with the rat. A similar finding was obtained when the retained dose was normalised to body surface area.

More than 90% of the total ^{14}C in the blood of both species was associated with butadiene metabolites. At all exposure concentrations, the largest percentage of ^{14}C, accounting for 60-80% of the total, was due to uncharacterised non-volatile metabolites. At 70 and 1,000 ppm, the concentration of epoxybutene in the blood of mice was statistically significantly higher than that in rats. In rats at 6 hours after exposure to 1,000 ppm, epoxybutene accounted for 7% (4 nmol/ml) of total ^{14}C in the blood, butadiene and CO_2 accounted for 6% (4 nmol/ml) each and 2% (1 nmol/ml) was attributable to diepoxybutane, with the remaining 82% as non-volatile metabolites. In the mouse, these values were 10% (15 nmol/ml) for epoxybutene, 2% each for butadiene (3 nmol/ml) and CO_2 (2 nmol/ml), 0.8% (1 nmol/ml) diepoxybutane and 70% non-volatile metabolites. In general, the blood of mice contained a 2-5 fold higher concentration of epoxybutene than did that of rats for the same exposure concentration.

At all exposure concentrations investigated for both species, urine and exhaled air were the major routes of excretion for ^{14}C, and accounted for ~80% of the total ^{14}C eliminated. There was minimal excretion in the faeces. At 65 hours post exposure, 10-20% of the total ^{14}C absorbed and retained following exposure was still present in the carcass. The $t_{½}$ for urinary excretion of ^{14}C was 5.6 hours for the rat and 4.6 hours for mice, while for fecal excretion, $t_{½}$ was 22 hours for the rat and 8.6 hours for the mouse. In both species at the same exposure concentration, urinary excretion accounted for about 40% of total retained ^{14}C while excretion as exhaled CO_2 accounted for about 15% and as exhaled butadiene and other volatile metabolites, about 25%. There appeared to be a metabolic shift in rats following exposure to 7,100 ppm. The elimination of ^{14}C as exhaled CO_2 became the most important pathway for excretion and there was a concomitant reduction in urinary excretion of ^{14}C. Exhaled CO_2 accounted for 51% of total retained ^{14}C, compared with 8% via urinary excretion. It is not clear at what stage in metabolism CO_2 is produced, but it may result from metabolism of epoxybutene or diepoxybutane.

The tissue distribution of butadiene following nose-only exposure was investigated in male Sprague-Dawley rats and male B6C3F1 mice (Bond et al., 1987). Groups of 39 rats and 39 mice were exposed to 670 and 65 ppm ^{14}C-butadiene respectively for 3.4 hours. These exposure concentrations were chosen to result in approximately equivalent amounts of butadiene retained in the two species. Groups of three animals were sacrificed at intervals from 1 hour to 13 days post-exposure and tissue and blood samples were analysed for ^{14}C. Radioactivity was found to be widely distributed throughout the body in both species within 1 hour after exposure. The highest concentrations of radioactivity were found in the bladder, respiratory tract, gastrointestinal tract, liver and kidney of both species and also the thyroid in the rat. There were no apparent qualitative species differences in tissue distribution of butadiene and its metabolites. Mouse tissue contained 15-100 times higher concentrations of ^{14}C per µmole butadiene inhaled, than did rat tissue. The concentration of radioactivity in all tissues showed a gradual reduction with time after exposure. Removal was rapid in both species, so that 77-99% of the initial radioactivity was eliminated with $t_{½}$ 2-12 hours. The remaining fraction was eliminated with $t_{½}$ 4-58 days. In general the half-lives were slightly higher in the rat compared with the mouse.

Kreiling et al. (1987) investigated the metabolism of epoxybutene produced endogenously as a result of butadiene exposure in rats and mice, in order to determine any species differences in the detoxification of this reactive metabolite of butadiene. Groups of 2 male Sprague- Dawley rats and 6 male B6C3F1 mice were exposed to a concentration of butadiene maintained between 2,000-4,000 ppm in a closed system for 15 hours. This exposure concentration, maintained >2,000 ppm, was chosen to ensure maximal metabolism to epoxybutene. Changes in the concentration of butadiene and in exhaled epoxybutene were monitored for up to 17 hours. Control animals were not exposed. The animals were sacrificed at the end of exposure and the hepatic non-protein sulfhydryl concentration was measured.

The concentration of epoxybutene exhaled by rats reached a plateau at around 4 ppm after 1-2 hours exposure. In contrast, in mice the concentration of exhaled epoxybutene increased to a peak concentration of about 10 ppm after 10 hours after which time a gradual reduction in epoxybutene concentration was seen. The metabolic elimination rate was calculated for both species. In rats, the metabolic elimination rate was constant throughout the exposure period while in mice, there was a reduction in the rate after about 8 hours of exposure. The reduction in epoxybutene formation in mice is therefore attributed to a reduction in butadiene metabolism. Signs of acute toxicity were observed in mice from about 12 hours onwards and lethality occurred when exposure in the closed chamber was maintained for over 15 hours. No toxicity was observed in rats. The authors had previously demonstrated that metabolism of inhaled epoxybutene is a saturable process in mice but not in rats. Therefore under conditions of saturated butadiene metabolism, the metabolism of epoxybutene by the mouse also becomes saturated and epoxybutene levels begin to increase, finally reaching toxic levels. This mechanism is supported by data for hepatic non-protein sulfhydryl content measured at the end of the 15-hour exposure. In butadiene-exposed mice, the hepatic non-protein sulfhydryl content was reduced to 4% of the unexposed control value. This compares with a reduction to 76% of control in exposed rats. This suggests that the main detoxification pathway for epoxybutene in mice may be conjugation with glutathione, a pathway that becomes saturated when hepatic non-protein sulfhydryl is depleted.

Species differences in the metabolism of butadiene are reported in a study in rats and mice (Himmelstein et al., 1994). Groups of 13-19 male B6C3F1 mice and 5-12 male Sprague- Dawley rats were exposed nose-only to 62.5, 625 or 1,250 ppm butadiene for up to 6 hours. Blood samples were collected at 2, 3, 4 and 6 hours during exposure for the measurement of butadiene and epoxybutene. Samples taken at 3 and 6 hours were also analysed for diepoxybutane. Blood samples were also taken at 2-10 minute intervals for 30 minutes post-exposure and analysed for the presence of butadiene, epoxybutene and diepoxybutane. Samples were analysed by gas chromatography or gas chromatography-mass spectrometry.

The concentration of butadiene in the blood of both mice and rats reached steady-state by 2 hours of exposure, at all three exposure concentrations. The steady-state concentration of butadiene was around 2-fold higher in the blood of mice compared with rats. The concentration of butadiene in the blood was not proportional to exposure concentration, indicating saturable uptake. Within 30 minutes post-exposure, the concentration of butadiene in the blood of both species at all exposure concentrations had fallen to 1-12% of the steady-state level. This rapid decline suggests that butadiene does not accumulate in the body. Following exposure to 62.5 and 625 ppm, the concentration of butadiene in the blood of mice decreased at a greater rate than in rats. At 1,250 ppm the reduction in butadiene concentration post-exposure was faster in rats than in mice. The steady-state concentration of butadiene in the blood increased 15-fold in both species when the exposure concentration was increased 10-fold from 62.5 to 625 ppm. When the exposure was doubled from 625 to 1,250 ppm, the blood butadiene concentration in rats also

doubled, while that in mice increased 1.6-fold. The metabolite, epoxybutene, was detected in the blood of both species, at all exposure concentrations. Steady-state concentrations of epoxybutene were achieved by 2 hours of exposure. The concentration of epoxybutene was 4-8-fold higher in the blood of mice compared with rats, at all exposure concentrations. In both species, the concentration of epoxybutene fell rapidly post-exposure, to between ~10-40% of the steady-state value by 10-20 minutes post-exposure. No diepoxybutane was detectable in the blood of rats, at any exposure concentration. In contrast, measurable concentrations of this metabolite were detected in the blood of mice, at 3-6 hours during exposure and at all exposure concentrations. The elimination of diepoxybutane post-exposure appeared to be dependent on the exposure concentration, with a decrease in the rate of elimination as exposure concentration increased.

Overall, the results of this study indicate that following exposure to equivalent concentrations of butadiene, mice have higher blood concentrations of butadiene than rats. Similarly, mice have higher blood concentrations of epoxybutene than do rats, for any given exposure concentration. In addition, the mouse produces measurable quantities of diepoxybutane, while this metabolite is not detectable in the rat. Elimination of butadiene and epoxybutene is rapid in both species. The rate of elimination of diepoxybutane in mice is inversely proportional to the exposure concentration of butadiene.

In a further extension of this study into species differences in metabolism, the same group of investigators measured tissue levels of epoxide metabolites as well as GSH depletion following single exposure to butadiene (Himmelstein et al., 1995). Groups of male Sprague- Dawley rats and B6C3F1 mice were exposed nose-only to 0, 62.5, 625, 1,250 and (rats only) 8,000 ppm butadiene for 3 or 6 hours. Samples of liver and lung tissue were taken at 0, 6 or 12 minutes post-exposure and analysed for epoxybutene and diepoxybutane by GC-MS. In addition, depletion of GSH was measured as non-protein sulfhydryl content. A total of 3-6 tissue samples were used for each analysis. Blood samples were also collected from rats exposed to 8,000 ppm, for analysis of butadiene and the two epoxide metabolites.

Epoxybutene was detected in both liver and lung tissue of rats and mice exposed to 625 ppm butadiene and above. The levels of epoxybutene in mouse liver and lung exceeded that in rat tissue at all exposure levels. The maximum tissue concentrations of epoxybutene in the lung, measured either at 3 or 6 hours, were 2.6 ± 0.2 and 3.7 ± 1.2 nmol/g lung tissue in mice exposed to 625 and 1,250 ppm respectively, compared with 0.16 ± 0.03, 0.31 ± 0.07 and 1.3 ± 0.2 nmol/g in rats exposed to 625, 1,250 and 8,000 ppm respectively. In the liver, tissue levels of up to 0.58 and 0.93 nmol/g were measured in the mouse at 625 and 1,250 ppm, compared with 0.06, 0.16 and 1.2 nmol/g in the rat at 625, 1,250 and 8,000 ppm. Post-exposure tissue levels of epoxybutene fell rapidly in both rats and mice; this decline was slower at higher exposure concentrations. $T_{½}$ for elimination of epoxybutene from lung and liver varied between 2.6 and 11.9 minutes. Detectable levels of diepoxybutane were found only in mouse lung tissue, at 625 and 1,250 ppm. Peak levels were 0.71 nmol/g tissue at 625 ppm (measured at 6 hours) and 1.5 nmol/g tissue at 1,250 ppm (at 3 hours). In contrast to the elimination of butadiene monoepoxide, the diepoxide level in the lung tissue remained elevated at 6 and 12 minutes post-exposure.

The concentration of GSH measured in the liver of mice exposed to 1,250 ppm butadiene was statistically significantly reduced compared with controls. In rats, statistically significant reductions in liver GSH were seen at 1,250 and 8,000 ppm. Both species showed comparable depletion of liver GSH at 1,250 ppm, with mean GSH content 57% and 62% of control in mice and rats respectively. In lung tissue, statistically significant depletion of GSH was seen in mice at 625 and 1,250 ppm at all time points during and post-exposure and also at 62.5 ppm at 6 hours and 6 and 12 minutes post-exposure. Maximum depletion occurred at 6 hours of exposure to 1,250 ppm (26% of control). GSH depletion in mouse lung exceeded that in rat lung at

equivalent exposure concentrations. In the rat lung, GSH depletion reached statistical significance at 1,250 and 8,000 ppm after 6 hours exposure and remained statistically significantly depleted up to 12 minutes post-exposure (8,000 ppm). Overall, therefore, this study indicates qualitative and quantitative species differences in the production of epoxide metabolites. At the same exposure concentration of butadiene, the mouse produces higher tissue levels of epoxybutene compared with the rat and also produces detectable levels of diepoxybutane in the lung, whereas no diepoxide was detectable in the rat. These differences may be associated in part with differences in GSH depletion, which was shown to be greater in mouse lung than in rat lung.

The comparative metabolism of butadiene in rats and mice and the tissue distribution of the epoxide metabolites have been investigated by Thornton-Manning et al. (1995). Male Sprague-Dawley rats and B6C3F1 mice were exposed nose-only to 0 or 62.5 ppm butadiene for 2 or 4 hours and sacrificed 0, 0.5 or 1 hour post-exposure. Blood samples were collected just prior to the end of exposure and immediately post-exposure; bone marrow samples and tissue samples from liver, lung, heart, fat, spleen and thymus were obtained at sacrifice. A multidimensional GC-MS technique was used for the quantitative analysis of epoxybutene and diepoxybutane in the blood, bone marrow and tissue samples pooled from 3-6 animals.

Both epoxybutene and diepoxybutane were detected in most rat tissues and all mouse tissues examined immediately after the 4-hour exposure. Tissue levels of both epoxides were consistently greater in mice than in rats, by factors of 3-12 fold for epoxybutene and 38-163 fold for diepoxybutane. In rat liver and lung tissue, epoxybutene was either not detected or was not above control levels; similarly, diepoxybutane was either not detected or was not above control levels in rat liver and bone marrow. Where detected, epoxybutene levels in rat tissue were always higher than the levels of diepoxybutane in the same tissue. In contrast, in mice, with the exception of blood and fat, tissue levels of diepoxybutane exceeded or were comparable with the epoxybutene levels. In both species, the highest levels of the monoepoxide were found in fat (267 pmol/g in rats; 1,302 pmol/g in mice) while the highest levels of the diepoxide were found in blood (5 pmol/g in rats; 204 pmol/g in mice). Liver and bone marrow had the lowest levels of each epoxide metabolite in both rats and mice, with rat lung also having non-detectable or low levels of metabolites. The low level of metabolites found in liver was unexpected, and may be due to post-exposure metabolism during removal of the tissue samples. Similarly, post-exposure metabolism may also have occurred in the lung. It is possible that this could have resulted in underestimation of epoxide levels in both these metabolically active tissues. Tissues and blood analysed at 0.5 and 1 hour post-exposure showed a marked reduction in the levels of both epoxide metabolites, to values close to control, with the exception of epoxybutene in mouse fat tissue and rat thymus tissue. In both these tissues, the epoxybutene levels remained statistically significantly higher than control at 1 hour post-exposure. Overall, this study shows quantitative differences in the production of the epoxide metabolites between rats and mice, with higher tissue levels of both epoxide metabolites produced in mice compared with rats. In both species, tissue levels of the epoxides generally return to control values within 0.5 – 1 hour post-exposure.

The metabolism of butadiene was investigated in three male cynomolgus monkeys (*Macaca fascicularis*) and compared with pre-existing data from rodents (Dahl et al., 1991). The animals were anaesthetised prior to exposure and exposed nose-only to 10, 310 or 7,760 ppm ^{14}C-butadiene for 2 hours. Each monkey was exposed to each concentration with a minimum of 3 months between exposures. Blood samples were taken during and after exposure. Exhaled air was collected during exposure and, along with urine and faeces, for 96 hours post-exposure. Blood samples were analysed for the presence of butadiene and the metabolites, epoxybutene, diepoxybutane, butenediol and CO_2;

exhaled air was analysed for the presence of parent compound, CO_2, alkenyl metabolites and any remaining ^{14}C; while urine was analysed for total ^{14}C.

Uptake of butadiene was calculated as the total ^{14}C excreted during and after exposure. This did not include any residue remaining in the body at 96 hours post-exposure and therefore is likely to underestimate uptake. At 96 hours, uptake of butadiene was calculated to be 1-3% for all exposure concentrations. This uptake was normalised to exposure concentration and duration and to bodyweight to allow comparison with rates calculated for rats and mice in another study (Laib et al., 1988). The uptake rate calculated for rodents was several fold higher than that for monkeys at all exposure concentrations, particularly at lower exposures, and was higher in mice than in rats. For example, at 10 ppm, uptake rate in the mouse and rat was 40- and 22-fold higher respectively than that in the monkey. When expressed as a percentage of inhaled butadiene, uptake was also lower in the monkey than in rodents, particularly at the two lower concentrations. At 10 ppm, uptake in the monkey was calculated to be 2.9% of the inhaled dose, compared with 15% in the rat and 12% in the mouse. At 7,760 or 8,000 ppm, uptake was 1.7% of inhaled dose in the monkey, 2.3% in the rat and 1.8% in the mouse.

The primate data showed that butadiene and CO_2 together formed the highest concentration of volatile material in the blood immediately post-exposure. Metabolites tentatively identified as epoxybutene and diepoxybutane or butenediol were also recovered. Uncharacterised nonvolatile material accounted for most of the radioactivity at 10 and 310 ppm. At 7,760 ppm butadiene was the main radioactive component in the blood. The butadiene concentration in blood relative to that in air increased as exposure concentration increased, which suggests that there is less efficient removal of butadiene from the blood at higher exposures. In comparison with rodents, the total concentration of epoxy, diepoxy and nonvolatile metabolites in the blood of the monkey was lower for equivalent exposure concentrations. This is partly related to differences in the rate of uptake between species. The major route of excretion of metabolites was the urine, except at the lowest exposure concentration, when slightly more radioactive material was exhaled, mainly as CO_2. There was minor excretion via the faeces. At 7,760 ppm, 1.08% of total inhaled butadiene was exhaled in the breath, 0.08% as CO_2, 0.58% was excreted in the urine and 0.002% was recovered in the faeces. The half-life for urinary excretion was estimated to be 9.4 hours. HPLC analysis of exhaled breath confirmed the presence of epoxybutene. A similar analysis of the urine showed only one major metabolite to be present, but it was not identified.

Sabourin et al. (1992) explored species differences in the major urinary metabolites produced following exposure of rodents and monkeys to up to ~8,000 ppm ^{14}C-butadiene. Groups of 4 F344 rats, Sprague-Dawley rats, B6C3F1 mice and Syrian hamsters were exposed nose-only to ~7,600 ppm butadiene for 2 hours and urine was collected for 24 hours post-exposure. Urinary metabolites were identified by HPLC. These data were compared with analysis of urine samples collected from the three cynomolgus monkeys in the experiment described above (Dahl et al., 1991).

Two mercapturic acids were identified as the major urinary metabolites and together accounted for 50-90% of the urinary ^{14}C-butadiene equivalents in all species. These were considered to be formed by glutathione conjugation with either butenediol (1,2-dihydroxy-4- (*N*-acetylcysteinyl)-butane (metabolite I) or with epoxybutene (*N*-acetylcysteine conjugate) (metabolite II). In the mouse, metabolite II accounted for ~62% of the total urinary metabolites, while metabolite I accounted for ~16%. The hamster and both rat species excreted 20-30% metabolite I with ~1.5-fold greater percentages of metabolite II in each case. In contrast, at both 7,760 and 310 ppm the monkey excreted mainly metabolite I (55%) with only a very small percentage of metabolite II (5%). Analysis of urine from one monkey at 10 ppm showed only metabolite I to be detected. It was also noted that the ratio of I:(I+II) was linearly related to hepatic epoxide hydrolase activity

in all four species. These data indicate that production of epoxybutene, which is then available for glutathione conjugation, is greatest in the mouse and least in the monkey.

The identity of the mercapturic acids and their relative proportions in the urine was confirmed in a second experiment by the same group of investigators, in which F344 rats and B6C3F1 mice were exposed to 11.7 ppm butadiene for 4 hours (Bechtold et al., 1994). Urine was collected 'overnight' post-exposure (exact duration not stated) and analysed for mercapturic acid metabolites. The mouse excreted approximately 3-fold greater amounts of metabolite II compared with metabolite I while in the rat, comparable amounts of both metabolites were excreted.

In a study to evaluate the use of measurement of epoxybutene adducts in haemoglobin as an estimate of internal butadiene dose, male B6C3F1 mice and male Sprague-Dawley rats were exposed to 0, 2, 10 or 100 ppm butadiene, 6 hours/day, 5 days/week for 4 weeks (Osterman-Golkar et al., 1993). Numbers of animals were not stated. Blood samples obtained at sacrifice were analysed for haemoglobin adducts of epoxybutene. There was a concentration-related linear increase in haemoglobin adduct levels in mice, from ~100 pmol/g globin at 2 ppm to ~3,800 pmol/g globin at 100 ppm. In rats, a deviation from linearity was noted above 10 ppm. The adduct levels were higher in mice compared with rats at all exposure concentrations, but reached statistical significance only at 10 and 100 ppm. At 100 ppm, the level of adducts in mice was approximately 4-fold higher than in rats.

A similar study to compare epoxybutene haemoglobin adduct formation in rats and mice was conducted by Albrecht et al. (1993). Female Wistar rats and female B6C3F1 mice were exposed to 0, 50, 200, 500 or 1,300 ppm butadiene, 6 hours/day on 5 consecutive days. Blood samples taken from 5 mice and 2 rats at sacrifice 18 hours post-exposure were pooled for analysis of adducts. There was a concentration-related increase in adduct levels in both species. Adduct levels were statistically significantly higher in the mouse than in the rat, even in control animals. At 1,300 ppm, the level of adducts was ~5-fold higher in mice than in rats. Comparison with data from a similar, separate experiment confirmed that there were no statistically significant differences in adduct levels between mice of different strains nor between males and females of the same strain.

The results from these two studies in rodents indicate that epoxybutene formed from metabolism of butadiene can bind to haemoglobin. Since measurement of haemoglobin adducts can be used as an indicator of the internal dose of epoxybutene, the data indicate that the internal dose in rats is lower than that in mice for the same butadiene exposure concentration.

In vitro studies

The metabolism of butadiene has been investigated in a number of *in vitro* studies. In a preliminary report it was shown that, in the presence of NADPH and air, postmitochondrial supernatant converted butadiene to butenediol and erythritol (Herschleb and Leibman, 1972). The same products were formed when epoxybutene was incubated under similar conditions. In experiments with rat liver microsomes under aerobic conditions, the primary metabolite of butadiene was identified as epoxybutene (Bolt et al., 1983; Malvoisin et al., 1979b; Malvoisin et al., 1982). Incubation of epoxybutene with rat liver microsomes under aerobic conditions yielded butenediol (Malvoisin et al., 1979b). When incubation was in the presence of NADPH, two diastereoisomers of both 3,4-epoxy-1,2-butanediol and 1,2:3,4-diepoxybutane were formed (Malvoisin et al., 1979a; Malvoisin and Roberfroid, 1982). Elfarra et al. (1991) demonstrated that the metabolism of butadiene to epoxybutene is mediated by cytochrome P450 in the

presence of mouse liver microsomes, and that crotonaldehyde is an additional metabolite of butadiene.

The ability of human and male B6C3F1 mouse bone marrow cells to metabolise butadiene to epoxybutene was investigated by Maniglier-Poulet et al. (1995). Human bone marrow samples were obtained from 3 adult volunteers. In addition, liver microsomes were isolated from male B6C3F1 mice and Sprague-Dawley rats for comparison of metabolism in liver and bone marrow. Analysis of butadiene and epoxybutene was by gas chromatography. Oxidative metabolism of butadiene in mouse bone marrow was shown to be catalysed by myeloperoxidase in a reaction that required the presence of hydrogen peroxide. There was no involvement of cytochrome P450 in oxidative metabolism in the bone marrow. Comparison of the formation of epoxybutene from butadiene by human and mouse bone marrow cells incubated with 50,000 ppm butadiene showed no statistically significant differences in the concentrations of epoxybutene produced, with similar concentrations in both species. In comparison with mouse or rat liver microsomes, production of epoxybutene by mouse bone marrow cell lysates was 3 orders of magnitude lower, by 281- and 108-fold respectively. Overall, this study demonstrates that human bone marrow cells have the potential to metabolise butadiene to epoxybutene, to an extent comparable with that in mouse bone marrow. However, metabolism of butadiene in mouse bone marrow is minor in comparison with metabolism in mouse liver.

Quantitative differences in the metabolism of butadiene were demonstrated using liver and lung tissue from male B6C3F1 mice, male Sprague-Dawley rats and humans (Csanády et al., 1992). Human liver samples were obtained from 12 trauma victims, while lung samples from 5 lung cancer patients were used. Liver and lung microsomes were exposed to 600 – 25,000 ppm butadiene or 20 – 200 ppm epoxybutene in sealed vials. In addition, tissue preparations were incubated with 2.5 – 74.5 mM epoxybutene and glutathione-S-transferase to investigate glutathione conjugation. In view of the fact that diseased human lung tissue was used, the results for this tissue are not considered to be conclusive. The V_{max} for oxidation of butadiene to epoxybutene in mouse liver microsomes was approximately 2-fold higher compared with that for human liver microsomes, which in turn was 2-fold higher than in the rat. In both human and rat, lung microsomes had a lower capacity than liver microsomes to oxidise butadiene, whereas the mouse lung was comparable with liver in its capacity to metabolise butadiene to epoxybutene. In addition, only mouse liver microsomes were capable of oxidation of epoxybutene to diepoxybutane. This reaction was negligible in rat and human tissue and in mouse lung microsomes. Hydrolysis of epoxybutene and conjugation with glutathione were demonstrated in liver tissue of all three species. Human liver had the highest V_{max} for enzyme-mediated hydrolysis of the epoxide compared with rat and mouse and the lowest V_{max} for conjugation with glutathione. Lung microsomes showed much lower capacity than the liver both for hydrolysis and conjugation of epoxybutene in all species, with no conjugation observed in human lung tissue. In all three species, the detoxification mechanisms were kinetically favoured over the oxidation of butadiene to the monoepoxide and the activation/detoxification ratio was an order of magnitude higher for mice than for rats or humans.

In contrast to the above findings, the results of a more recent comparative metabolism study suggest that in some cases, human liver metabolism *in vitro* is quantitatively similar to that in the mouse (Duescher and Elfarra, 1994). In this study, the metabolism of butadiene to the monoepoxide was measured in rat, mouse and human liver microsomes. Human liver samples were obtained from 4 female and 2 male organ donors. The donors included one non-drinker of alcohol, the remaining 5 donors were described as occasional to moderate alcohol drinkers. Rodent liver microsomes were prepared from male B6C3F1 mice and male Sprague-Dawley rats. Liver microsomes were incubated with 0.2 – 4.4 mM butadiene in the presence of NADPH. In

addition, the relative ability of 7 specifically expressed human cytochrome P450 enzymes to metabolise butadiene was evaluated. In all cases, the production of the metabolites butadiene monoepoxide and crotonaldehyde was determined quantitatively by gas chromatography. The kinetic constants, V_{max} and K_m were calculated for the oxidation of butadiene to the monoepoxide.

Both butadiene monoepoxide and crotonaldehyde were formed by human liver microsomes, with butadiene monoepoxide the major metabolite. The formation of epoxybutene by the 6 human liver microsome samples was NADPH-dependent and showed marked inter-individual variation, with approximately a 3-fold difference in the amount detected after 20 minutes. The kinetic constants for the butadiene oxidation reaction were calculated for 2 human samples, one high and one low metabolic rate, and compared with the values obtained for rat and mouse. The V_{max} values obtained for the 2 human samples were 10.4 and 22.8 nmol/mg protein/min compared with 9.2 and 2.0 nmol/mg protein/min for mouse and rat liver microsomes respectively. The $V_{max/Km}$ ratios were comparable for human and mouse, and were approximately 3-fold higher than for the rat. There was clear variation in the relative abilities of different human P450s to oxidise butadiene to the monoepoxide. Two isozymes, P450 2A6 and 2E1, were found to be most active in metabolism of butadiene to the monoepoxide. In addition, P450 2A6 was apparently more important for metabolism at higher butadiene concentrations, while 2E1 was predominant at lower butadiene concentrations. In summary, this study provides evidence for interindividual variability in the metabolism of butadiene to butadiene monoepoxide, and suggests that in some cases, the formation of the monoepoxide in human liver tissue *in vitro* may be similar to or exceed that in the mouse. This variability may be due to differences in the expression of P450 isozymes, specifically 2A6 and 2E1, which appear to be most active in human liver metabolism of butadiene.

The formation of epoxybutene has been measured in liver and lung preparations from Sprague-Dawley and Wistar rats, male B6C3F1 and NMRI mice, rhesus monkeys and one human (Schmidt and Loeser, 1985). Tissue homogenates were exposed to about 30,000 ppm butadiene in sealed vials. In liver tissue, the highest concentration of the epoxide was formed in mouse liver, particularly females, the monkey had the lowest concentration, with human liver similar to the rat, and intermediate between mouse and monkey. The production of the epoxide was about 3-fold higher in female mouse liver than in human liver. In lung tissue preparations, epoxide formation was detected only in the mouse and rat, with epoxide production in the mouse 6-7 fold higher than in the rat. The formation of diepoxide was not detected.

The ability of rat, mouse and human liver microsomes and cDNA expressed human P450 (CYP) isozymes to metabolise butadiene monoepoxide to the diepoxide has been investigated by Seaton et al. (1995). Rodent liver samples were obtained from male Sprague-Dawley rats and B6C3F1 mice. Human liver tissue was obtained from 10 Caucasian trauma victims, 7 males and 3 females, aged 3-60 years. In addition, microsomes were prepared from human β-lymphoblastoid cells, expressing cDNAs for individual CYP isozymes. Liver microsomes were incubated with 80 µM or 5 mM butadiene monoepoxide for 1 hour after which time the concentration of butadiene diepoxide was determined. Only human liver microsomes which expressed CYP 2E1 were able to convert the monoepoxide to detectable levels of butadiene diepoxide at the lower concentration tested (80 µM), whilst both CYP 2E1 and 3A4 produced detectable levels of the diepoxide after incubation with 5 mM epoxybutene. A 60-fold variation in the rate of transformation of butadiene monoepoxide to butadiene diepoxide was demonstrated in the 10 human liver samples, with transformation rates in the range 0.005 – 0.324 nmol/mg protein/min compared with values of 0.166 and 0.473 nmol/mg protein/min for rat and mouse pooled liver samples, respectively. The rate of transformation in the human samples correlated well with the

concentration of CYP 2E1. Michaelis-Menten kinetic parameters calculated for the human and rodent liver samples indicated that the $V_{max/Km}$ ratios for 3 human samples varied between 1.2 – 3.8, compared with 2.8 for the rat and 9.2 for the mouse. Overall, this study demonstrates that human hepatic CYP 2E1 and 3A4 can convert butadiene monoepoxide to butadiene diepoxide although only CYP 2E1 is active at low concentrations of the monoepoxide. There was large variation in the rate of transformation in the human samples tested, with all samples showing lower transformation rates than that for mice, and which were comparable with or higher than that for rats.

4.1.2.1.2 Studies in humans

There is only very limited information on the toxicokinetics of butadiene in humans. In a human volunteer study, 30% of inhaled butadiene was reported to be retained following a 20-minute exposure to 100 ppm butadiene (Wagner, 1974). However, in view of the limited nature and reporting of this study, no firm conclusion can be drawn from it.

The formation of adducts of epoxybutene with haemoglobin in butadiene-exposed workers has been reported. In the first of these, blood samples were taken from male workers at a chemical production plant (Osterman-Golkar et al., 1993). Four workers were exposed to an estimated 8-hour TWA exposure to butadiene of < 3.5 ppm. A control group of 5 workers (4 males) at the same plant, working in non-production areas, was also included. Air sampling measurements from part of the non-production area indicated butadiene levels of ~0.03 ppm (presumably an 8-hour TWA). In addition, a blood sample was taken from one university employee with no known exposure to butadiene. All participants in the study were non-smokers and potential participants who had recently been exposed to x-irradiation or mutagenic drugs were excluded. The adduct levels measured in the butadiene-exposed workers were in the range 1.1-2.6 pmol/g globin, approximately two orders of magnitude lower than adduct levels measured in rodents exposed to 2 ppm butadiene in the same study. Adducts were detectable in only one of the five non-production workers and were not detectable in the outside control. The one positive control subject was reported to be a snuff user, which may explain the increased adduct level. Overall, this study demonstrates that epoxybutene is formed and can bind to haemoglobin to produce very low, but detectable levels of haemoglobin adducts in workers exposed to < 3.5 ppm butadiene (8-hour TWA).

In a second study by the same group, haemoglobin adducts of epoxybutene were measured in 17 butadiene-exposed workers and 9 non-exposed controls employed at a Portugese petrochemical plant (Osterman-Golkar et al., 1996). Blood and urine samples were collected from each worker post-shift and exposure to butadiene during at least one shift per person was performed by personal sampling; a number of static sampling measurements were also performed in the work area. Blood samples from each of the 26 subjects were analysed for 2-hydroxy-3-butenylvaline, with a limit of detection of 0.03-0.05 pmol/g globin. Personal sampling results indicated that of the 17 exposed workers, exposure levels were higher for production workers (mean 5 ppm, 8-hour TWA; 10 workers) compared with laboratory and maintenance workers (mean exposure 0.27 ppm butadiene, 8-hour TWA; 7 workers). The mean level of adducts measured in the laboratory and maintenance workers was 0.05 pmol/g globin, which was not increased significantly above the control level of 0.06 pmol/g globin. In comparison, elevated adduct levels of 0.16 pmol/g globin were measured for production workers. The contribution of exposure to butadiene from cigarette smoking was estimated to be very small. The authors noted that the level of adducts measured in the control population was higher than would be expected from general background environmental exposure to butadiene, but may indicate intermittent exposure

at the plant. As in the previous study, reported above, the results of this study indicate that for a comparable butadiene exposure concentration, the adduct levels measured in exposed workers are considerably lower than in rodents.

Bechtold et al. (1994) investigated urinary metabolites in a small sample of workers at a butadiene extraction plant. Exposed workers were subdivided into three groups according to exposure, as low, intermediate or high exposure. High exposure employees worked in areas in which the 8-hour time-weighted average concentration of butadiene was measured as 3-4 ppm. Employees in the intermediate exposure group spent variable amounts of time in high and low exposure areas, while those in the low exposure group worked in areas in which the historical 8-hour TWA concentration was <0.1 ppm. A control group of non-exposed workers not associated with the plant was included for comparison. Urine samples were obtained from 7, 3, 10 and 9 employees from each of the four groups, respectively. The samples were taken at the end of an 8-hour shift and analysed for the two mercapturic acid metabolites previously identified from animal studies – 1,2-dihydroxy-4-(*N*-acetyl-cysteinyl- *S*-)butane (I) and 1-hydroxy-2-(*N*-acetylcysteinyl-*S*-)-3-butene (II). The average concentration of metabolite I in urine from controls was 320 ng/ml urine, compared with 630, 1,390, and 3,200 ng/ml in the low, intermediate and high exposure groups respectively. The values for all exposed groups were statistically significantly different from control. Metabolite II was not detectable in any of the urine samples. These data suggest that in humans, metabolism of butadiene to epoxybutene is followed by hydrolysis to butenediol as the predominant detoxification pathway. There is no evidence for epoxybutene conjugation as a detoxification pathway in humans.

4.1.2.1.3 Physiologically-based pharmacokinetic (PBPK) models

Various PBPK models have been developed to simulate the toxicokinetics of butadiene and its metabolites.

Differences in the internal dose of the monoepoxide metabolite between the rat and mouse following exposure to butadiene were considered in a PBPK model developed by Johanson and Filser (1993). *In vitro* studies were performed with various rat tissues to obtain blood and tissue partition coefficients for butadiene and butadiene monoepoxide. Other physiological and metabolic parameters were taken from standard models and from published experimental *in vitro* rat and mouse liver data. The model comprised five separate compartments of chamber air, lungs, liver, fat and richly perfused tissue. Metabolism was assumed to occur only in the liver. The liver compartment was subdivided to take account of glutathione-S-transferase (GSH) kinetics and intrahepatic first pass metabolism. The model was tested by comparison with experimental observations for rats and mice and was found to correctly predict the observed toxicokinetic profiles and quantitative levels of both butadiene and butadiene monoepoxide for rats and mice. The model also predicted the experimentally observed GSH depletion. The model data suggested that GSH depletion becomes significant in determining differences in monoepoxide levels between rats and mice only at very high exposure levels for exposure periods of several hours. At butadiene exposure concentrations below about 1,000 ppm, the monoepoxide levels in the mouse were predicted to exceed those in the rat by about 1.6-fold. At exposure concentrations above 1,000 ppm for 6-9 hours, GSH depletion occurs in the mouse, but not the rat, and leads to internal levels of monoepoxide in the mouse which are of the order of 2-3 times higher than in the rat. The relatively small species difference in the internal predictions of monoepoxide concentrations, particularly at the lower butadiene exposure levels, were considered to be insufficient to explain the very marked species difference in the carcinogenicity

of butadiene. One possible explanation for this is that another metabolite, in particular butadiene diepoxide, may be important in the carcinogenic process in rodents.

In a second PBPK model, differences in epoxide formation and detoxification between rat, mouse and human were investigated for simulations of a 6-hour exposure to up to 10,000 ppm butadiene (Kohn and Melnick, 1993). The model consisted of compartments for lung, blood, fat, liver, viscera (i.e. other rapidly perfused tissues) and muscle (slowly perfused tissue). Butadiene metabolism was assumed to occur in lung, liver and viscera. Values for standard physiological parameters and partition coefficients were taken from the published literature. Kinetic parameters were taken from the *in vitro* data of Csanády et al. (1992). Production of diepoxybutene was included in the model only for mouse liver. The model predictions of butadiene absorption for mouse and rat were broadly comparable with published data from *in vivo* experiments in these species. In addition, it was found that the model was more sensitive to physiological parameters than metabolic parameters. Thus, in this model, body burden of butadiene and the monoepoxide metabolite is dependant on retention of inhaled butadiene. Therefore, for equivalent atmospheric concentrations, much higher levels of epoxybutene are predicted in mouse compared with the human, but for equivalent inhaled dose, these species differences in body burden of butadiene monoepoxide become less important, although the predicted levels remain highest in the mouse and least in the human. For example, for an equivalent internal dose of 200 µmol/kg, the ratio of predicted concentration of the monoepoxide in the blood is 5.4:3.1:1 for mouse, rat and human respectively. Accumulation of monoepoxide in the human liver was predicted to be higher than that in the mouse or rat, for equivalent absorbed doses of butadiene, up to about 440 µmol/kg. The model also predicted that for a scenario of repeated daily exposure to butadiene for 8 hours, elimination of butadiene from the fat would be complete in the mouse, but not in humans, within the 16-hours of non-exposure. Thus, in humans, the model predicts that repeated daily exposure would lead to the accumulation of butadiene in the fat, and thus the potential for continued production of the monoepoxide metabolite. Overall, this model suggests that physiological parameters are more important than biochemical differences in determining the uptake and retention of butadiene and thus formation of epoxybutene in rats, mice and humans. It predicts that for an equivalent internal dose of butadiene, blood epoxybutene levels will be highest in mice, which in turn will be higher than those in rats, and will be lowest in humans. However, the predicted differences in tissue levels of epoxybutene are not in themselves sufficient to explain the differences in carcinogenic response seen between mice and rats.

Evelo et al. (1993) developed a PBPK model to simulate the uptake, distribution and metabolism of butadiene, in particular to characterise the relative importance of lung and liver metabolism at different butadiene exposure concentrations. The model comprised 5 compartments, lung, fat, muscle, richly perfused tissue and liver. The lung compartment was sub-divided into alveolar and bronchial regions. Butadiene metabolism was assumed to occur only in the lung and liver. Physiological parameters for mice and rats were obtained from the published literature. Model simulations were optimised against real exposure data to obtain metabolic parameters, which were validated against independent metabolic data from published sources. Tissue-blood partition coefficients were calculated from octanol-water partition coefficients. After optimisation of the metabolic parameters, the model was found to give a close fit to real data from closed chamber studies for both rats and mice. The model simulations indicated that the ratio of total metabolic activity between lung and liver in mice, for a continuous 8-hour exposure to 1-1,000 ppm butadiene, is dependant on the exposure concentration. The ratio of lung:liver metabolic activity decreased as exposure concentration increased, indicative of a shift in the relative importance of lung metabolism towards metabolism in the liver at higher exposure concentrations. The model also indicated a strong effect of first-pass metabolism in the lung at

low exposure concentrations. In the mouse, metabolic activity in the lung exceeded that in the liver at exposure concentrations below about 600 ppm, with the ratio of the activity in lung:liver in excess of 1. In comparison, when the model simulations were repeated using rat and human kinetic parameters, although there was again a reduction in the ratio of metabolic activity in the lung compared with liver with increased butadiene exposure concentration, the ratio was always less than 1, for exposure concentrations between 1 and 1,000 ppm. Thus, in rats and humans, in contrast to the mouse, the model indicates that hepatic metabolism is more important than lung metabolism, at all exposure levels, although lung metabolism increases in relative importance at lower exposure concentrations. Overall, this model indicates differences in the relative importance of lung and liver metabolism at different butadiene exposure concentrations, with lung metabolism becoming relatively more important at low concentrations. The model also indicates a clear species difference in lung metabolism, which in the mouse, predominates over hepatic metabolism at concentrations below about 600 ppm. This could explain the increased susceptibility of mice to the development of local lung tumours at low butadiene exposure concentrations.

The most recently developed PBPK model is a refinement of that developed by Medinsky et al. (1994), and is the only model to include a prediction of the distribution and elimination of the diepoxide metabolite of butadiene, as well as the monoepoxide (Sweeney et al., 1997). Partition coefficients for butadiene, epoxybutene and diepoxybutane were determined experimentally and reaction rates for non-enzymatic losses of the epoxide metabolites occurring in tissue were also determined. Rate constants for oxidation of butadiene and epoxybutene, and for hydrolysis and glutathione conjugation of epoxybutene and diepoxybutane in liver and lung, were obtained from *in vitro* or *in vivo* data. The model assumed that there are two pathways for metabolism of butadiene, one of which is oxidation to epoxybutene and the second is the production of unknown volatile metabolites. Model simulations were compared with experimental data for metabolism of inhaled butadiene in Sprague-Dawley rats and B6C3F1 mice *in vivo* and clearance of epoxybutene and diepoxybutane after intravenous injection in rat and/or mouse. The results of the model simulation in comparison with epoxide clearance following intravenous injection suggested that metabolism may also occur in tissues other than the liver and lung. The model was found to give a reasonable prediction of blood levels of butadiene following inhalation exposure of rats and mice, but overpredicted blood levels of epoxybutene if the model assumed that all butadiene was metabolised to epoxybutene; a more accurate prediction of both epoxybutene and diepoxybutane concentrations in the blood was obtained when the model assumed that only a fraction of inhaled butadiene was metabolised to epoxybutene. Thus, the results of this PBPK model simulation raise the possibility that *in vivo* metabolism of butadiene involves a pathway additional to that of oxidation to epoxybutene. However, the possible relevance and importance of this postulated second pathway to humans is not known.

4.1.2.1.4 Summary of toxicokinetics

There is very limited information on the toxicokinetics of butadiene in humans. In workers exposed by inhalation to 3-4 ppm butadiene, metabolism to epoxybutene with subsequent hydrolysis to butenediol occurs. Epoxybutene hemoglobin adducts have been identified in the blood of exposed workers. In one study, the mercapturic acid (glutathione) conjugate of butenediol has been identified as a urinary metabolite although no detectable levels of the epoxybutene mercapturate were found in the same study. This suggests that detoxification of epoxybutene proceeds by hydrolysis to butenediol, with subsequent conjugation. There are no data on the toxicokinetics of butadiene following other routes of exposure. The possibility that butadiene is absorbed and metabolised via the oral and dermal routes cannot be entirely

discounted, although given its physicochemical characteristics, the potential for uptake via these routes is anticipated to be minor, particularly in relation to the inhalation route. The only other information in relation to toxicokinetics in humans comes from *in vitro* studies using human tissue, which indicate that metabolism of butadiene to epoxybutene occurs in human liver, lung and bone marrow. In the one study that has investigated further metabolism of the monoepoxide to diepoxybutane, in liver and lung tissue, no detectable levels of the diepoxide were measured. Human liver tissue has greater capacity for metabolism to epoxybutene compared with lung tissue. However, the results for lung tissue must be treated with some caution as diseased tissue was used. There is evidence for considerable inter-individual variation in the capacity of human liver tissue to metabolise butadiene to epoxybutane, with some human liver tissue samples showing capacity for metabolism comparable to, or exceeding, that in the mouse. The involvement of specific P450 isozymes in metabolism of butadiene to the monoepoxide has been demonstrated, and raises the possibility that differences in expression of P450 isozymes may explain some of the intra-individual variability that has been seen *in vitro*.

Studies in rodents and non-human primates have shown that butadiene is absorbed via the lungs. In rodents, uptake and metabolism of butadiene obeys simple first order kinetics at concentrations up to about 1,500 ppm, above which saturation of the process appears to occur. Butadiene is widely distributed throughout the body. The first step in the metabolic pathway is the formation of epoxybutene, catalysed by mixed function oxygenases. The further metabolism of epoxybutene can proceed by a number of different pathways. There is some conjugation with glutathione. A second possible pathway is hydrolysis to butenediol, catalysed by epoxide hydrolase. Another possibility is further epoxidation to diepoxybutane. Further epoxidation and/or hydrolysis reactions can then occur, which ultimately lead to erythritol formation. It is not clear at which stage or stages in the pathway CO_2 is formed. The main route of elimination of butadiene and its metabolites in rodents and primates is urinary excretion or exhalation in the breath. Minor faecal excretion also occurs. In rodents, urinary excretion takes place in two phases with 77-99% of the inhaled dose excreted with a half-life of a few hours in rodents, while the remainder is excreted with a half-life of several days. There is no evidence for bioaccumulation of butadiene. There are no data on the toxicokinetics of butadiene following oral or dermal exposure, and although the possibility of uptake via these routes cannot be entirely discounted, their contribution to uptake and metabolism of butadiene is anticipated to be negligible. In addition, there is no evidence of any significant potential for dermal uptake from a comparison of the results of whole-body inhalation exposure studies compared with those in which exposure was nose-only.

There are quantitative species differences in the toxicokinetics of butadiene. In comparison with the rat, the mouse absorbs and retains approximately 4-7 fold higher concentrations of butadiene per kg bodyweight. The mouse also produces approximately 2-20 fold higher concentrations of the metabolite, epoxybutene, than does the rat, for equivalent exposures. Very low concentrations of the diepoxide metabolite have been detected in the blood and various tissues of rats and mice; this metabolite has been tentatively identified in the blood of monkeys, *in vivo*. Again, where measurements are available, tissue levels of diepoxybutane are generally higher in mice compared with rats, by up to 163-fold. *In vitro* studies indicate that in the mouse, lung and liver tissue have similar capacity for butadiene metabolism while in rats and humans, liver tissue has a greater capacity for metabolism than does lung tissue, although some metabolism does take place in lung tissue. Detoxification pathways are kinetically favoured over activation pathways in rodent and human tissue, although the ratio of activation:detoxification is highest in mouse tissue compared with rat or human tissue. In mouse liver and lung tissue, detoxification of epoxybutene appears to be mainly by conjugation with glutathione, with hydrolysis to butenediol a relatively minor pathway. In comparison, in human liver and lung, detoxification of

epoxybutene is primarily by hydrolysis, with only some glutathione conjugation; this finding from *in vitro* studies supports the *in vivo* human metabolism data.

Formation of the diepoxide has been demonstrated in mouse liver tissue exposed to butadiene *in vitro*, but not in rat or human tissue, although formation of diepoxybutane has been demonstrated cDNA-expressed human liver microsomes exposed to epoxybutene.

From the limited comparative information available from *in vitro* and *in vivo* studies, it appears that in relation to the formation of epoxide metabolites, the metabolism of butadiene in humans is quantitatively more similar to that in the rat, rather than the mouse. However, *in vitro* studies have demonstrated considerable inter-individual variability in the oxidative metabolism of butadiene.

A number of PBPK models have been developed to try to characterise the internal tissue levels of butadiene and its epoxide metabolites. In general, whilst these models are useful and aid understanding of the kinetics of butadiene and its epoxide metabolites between species, they do not yet provide any clearer understanding of the basis for the marked species differences in susceptibility. Although the known quantitative species differences in the metabolism of butadiene to its epoxide metabolites, demonstrated *in vitro*, *in vivo* and in PBPK modelling, may explain in part the very marked difference in toxicity of butadiene between rats and mice, it is not possible, on the basis of the currently available evidence, to attribute the differences in toxicity between the rat and mouse solely to these quantitative differences in metabolism. Nor is it possible, on the basis of the available *in vitro* data in rodents and humans which indicate considerable inter-individual variability in human tissue metabolic capacity, to exclude the possibility that some humans could be similar to mice in their capacity for metabolism of butadiene to more active intermediates.

The currently understood metabolic pathway for butadiene *in vivo* is shown in **Figure 2**.

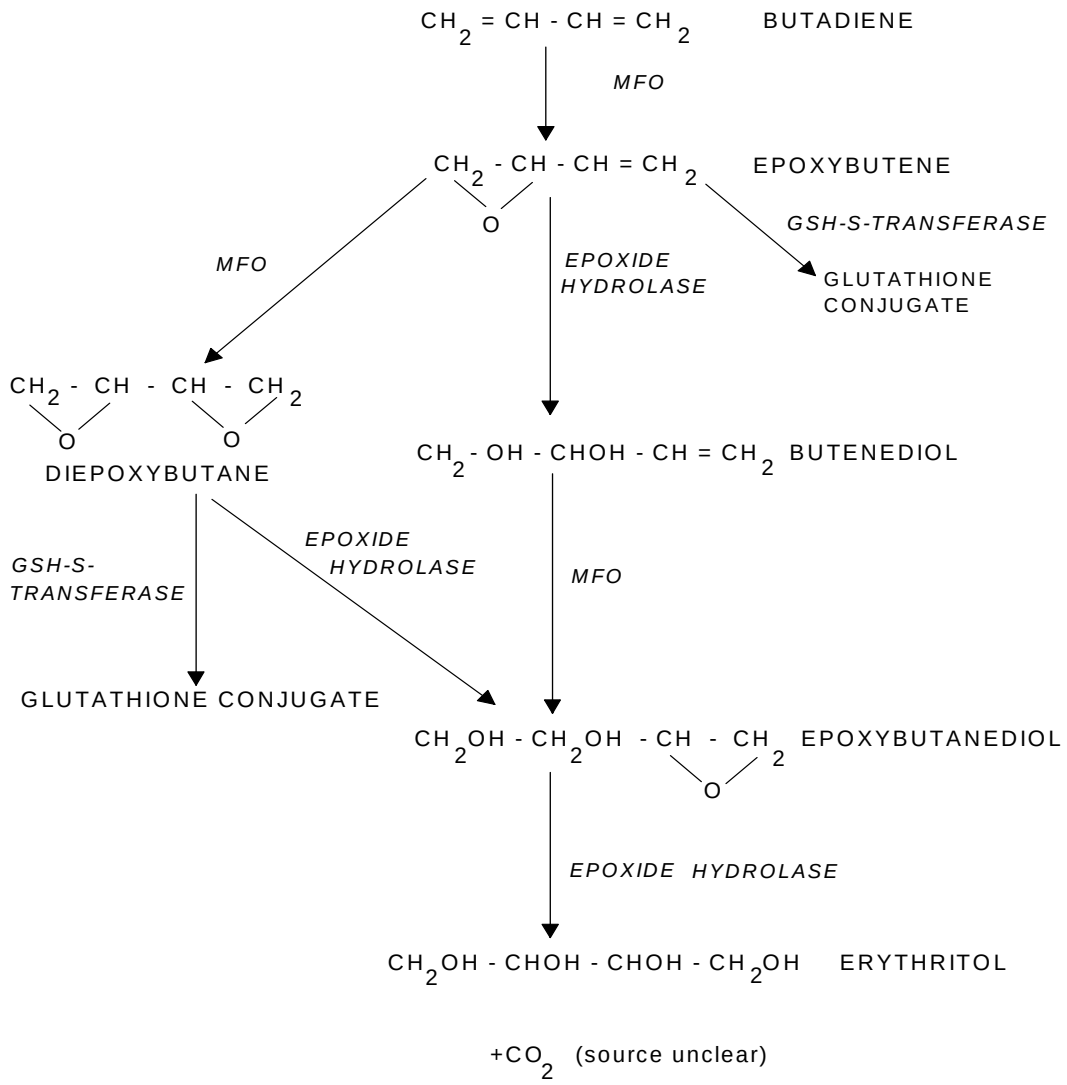

Figure 2 Metabolic pathway for 1,3-butadiene

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

The data on the acute toxicity of butadiene are of poor quality. In the rat, the inhalation LC_{50} value for a 4-hour exposure is 129,000 ppm (Shugaev, 1969). Deep narcosis was observed at 129,000 ppm after exposure for 1 hour. The same author reports a 2-hour LC_{50} of 121,000 ppm in the mouse. In mice, exposure to 200,000 ppm for 6-10 minutes or to 400,000 ppm for up to 1 minute resulted in narcosis; deaths occurred after 11-14 minutes exposure to 400,000 ppm (Killian, 1930). Larionov et al. (1934) reported the minimum concentration for narcosis and death in mice to be 90,000 – 140,000 ppm, though the exposure period was not stated. At narcotic vapour concentrations, > 90,000 ppm, respiratory obstruction caused by severe nasal and bronchial irritation, hyperventilation and congestive hyperaemia in the liver and kidneys have been noted in mice (Killian, 1930; Larionov et al., 1934). In rabbits, narcosis and deaths occurred at 250,000 ppm for an unstated period of time, but these effects were not seen at around 150,000 ppm for 25 minutes (Larionov et al., 1934). Nasal irritation and congestive hyperaemia in the liver and kidney was seen at 250,000 ppm for an unstated exposure period. Mild leucocytosis, neutrophilia, lymphopenia and monocytosis were observed in rabbits following exposure to 90,000 ppm butadiene for 2 hours (Pokrovskii and Volchkova, 1968; Volchkova, 1972).

Oral LD_{50} values of 5,480 mg/kg and 3,210 mg/kg have been reported for the rat and mouse respectively (Ripp, 1969).

4.1.2.2.2 Studies in humans

There is little information available on the effects of single exposure and the data are of poor quality.

A slight increase in pulse rate was noted as a result of breathing 10,000 ppm butadiene for 5 minutes (Larionov et al., 1934). Blood pressure and respiration were apparently not markedly affected. Two volunteers exposed to 8,000 ppm butadiene for 8 hours reported feeling alert and "capable of meeting emergencies" (Carpenter et al., 1944). Unsteadiness was noted in psychomotor response, measured by a tapping test, at 4,000 ppm but not at 8,000 ppm.

In separate studies with 4 volunteers per test, sensitivity of the eye to light was reported to be altered following exposure to 1.7 ppm butadiene and an electrocortical conditioned response (light-stimulated desynchronisation of α-rhythm of the brain) occurred at 1.6 ppm (Ripp, 1965a, b, 1967). No effect levels were 1.6 ppm and 1.4 ppm, respectively. However these studies are unconventional and unreliable and the results are considered of doubtful significance.

4.1.2.2.3 Summary of acute toxicity

There are only limited, poor quality data on the single exposure toxicity of butadiene. However, it can be concluded that butadiene is of low acute toxicity following single inhalation or oral exposure.

The limited data available indicate that butadiene is of low acute toxicity in humans. A concentration of 8,000 ppm can be tolerated for several hours without adverse symptoms. The

main acute effect of butadiene is irritancy. Butadiene is an irritant to the eyes, nose and mouth at high concentrations, of the order of thousands of ppm.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

No data are available on the skin irritation potential of butadiene and limited information is available on eye irritation.

Acute exposure to 90,000 – 140,000 ppm butadiene was reported to cause conjunctivitis in mice, and conjunctivitis and lacrimation were observed in rabbits exposed to 150,000-250,000 ppm (Larionov et al., 1934). In another study with rabbits, ophthalmoscopy revealed no signs of eye injury following exposure up to 6,700 ppm butadiene 7.5 hours/day, 6 days/week for 8 months; the same result was recorded for dogs, for which only one animal per exposure level was used (Carpenter et al., 1944).

4.1.2.3.2 Studies in humans

Slight irritation and dryness of the nose and mouth were reported by human volunteers exposed to 10,000 ppm butadiene for 5 minutes (Larionov et al., 1934). In another study, 2 subjects exposed to 2,000 ppm butadiene for 7 hours or 4,000 ppm for 6 hours reported eye irritation and blurred vision; repeated exposure resulted in less awareness of these symptoms (Carpenter et al., 1944). Irritation of mucosal surfaces has been reported by volunteers exposed to 226 ppm butadiene for 1 minute (Gostinsky, 1965). However, in the context of other information available, any effects must have been negligible. No eye irritation was noted under laboratory conditions as a result of exposure to less than 1 ppm (Altshuller et al., 1966).

Irritation of the eyes, nasal passages, throat and lungs with, on occasion, coughing and drowsiness, were noted in men exposed to butadiene (exposure concentration not stated) in American synthetic rubber plants (Wilson, 1944). A full recovery was made when exposure ceased and the results of physical examination, chest X-ray, and blood and urinalysis were found to be normal. It is possible that this was a mixed exposure. Irritation of the upper respiratory tract was also reported in workers in Russian synthetic rubber plants (Bashirov, 1975; Mukhametova et al., 1976; Nadirova, 1967; Ripp, 1967). However, it is not possible to relate these effects to butadiene because there was also exposure to other chemicals (Abdullaeva, 1974).

4.1.2.3.3 Summary of irritation

No skin irritation data are available for butadiene. However, as no skin irritation has been mentioned in any studies in humans following single exposure to high concentrations, this suggests that butadiene does not exhibit this property. Eye irritation has been reported in humans at very high exposure concentrations. The gaseous nature of butadiene precludes the conduct of conventional skin and eye irritation tests in animals.

4.1.2.4 Corrosivity

The studies in animals and humans reported in Section 4.2.3 indicate that butadiene is not corrosive to the skin or eyes.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

There are no data on the skin or respiratory sensitisation potential of butadiene in animals. However, the gaseous nature of butadiene precludes the conduct of conventional skin sensitisation tests in animals.

4.1.2.5.2 Studies in humans

There are no data on the skin or respiratory sensitisation potential of butadiene in humans. However, it is significant that there have been no reports of skin or respiratory sensitisation caused by butadiene.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Inhalation

Studies in the rat

An extensive and well-reported study was performed in which groups of 40 Sprague-Dawley rats per sex were exposed to 0, 1,000, 2,000, 4,000 or 8,000 ppm butadiene, 6 hours/day, 5 days/week for up to 3 months (Crouch and Pullinger, 1977; Crouch et al., 1979; Pullinger et al., 1979). Animals were sacrificed at 2 weeks, 6 weeks or 3 months. No toxicologically significant effects were seen in clinical signs, clinical chemistry or haematological parameters, nor following histopathological examination. From this study, the NOAEL in the rat exceeded 8,000 ppm.

In an older, less reliable study, rats were exposed to 0, 600, 2,300 or 6,700 ppm butadiene, 7.5 hours/day, 6 days/week, for 8 months (Carpenter et al., 1944). Clinical chemistry, haematology and histopathological investigations were conducted. The only notable effects seen were a concentration-dependent reduction in bodyweight gain and an increased incidence of cloudy swelling in the liver at 6,700 ppm.

Information on the repeated dose toxicity of butadiene to the rat is also available from a carcinogenicity study, described in detail in the section on carcinogenicity. Three groups of 110 rats per sex, were exposed to 0, 1,000 or 8,000 ppm butadiene, 6 hours/day, 5 days/week for up to 105 weeks for females or 111 weeks for males (Owen, 1981; Owen and Glaister, 1990). An interim kill of 10 animals per sex per group was conducted at 52 weeks. Clinical chemistry and haematological parameters were investigated at 3-6 monthly intervals and all animals were

subjected to gross necropsy and comprehensive histopathological examination at sacrifice. The study was well-conducted and conformed to current regulatory guidelines.

There was a slight, statistically significant reduction in survival in animals exposed to 8,000 ppm. In the first 12 weeks of exposure, a transient, statistically significant reduction in body weight gain was seen in both sexes at 8,000 ppm and in males at 1,000 ppm. Minor, treatment-related clinical signs of toxicity – wet and ruffled fur together with slight limb weakness or incoordination following dosing on the first day of the 5-day schedule – were seen between 2 and 5 months of treatment in animals at 8,000 ppm. At the end of the study, statistically significant increases were seen in liver weight in all exposure groups, but there was no associated pathology. In addition, males at 8,000 ppm had statistically significantly increased kidney, heart, lung and spleen weights, with associated nephrosis of the kidney and focal metaplasia in the lung. There were no treatment related changes in clinical chemistry or haematological parameters, urinalysis or neuromuscular function. Overall, butadiene is of low toxicity to the rat when administered at high concentrations over an extended period. A no adverse effect level of 1,000 ppm for systemic toxicity can be identified, with minimal toxic effects at 8,000 ppm.

In marked contrast to all other studies, a wide range of toxic effects have been described to occur in rats at low exposure concentrations in two poorly reported studies (Batkina, 1966; Nikiforova et al., 1969; Ripp, 1967; Ripp, 1969; Ripp and Lyutikova, 1966). Effects were reported following continuous exposure to 13.8 ppm butadiene for 81 days, or exposure to 4.5 ppm butadiene daily, 4 hours/day for 4 months. Given that these results are contradictory to the results of other, more recent, well-conducted studies using higher dose levels and given the lack of adequate detail in reporting, it is considered that these data should be discounted and no significance be accorded to them.

Studies in the mouse

The only comprehensive information available for the mouse is from two carcinogenicity studies in B6C3F1 mice, described in detail in the section on carcinogenicity.

In the first study, 50 animals per sex were exposed to 0, 625 or 1,250 ppm butadiene, 6 hours/day, 5 days/week for 60 – 61 weeks (Huff et al., 1985; Melnick et al., 1988; National Toxicology Program, 1984). Reporting was mainly limited to carcinogenic effects. Histopathological examination was conducted. Survival was markedly reduced in exposed animals, due primarily to the development of malignant tumours. A wide range of organs was affected by exposure to butadiene. Non-neoplastic effects seen at 625 and 1,250 ppm were ovarian and testicular atrophy, congestion, haemorrhage and hyperplasia of the lungs, haemorrhage and necrosis of the liver, thymus and bone marrow atrophy, epithelial hyperplasia of the forestomach and endothelial hyperplasia and mineralisation of the heart. Chronic inflammation and fibrosis developed in the nasal cavities of males exposed to 1,250 ppm. This study demonstrates that butadiene causes severe toxicity in the mouse at these concentrations.

Only limited information on repeated dose toxicity is available from a follow-up to this study (Melnick et al., 1990a), conducted using lower exposure concentrations. Groups of 70 or 90 B6C3F1 mice were exposed to 0, 6.25, 20, 62.5, 200 or 625 ppm butadiene 6 hours/day, 5 days/week for up to 2 years. Animals were subjected to full histopathological examination at sacrifice. There was a statistically significant reduction in survival at 20 ppm and above, due mainly to the development of treatment-related malignant tumours. All other reporting of effects was related to carcinogenicity.

Overall, butadiene is highly toxic to the mouse following repeated exposure. Deaths and tumour formation are seen at 20 ppm.

Irons et al., (1986a,b) investigated the effect of exposure to 0 or 1,250 ppm butadiene on a range of haematological parameters in male B6C3F1 or NIH Swiss mice. In addition, bone marrow analysis was conducted in B6C3F1 mice. B6C3F1 were exposed 6 hours/day, 6 days/week for 3, 6, 12, 18 or 24 weeks while Swiss mice were exposed 6 hours/day, 5 days/week for 6 weeks. Bodyweight gain was unaffected by exposure to butadiene. The effect on haematological parameters was similar in both strains. Mice exposed to butadiene had anaemia, with statistically significant reductions in circulating erythrocytes, haemoglobin and haematocrit. In addition, B6C3F1 mice had leukopaenia. Bone marrow cellularity was statistically significantly reduced in Swiss mice. In butadiene-exposed B6C3F1 mice, there was an increase in the number of bone marrow cells in S-phase, indicative of cell cycle delay or an increase in proliferation. Overall, these data are consistent with macrocytic- megaloblastic anemia and indicate that the bone marrow is a target for butadiene toxicity in the mouse.

An alteration in hematopoietic stem cell development was reported in male B6C3F1 mice (Leiderman et al., 1986). Groups of mice were exposed to 0 or 1,250 ppm butadiene 6 hours/day, 5 days/week for 6 or 30/31 weeks. Quantitative assessment of pluripotent stem cells was made using the spleen colony-forming unit assay (CFU-S) in which lethally irradiated recipient mice were injected with nucleated viable bone marrow cells from control or butadiene-exposed mice. The injected mice were sacrificed after 12 days and spleen colonies counted. In addition, committed stem cell activity was assessed using an *in vitro* assay for the granulocyte/macrophage progenitor cell (CFU-GM). There was no change in frequency of pluripotent stem cells at 6 weeks in butadiene-exposed mice compared with controls, but colonies from treated animals were smaller than those of controls, suggesting an alteration in the relative proportion of immature to mature cells in treated animals. This was confirmed by results of long-term bone marrow cell cultures in which a shift in the time course of differentiation of the granulocyte/macrophage progenitor cell was observed. After 30-31 weeks exposure to butadiene, a reduction in numbers of both CFU-S and CFU-GM was seen. This alteration in stem cell development may play a role in the pathogenesis of murine thymic lymphoma.

The effect of repeated exposure to butadiene on murine immune function was investigated by Thurmond et al. (1986). Male B6C3F1 mice were exposed to 0 or 1,250 ppm butadiene 6 hours/day, 5 days/week for 6, 12 or 24 weeks. There were 4-6 mice per group. Bodyweight, spleen and thymus weights were recorded at sacrifice and the lymphoid organs from the 24-week exposure group were retained for histological examination. A series of immune function assays were conducted on animals exposed for 6 and 12 weeks. Moderate changes in the spleen and thymus were detected in mice exposed to butadiene for 24 weeks. Effects noted in the spleen were an increase in erythroid hyperplasia, significant extramedullary hematopoiesis and a minor reduction in spleen cellularity; in the thymus, a moderate decrease in the number of cortical lymphocytes was observed. Although some minor changes in immunological function were observed in butadiene-exposed mice compared with controls, overall, there were no toxicologically significant persistent effects on immune function due to butadiene exposure.

Studies in other species

In the study mentioned previously (Carpenter et al., 1944) guinea pigs, rabbits and dogs were exposed to 0, 600, 2,300 or 6,700 ppm butadiene 7.5 hours/day, 6 days/week, for 8 months. Clinical chemistry, haematology and histopathological investigations were conducted. An increased incidence of cloudy swelling in the liver of rabbits at 6,700 ppm was the only toxic effect of significance. However, only one dog per group was used and the number of rabbits (4

per group) was limited. Although no firm conclusions can be drawn because of the small group sizes, it appears from this study that butadiene is of low toxicity in these species when administered repeatedly at high concentrations.

In the study reported by Batkina (1966), Nikiforova et al. (1969), Ripp (1967), Ripp (1969) and Ripp and Lyutikova (1966), and referred to previously, effects were reported in rabbits following exposure to 45 ppm butadiene daily, 4 hours/day for 4 months. Again, these data should be discounted and no conclusions should be drawn from them.

Oral

Studies on the effects of butadiene administered orally in vegetable oil have been conducted in rats and rabbits (Donetskaya and Shvartsapel, 1970; Shvartsapel, 1970). However, the studies were poorly conducted and reported and no firm conclusions can be drawn from them.

4.1.2.6.2 Studies in humans

An analysis of morbidity and haematological parameters was included within a mortality study in a cohort of male workers potentially exposed to butadiene at a US butadiene monomer manufacturing facility (Cowles et al., 1994). All male employees with a minimum of 5 years in jobs with potential exposure to butadiene or who had worked at least half of their total employment in jobs with potential exposure (minimum 3 months) were eligible for a study cohort. A total of 614 employees met these criteria and 438 of these were still employed during the period of the morbidity study, 1982-1989. Account was taken of smoking history, blood pressure, cholesterol level and obesity as health risk factors. A morbidity event was defined as a specific diagnostic condition which caused an absence of more than 5 days in the period 1982-1991. Only one morbidity event per employee was counted in any diagnostic category, although if an employee had more than one morbidity event in different diagnostic categories, each was counted. Haematological parameters – red cell count, haemoglobin concentration, mean corpuscular volume, platelet count, white blood cell count, neutrophil count and lymphocyte count – were also measured in 429 of these employees and mean values were adjusted for the effects of age and smoking status. Over 2,600 non-exposed employees at the same plant were used as controls. Exposure data for 1979-1992 indicates that in this period, 8-hour TWA exposures were in the range <0.1 to 143 ppm, with most below 1 ppm and a mean exposure of 3.5 ppm.

There was no evidence of any excess of ill health in the butadiene group compared with controls. Similarly, haematological parameters showed no differences between butadiene workers and controls, including a separate subgroup of workers identified as having the potential for the highest butadiene exposures (8-hour TWA ~ 10 ppm). Overall, this study shows no significant differences in health status or haematology parameters in butadiene- exposed workers compared with non-exposed workers at the same plant. However, it is a limited study in terms of cohort size and lack of exposure data for the period under study.

A haematological survey was performed on all workers at a US styrene-butadiene rubber manufacturing plant (Checkoway and Williams, 1982; IARC, 1992). Air and blood samples were obtained during a single week in 1979. A total of 163 workers participated in the hygiene study, 154 of whom also participated in the blood survey. Blood samples were analysed for red cell count, haemoglobin concentration, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin concentration, reticulocyte count, platelet count and total and differential white cell count. There were minimal changes in haematological parameters in 8 workers exposed to about

20 ppm butadiene, 14 ppm styrene and 0.03 ppm benzene compared with the majority of workers exposed to ≤1.7 ppm butadiene, 2 ppm styrene and 0.1 ppm benzene (8-hour TWAs). These changes are not considered to provide evidence of an effect of exposure to butadiene, because of their minimal nature, the mixed exposures and because other confounding factors such as alcohol consumption were not considered.

Effects on haematological parameters have been noted in workers from the butadiene department of a Bulgarian synthetic rubber plant (Khristeva and Mirchev, 1981). In the plant as a whole, atmospheric levels of butadiene, styrene and ethylbenzene were several times those of the maximum permitted concentrations. However, in the butadiene department, workers were exposed apparently to butadiene alone, presumably to more than 45 ppm (International Labour Office, 1977). The butadiene workers had a statistically significantly increased haemoglobin concentration and reticulocyte count. In addition, prothrombin time was increased and platelet count and leukocyte peroxidase activity were decreased, all statistically significantly. However, the biological significance of the results is impossible to assess because of the absence of numerical data to support the claim that these workers were exposed to butadiene alone and the lack of information on the control group.

No effect on immune function was apparent in a poorly reported study of workers in the butadiene division of a petrochemical refinery (Zeman et al., 1989). A second poorly reported study in the same group of workers reported an increase in levels of γ-glutamyltransferase and glycine transamidase compared with local unexposed populations (Tomaszewski et al., 1987). However, because of a lack of detail and quantitative information, no conclusions can be drawn from this.

The health effects of repeated butadiene exposure has been investigated in workers at synthetic rubber production plants in Russia, in numerous studies (Alberton et al., 1981; Alekperov et al., 1970; Balan and Sergeta, 1973; Bashirov, 1968, 1969a,b, 1970, 1971, 1975; Batkina, 1966; Drogichina et al., 1959; Gus'kova, 1971; Kapkaev, 1963; Kats, 1962; Khusainova, 1971; Klein et al., 1967; Konstantinovskaya, 1970, 1971; Lukoshkina et al., 1973; Mukhametova et al., 1976; Nadirova, 1967; Netesa et al., 1969; Ogleznev, 1980; Putalova, 1979; Ripp, 1967; Sergeta et al., 1975; Vinokurova, 1969, 1970; Volkova and Bagdinov, 1969). However, in all of these reports, co-exposure to a range of other chemicals was noted and the effects seen were not associated with exposure to any specific chemical. In addition, very limited information was given on exposure levels. Thus the reports are of little value for assessing the health effects of butadiene. In some of these workers, the incidence of health effects increased in workers with longer service (Abdullaeva, 1973). However, when it was attempted to correlate sickness rates with exposure to individual chemicals, there was no evidence that butadiene exposure was associated with significant adverse health effects (Abdullaeva, 1974).

4.1.2.6.3 Summary of repeated dose toxicity

The repeated dose toxicity of inhaled butadiene has been well investigated in rodents. There is a marked difference in the toxicity of butadiene in rats and mice following repeated exposure. Butadiene has low toxicity in the rat, with minimal effects seen following exposure to 8,000 ppm for 2 years. In contrast, butadiene is severely toxic to the mouse. In a 2-year bioassay, concentrations of 20 ppm and above produced multi-organ tumours and deaths. In addition, the bone marrow has been identified as a target organ for butadiene toxicity in shorter-term repeated dose studies in mice exposed to 1,250 ppm. Effects were consistent with macrocytic-megaloblastic leukaemia and included anaemia and leucopenia; an alteration in hematopoietic

stem cell development has also been seen at this exposure concentration. Changes in the spleen and thymus have also been reported in mice at this exposure concentration.

Limited information suggests that butadiene is also of low toxicity in several other animal species (guinea-pig, rabbit, dog) and supports the conclusion that the mouse is particularly susceptible to butadiene-induced toxicity.

There is little useful information on the health effects in humans of repeated exposure to butadiene. The results of one modern, well-reported study show no excesses of morbidity nor any changes in haematological parameters in workers at a butadiene production facility, where the mean 8-hour TWA, measured after the period of the study, was 3.5 ppm. None of the other studies available are of a quality and reliability that permits meaningful conclusions to be drawn.

4.1.2.7 Mutagenicity

4.1.2.7.1 *In vitro* studies

Bacterial studies

Butadiene has been tested in the Ames test with *Salmonella typhimurium* in a number of studies of reasonable quality. Details of the studies are available from ECETOC (1992) and IARC (1992). Butadiene was tested in the gas phase, or in one study as a solution in ethanol in a plate incorporation assay. Negative results were obtained in all tests in the absence of metabolic activation. However, both positive and negative results have been obtained in the presence of metabolic activation.

Positive results were obtained in strain TA1530 in the presence of S9 mix derived from rats pre-treated with phenobarbital or Aroclor 1254 (de Meester et al., 1980). Arce et al. (1990) tested butadiene in strains TA97, TA98, TA100 and TA1535, at up to 60% in air, in the presence of rat, mouse and human metabolic activation systems. Positive results were obtained only in strain TA1535, in the presence of Aroclor induced rat liver S9, and S9 from uninduced rats or mice. A slight increase (< 2-fold) in the number of revertants was also seen in this strain in the presence of uninduced human S9. A positive result was similarly obtained when butadiene was tested using a gas sampling bag method, at up to 50% in strain TA1535 in the presence of rat liver S9 (Araki et al., 1994). In another study, a negative result was obtained when butadiene was tested as a solution in ethanol in the presence of Aroclor induced rat liver S9 mix, both with and without preincubation (Poncelet et al., 1980). The study was not well reported and only one unstated concentration of butadiene was used.

In conclusion, butadiene gas is mutagenic in bacterial test systems in the presence of a metabolic activation system.

Mammalian cell studies

No *in vitro* cytogenetics assay is available for butadiene.

The potential for butadiene to induce forward mutations at the thymidine kinase (*tk*) locus of L5178Y mouse lymphoma cells has been investigated by McGregor et al. (1991). Cells were exposed for 4 hours to 0-30% butadiene in air, in the presence and absence of metabolic activation (rat liver S9 mix). However, the actual concentration of butadiene in the culture

medium, to which the cells were exposed, was not known. Two independent experiments were conducted. Exposure to butadiene did not cause a statistically significant increase in mutation frequency (MF), either with or without S9, although a very marginal increase in MF was apparent in the presence of S9. There was no evidence of cytotoxicity, even at the top dose tested. An adequate response was obtained with the positive control. Although a negative result was obtained in this study, it is not clear whether the cells were adequately exposed to butadiene. For this reason, no conclusions about the genotoxic potential of butadiene can be drawn from this study.

A second mouse lymphoma assay is reported only as an abstract (Sernau et al., 1986). L5178Y cells were incubated with 20-80% butadiene in the presence and absence of Aroclor induced rat liver S9. Dose-related cytotoxicity was observed with S9 and at the top dose without S9.

There was no significant increase in MF in the absence of exogenous metabolic activation but there was a dose-related increase in MF in the presence of S9. At the top dose, MF was 128 mutants per 10^6 viable cells at 80% butadiene compared with 47 per 10^6 cells in control. The induced mutations were reported to be mainly small colonies, an indication that butadiene may have clastogenic activity.

Three *in vitro* sister chromatid exchange (SCE) assays have been reported, one with Chinese hamster ovary (CHO) cells and two with human lymphocytes (ECETOC, 1992; IARC, 1993). Conflicting results have been obtained. The assay using CHO cells was positive only in the presence of metabolic activation (Sasiadek et al., 1991a). With human lymphocytes, one study reported negative results, following exposure to 30-100% butadiene gas, in the presence and absence of metabolic activation (uninduced and induced rat liver S9, uninduced mouse and human S9), although there was no evidence of cytotoxicity (Arce et al., 1990). The second study in human lymphocytes gave a positive result in the absence of metabolic activation and a weak positive result in the presence of S9 (Sasiadek et al., 1991b). Overall, these results suggest that butadiene induces SCE *in vitro*; however, results in this test system in itself cannot be regarded to provide clear evidence for the genotoxicity of butadiene.

In summary, there is a lack of good quality studies that investigate the genotoxic potential of butadiene in mammalian cells *in vitro*. There is some evidence that it has genotoxic potential *in vitro* from a poorly reported mouse lymphoma cell mutagenicity assay, in which positive results were seen in the presence of metabolic activation. Conflicting results have been obtained in SCE tests.

4.1.2.7.2 Studies in Drosophila

There is one study reported of a somatic mutation and recombination test in *Drosophila* melanogaster (Victorin et al., 1990). There was no significant difference in the number of wing spots between the butadiene exposed group and control, indicating that butadiene is not mutagenic in this test system.

4.1.2.7.3 *In vivo* studies in mammals

Somatic cells

Micronucleus assays

Positive results have been reported for the bone marrow and peripheral blood micronucleus assay in the mouse, in a number of independent studies. Very few studies are available for other rodent species, but data for the rat and hamster indicate negative results in the bone marrow and peripheral blood micronucleus assay. These studies meet current regulatory standards.

In a study by Cunningham et al. (1986), male B6C3F1 mice and male Sprague-Dawley rats were exposed nose-only to 0 or 10 – 10,000 ppm butadiene for 6 hours/day on two consecutive days. The animals were sacrificed 24 hours after the second exposure and bone marrow cells from 5 animals per exposure concentration were examined for the presence of micronuclei. At least 500 PCEs per mouse were examined. Two independent experiments were performed.

Exposure to 10,000 ppm butadiene caused 4 deaths among 23 mice. No mortalities occurred among rats. There was a gradual dose-related reduction in the PCE/NCE ratio, in both species, with a statistically significant reduction of 33% in rats and 69% in mice at 10,000 ppm. In mice, a marked, dose-related increase in the incidence of micronuclei was seen at butadiene concentrations of 100 ppm and higher. The incidence of micronuclei increased to 30 per 1,000 PCEs at 10,000 ppm compared with a control level of 0.8 per 1,000. There was no difference in the incidence of micronuclei between control and exposed rats at any exposure concentration. This study therefore clearly demonstrates butadiene to have genotoxic activity in the mouse but not in the rat.

A second positive result was obtained in a study to investigate the induction of micronuclei in the bone marrow of male NMRI mice (Victorin et al., 1990). Groups of 5 mice were exposed to 10 or 500 ppm butadiene for 23 hours and sacrificed 30 hours after the start of exposure. Ten negative control animals were used. Approximately 1,000 PCEs per animal were scored for the presence of micronuclei. The PCE/NCE ratio was decreased at both exposure concentrations compared with control. There was a statistically significant concentration- related increase in the incidence of micronuclei at both exposure concentrations, from 1.4 per 1,000 cells in controls, to 8.2 per 1,000 at 10 ppm and 19.4 per 1,000 at 500 ppm.

A bone marrow micronucleus assay in mice and hamsters is reported only as an abstract (Przygoda et al., 1993). Mice were exposed to 0 or 1,000 ppm butadiene and hamsters to 0 – 8,000 ppm butadiene (exposure duration and sample time not stated) and the bone marrow was examined for the presence of micronuclei. A statistically significant reduction in the percentage of PCEs was reported to occur in butadiene-exposed mice but not in hamsters, evidence of bone marrow toxicity in the mouse. In mice, but not in hamsters, exposure to butadiene was reported to cause a substantial increase in the frequency of micronuclei, although actual data were not provided.

A negative bone marrow micronucleus assay in the rat is very briefly reported (Mäki-Paakkanen et al., 1993, in preparation; cited in Norppa and Sorsa, 1993). No increase in the incidence of micronuclei was seen in bone marrow following exposure to 250-1,000 ppm butadiene for 2 weeks. No further details are available.

The induction of micronuclei in the bone marrow and peripheral blood of mice and rats was investigated by Autio et al. (1994). Groups of 20 female B6C3F1 mice and 10 male Wistar rats were exposed to 0, 50, 200, 500 or (mice only) 1,300 ppm butadiene 6 hours/day for 5 days.

Animals were sacrificed 1 day after the last exposure. Blood and bone marrow samples were prepared for analysis. For the peripheral blood analysis, 1,000 reticulocytes per rat and 2,000 reticulocytes per mouse were examined for the incidence of micronuclei. For the bone marrow micronucleus assay, 1,000 PCEs per rat and 1,000 or 2,000 PCEs per mouse were examined. Evidence of slight bone marrow toxicity in the rat was apparent from a dose-related reduction in the PCE/NCE ratio, which reached statistical significance at 500 ppm (0.31 compared with 0.48 in controls). There was no evidence of a dose-related increase in micronuclei in either the peripheral blood or in the bone marrow of rats exposed up to 500 ppm butadiene. In contrast, in the mouse, there was a clear dose-related increase in the incidence of micronucleated erythrocytes in both the peripheral blood and bone marrow.

These increases were statistically significant at all exposure concentrations and at 1,300 ppm represented a 9-10-fold increase in the frequency of micronucleated cells over control, for both bone marrow and peripheral blood. Overall, this study provides a clear positive result in the mouse. However, the maximum dose to the rat, 500 ppm, is low in comparison to that which produces minimal systemic toxicity following repeated exposure (8,000 ppm). Therefore although a negative result was obtained in the rat, the study is considered to provide inadequate evidence for a clear lack of mutagenic effect in the rat, and no firm conclusion can be drawn from it.

The induction of micronuclei in bone marrow and peripheral blood erythrocytes was among a number of genotoxic endpoints investigated in mice by Adler et al. (1994). Mice were exposed to 0, 50, 200, 500 or 1,300 ppm butadiene, 6 hours/day for 5 days. Bone marrow samples from 5 mice per sex and blood samples from 2 mice per sex were taken 18-24 hours after the last exposure. A total of 2,000 PCEs from bone marrow and 1,000 PCEs from peripheral blood were counted for the incidence of micronuclei. Peripheral blood samples were not taken from the 500 ppm exposure group. There was a statistically significant increase in the frequency of micronucleated cells in the bone marrow at all exposure concentrations. The increase was dose-related, although the dose-response curve was non-linear, and tended to become flatter as exposure concentration increased. This may be explained in part by the saturation of butadiene metabolism to the reactive epoxybutene. The incidence of micronucleated PCEs per 1,000 at 1,300 ppm was 19.5 compared with 1.3 in controls. In addition, at 500 and 1,300 ppm a sex-related difference was apparent, with the frequency of micronuclei in males statistically significantly higher than in females. There was no effect of exposure on erythroblast proliferation. The frequency of micronuclei in PCEs in peripheral blood was also increased at all concentrations, in a dose-related manner, with the dose-response curve similar in shape to that for bone marrow. At 1,300 ppm, the incidence of micronucleated PCEs increased from 1.6 per 1,000 in controls to 19 per 1,000. Again, a sex-related difference was apparent at the higher doses, with a higher incidence of micronuclei in males compared with females at 200 and 1,300 ppm. These data demonstrate the induction of micronuclei in bone marrow and peripheral blood of exposed mice, with male mice more sensitive than females at the higher exposure concentrations. The dose-response curve is consistent with the metabolism of butadiene to epoxybutene, which may then induce micronuclei, although other reactive metabolites may also play a role.

Irons et al. (1986a,b) investigated the induction of micronuclei in the peripheral blood of male B6C3F1 mice and male NIH Swiss mice. Groups of 8 mice were exposed to 0 or 1,250 ppm butadiene for 6 hours/day, 6 days/week for up to 24 weeks in the case of B6C3F1 mice or 6 hours/day, 5 days/week for 6 weeks in the case of NIH Swiss mice. The incidence of micronuclei was determined from a count of 1,000 cells per animal. There was a 5-8 fold increase in the

incidence of micronuclei in peripheral blood cells in both strains after 6 or 24 weeks exposure to butadiene.

The induction of micronuclei in erythrocytes in the peripheral blood of B6C3F1 mice was investigated in NTP-sponsored studies reported by Jauhar et al. (1988) and MacGregor et al. (1990). Mice were exposed by inhalation to 0, 6.25, 62.5 or 625 ppm butadiene for 6 hours/day, 5 days/week for 90 days. Tail vein blood was taken from 10-12 mice per sex per group at 14 and 90 days and scored for the presence of micronuclei. The incidence of micronucleated PCEs at 14 and 90 days was scored from at least 1,000 PCEs per animal. The incidence of micronucleated NCEs was also scored at 90 days, from at least 10,000 red blood cells per animal. The incidence of micronuclei was comparable for the 14- and 90-day samples taken for each exposure concentration, indicating that a steady-state condition was achieved at each exposure level. At 14 and 90 days there was a dose-related statistically significant increase in micronucleated PCEs at concentrations of 62.5 and 625 ppm. At 6.25 ppm, the incidence was not statistically different from control. The incidence of micronucleated NCEs per 1,000 cells was statistically significantly increased in all exposure groups compared with control. Overall, this study demonstrates the induction of micronuclei in NCEs at the lowest exposure concentration, 6.25 ppm.

In the same series of NTP-sponsored studies, Tice et al. (1987) looked at a number of endpoints for genotoxicity in B6C3F1 mice exposed to butadiene, including the induction of micronucleated PCEs and NCEs in the peripheral blood. Average generation time (AGT) and mitotic index (MI) were used as a measure of cytotoxicity.

The exposure regime was as described above, with animals exposed for 14 days. There were 12 male mice per group. Animals were sacrificed 18.5-22.5 hours after the last exposure and a total of 1,000 PCEs and NCEs per animal were examined for the presence of micronuclei.

Trend analysis showed a statistically significant reduction in MI and an increase in AGT with increasing exposure concentration, an indication of cytotoxicity. There was also a statistically significant positive trend in the number of micronucleated PCEs and NCEs in peripheral blood with increasing exposure concentration. The incidence of micronucleated PCEs at 62.5 and 625 ppm and in micronucleated NCEs at 625 ppm was statistically significantly increased compared with control. There were no statistically significant differences in the incidence of micronuclei at 6.25 ppm. This study provides further evidence that butadiene has genotoxic potential in the mouse in this assay.

Chromosome aberration studies

The potential for butadiene to cause chromosome aberrations in the mouse has been investigated in two studies, both of which gave positive results.

In the same study referred to previously (Tice et al., 1987), the potential for butadiene to induce chromosome aberrations in the bone marrow of B6C3F1 mice was investigated. Mice were exposed to 0, 6.25, 62.5 or 625 ppm butadiene for 6 hours/day, 5 days/week for 90 days. Fifty metaphases per animal were examined for the presence of chromosome aberrations.

There was an exposure-related increase in the number of aberrations per cell (excluding gaps) and in the frequency of cells affected (excluding gaps), which reached statistical significance at 625 ppm. Aberrations were mainly chromatid gaps and breaks. Chromosomal rearrangements were seen only at 625 ppm. This study therefore demonstrates the potential for butadiene to damage DNA in mammalian cells.

Irons et al. (1987a) exposed groups of male Swiss mice and male B6C3F1 mice to 0 or 1,250 ppm butadiene for 6 hours. Three animals per group were sacrificed at 24, 48, 72 or 96 hours after exposure. Fifty metaphases per animal were examined for chromosome aberrations.

Treated animals of both strains showed a statistically significantly higher frequency of chromatid gaps and breaks compared with controls at 24 hours. The effect on chromatids diminished with time after exposure, although a slightly increased frequency of chromatid aberrations was still apparent at 96 hours. There were no statistically significant numerical chromosome abnormalities observed in any strain at any time point, although there was some evidence of segmental aneuploidy in treated animals compared with controls. No extranumerary chromosomes were observed. Again, this study provides evidence that butadiene can produce DNA damage in mammalian cells.

Two *in vivo* SCE studies in B6C3F1 mice are also available for butadiene (ECETOC, 1992; IARC, 1992). Positive results were obtained in both studies, with SCEs found in the bone marrow following exposure to butadiene. A third *in vivo* SCE study in the rat is very briefly reported (Mäki-Paakkanen et al., 1993, in preparation; cited in Norppa and Sorsa, 1993). SCEs were reported to be induced in lymphocytes and in primary lung cells.

Studies in transgenic mice

Recio et al. (1992, 1993), Recio and Meyer (1995) and Sisk et al. (1994) have reported positive findings in two *in vivo* mutagenicity assays in transgenic mice, although no criteria are available for evaluation of these studies. In the first of the two studies, groups of 10 $CD2F_1$ mice were exposed to 0 or 625 ppm butadiene for 6 hours/day on 5 consecutive days (Recio et al., 1992). A positive control group of 10 mice were given a single intraperitoneal injection of 250 mg/kg *N*-ethyl-*n*-nitrosourea. At 14 days the *lacZ* mutation system was employed to determine mutant frequency (MF) in bone marrow, lung and liver. The authors reported a statistically significant, 2-fold increase in MF in the lung tissue of exposed animals compared with controls. No increases were seen in the bone marrow or liver. The positive control gave significantly elevated MF in all three tissues.

The second assay was conducted with transgenic B6C3F1 mice, utilising the *lacI* mutation system (Recio et al., 1993; Sisk et al., 1994, Recio and Meyer, 1995). In this study, groups of 5 animals were exposed whole-body to 0, 62.5, 625 or 1,250 ppm butadiene, 6 hours/day, 5 days/week for 4 weeks. A positive control group of 5 mice received a single intraperitoneal injection of 250 mg/kg *N*-ethyl-*n*-nitrosourea. Mice were sacrificed 14 days post-exposure and the *lacI* mutant frequency (MF) in the bone marrow was determined from bone marrow samples from 3 animals per group. In addition, the *lacI* gene was sequenced from *lacI* mutants isolated from controls and mice from the 625 ppm exposure group, which had the highest mutation frequency, and the 1,250 ppm group. There was a statistically significant 2 – 4-fold increase in the mean *lacI* MF at all exposure concentrations. The response increased in a dose-related manner at 62.5 and 625 ppm, with no further increase at 1,250 ppm, suggestive that the response reached a plateau above 625 ppm. The positive control gave a statistically significant, greater than 10-fold elevation in MF. Gene sequencing indicated that there was a shift in the spectrum of mutations in butadiene-exposed animals compared with controls, with a statistically significantly, more than 10-fold, higher frequency of mutations at A:T sites in mice exposed to 625 or 1,250 ppm butadiene. Base substitutions accounted for 82-92% of all analysed mutations in exposed and control animals, of which mutations at A:T base pairs accounted for 4% of the point mutations analysed in controls, compared with 23% in the 625 ppm group and 20% at 1,250 ppm.

Molecular studies

The study of DNA adducts in male B6C3F1 mice and male Wistar rats following exposure to 500 ppm ^{14}C-butadiene was reported by Jelitto et al. (1989). Animals were exposed in a closed system for an unstated period until >98% of the total radioactivity was absorbed. Animals were sacrificed 30 minutes after exposure and liver DNA hydrolysates were assayed by column chromatography. Reaction products of epoxybutene and diepoxybutane with guanine were identified in the mouse, but not in the rat, by comparison with reference standards. This study demonstrates that in the liver of mouse, but not the rat, butadiene exposure leads to the formation of DNA adducts with reactive metabolites.

In a similar study, 24 male B6C3F1 mice and 4 male Wistar rats were exposed to approximately 770 ppm ^{14}C-butadiene in a closed chamber for 4-7 hours, at which time >98% of the total radioactivity had been taken up (Kreiling et al., 1986a). Animals were sacrificed 30 minutes after the end of exposure. Liver hydrolysates (livers of 6 mice pooled) were assayed by column chromatography and individual nucleosides were resolved. Covalent binding of radioactivity to nucleoprotein fractions and to total liver DNA was demonstrated. Covalent binding of radioactivity to nucleoproteins was found to be approximately twice as high in the mouse compared with the rat although binding to liver DNA was comparable in both species.

Alkaline elution was used to evaluate single strand breaks and DNA crosslinks in the liver and lung of male B6C3F1 mice and male Sprague-Dawley rats (Vangala et al., 1993). Groups of 6 mice or 3 rats were exposed to 0 or 2,000 ppm butadiene 7 hours/day for 6 days, with a 16 hour overnight exposure on day 6 or to 0, 100, 250, 500, 1,000 or 2,000 ppm butadiene for 7 hours. Animals were sacrificed either immediately or 5 hours after exposure. Single strand breaks were apparent in hepatocytes of mice and rats sacrificed immediately after exposure to 2,000 ppm and in rats but not in mice sacrificed 5 hours post-exposure. Crosslinks were apparent in liver and particularly in lung tissue of mice exposed to 100 or 250 ppm and above. There was no evidence for crosslinking activity in rat lung or liver tissue at any exposure concentration.

In a very briefly reported paper by Jelitto et al. (1989), male B6C3F1 mice and male Wistar rats were exposed to 0, 250, 500 or 1,000 ppm butadiene for 7 hours and liver and lung tissue were subjected to alkaline elution. DNA-protein and DNA-DNA crosslinks were reported in liver and lung tissue of all butadiene-exposed mice, although not all the data were presented. There was no evidence of DNA-DNA crosslinking in liver and lung tissue from rats at any exposure concentration.

DNA-DNA crosslinks in B6C3F1 mice and rats following butadiene exposure were investigated by Ristau et al. (1990). Only brief details are given. Male mice or rats (numbers not given) were exposed to 2,000 ppm butadiene 8 hours/day for 7 days. There was no evidence of DNA-DNA crosslinking in mice or rats exposed to butadiene.

Other studies

Butadiene has been tested in an *in vivo*/*in vitro* liver UDS assay in male B6C3F1 mice and male Sprague-Dawley rats (Vincent et al., 1986). The study was reported only briefly as an abstract. Animals (numbers not stated) were exposed nose-only to 0 or 10,000 ppm butadiene in two exposure regimes, either for 6 hours on day 1, 3 hours on day 2 and sacrificed 2 hours after the second exposure; or for 6 hours/day for 2 days and sacrificed 18 hours after the second exposure. No UDS was detected in either rats or mice in this study. It is noted that since a negative result was obtained for the mouse in this study, while clear positive results are demonstrated in the

micronucleus test, this assay may not be appropriate for the investigation of the mutagenic potential of butadiene.

An *in vivo* mutagenicity assay to evaluate mutation frequency at the *hprt* locus in splenic T cells has been conducted in male B6C3F1 mice (Cochrane and Skopek, 1993, 1994b). Animals were exposed to 0 or 625 ppm butadiene, 6 hours/day, 5 days/week for 2 weeks and sacrificed 2 weeks post-exposure, to allow expression of the *hprt* phenotype. Splenic T cells were isolated and cultured for 10 days to allow growth of mutant *hprt*$^-$ colonies. No evidence of acute toxicity was seen in exposed animals although some 'growth retardation' was reported, with a reduction in spleen size compared with controls. Recovery of T-cells in was also reduced to less than half that in controls. In cells from exposed animals, there was a statistically significant 5-fold increase in mutation frequency, from $1.25 \cdot 10^{-6}$ in controls to $6.25 \cdot 10^{-6}$ at 625 ppm. This indicates that repeated exposure to 625 ppm butadiene can cause gene mutations in mice.

A similar assay to evaluate mutations at the *hprt* locus in $(102/E1xC3H/E1)F_1$ male mice is reported by Tates et al. (1994). Two experiments utilising different sacrifice times (expression time) were conducted. In the first experiment a control group of 3 mice was exposed to 0 ppm butadiene while 6 mice per group were exposed to 500 or 1,300 ppm butadiene 6 hours/day for 5 days. The animals were sacrificed 109 days post-exposure. In the second experiment, groups of 10 mice were exposed to 200, 500 or 1,300 ppm butadiene 6 hours/day for 5 days while 9 animals served as a negative control group, exposed to 0 ppm butadiene. These animals were sacrificed 77 days post-exposure. Lymphocytes were isolated from the spleen for evaluation of cloning efficiency (CE) and mutant frequency (MF). In the first experiment, there was a marked reduction in the cloning efficiency of splenocytes from animals exposed to 1,300 ppm suggesting butadiene toxicity (5.4% CE at 1,300 ppm compared with 15.5% in controls). This was accompanied by a marked increase in mutant frequency at this exposure concentration, from $1.4 \cdot 10^{-6}$ in controls to $7.8 \cdot 10^{-6}$ at 1,300 ppm. No statistics were performed for this experiment, but the data are indicative that exposure to 1,300 ppm butadiene may induce an increase in mutation frequency. In the second experiment, an enhanced cloning efficiency was achieved. The CE in controls was 34%, and no evidence of a dose-related effect of butadiene on CE was apparent. There was a statistically significant, 3-fold increase in MF at 1,300 ppm, from $0.7 \cdot 10^{-6}$ in controls to $2.2 \cdot 10^{-6}$. An increase in MF to $1.1 \cdot 10^{-6}$ at 500 ppm was not statistically significant. Overall, this study shows a positive mutagenic effect of butadiene in mice, following repeated exposure to 1,300 ppm.

A positive result in the mouse spot test has been reported (Adler et al., 1994). The test was performed with females, homozygous for specific coat colour loci, mated with males, also homozygous for specific loci. The resulting offspring are heterozygous for a number of coat colour loci. Pregnant females were exposed to 0 or 500 ppm butadiene on days 8-12 of gestation. There were 37 animals in the control group and 19 in the exposed group. Offspring were inspected for coat colour spots and for gross abnormalities at 2 and 3 weeks. There was a statistically significant increase in the number of offspring with spots of genetic relevance in the butadiene exposed group compared with control (9.6% in exposed group compared with 1.5% controls). There was no evidence of toxicity in the dams nor were any gross abnormalities observed in the offspring. This result indicates that exposure to butadiene *in utero* can cause mutations in the embryos.

In summary, butadiene is genotoxic to somatic cells *in vivo* in the mouse. Positive results have been obtained in a number of modern, well-conducted standard assays, with additional supporting evidence from other less well-validated assays. Evidence from a limited number of studies in the rat indicates that butadiene is not genotoxic in this species. Negative results have been reported in one well-conducted micronucleus study, and a negative result in an *in vivo*/*in vitro* liver UDS assay has been reported.

Germ cells

Four dominant lethal assays in the mouse and one in the rat are available for butadiene.

In the first of the mouse studies, groups of 20 male CD-1 mice were exposed to 0, 200, 1,000 or 5,000 ppm butadiene, 6 hours/day for 5 days (Hackett et al., 1988b). There was no positive control group. Each male was then placed with 2 unexposed females per week in a series of 8 sequential weekly matings. A total of 1,240 females were used. Females were sacrificed 12 days after the last day of cohabitation with the male and examined for reproductive status, number of early and late resorptions and live and dead fetuses.

There were no treatment-related deaths among the exposed males. Bodyweight was unaffected by treatment. The only clinical evidence of toxicity was piloerection and dyspnea seen during exposure to 5,000 ppm. There was no effect on pregnancy rate or on male fertility and no statistically significant differences in the number of implantations per pregnancy in exposed animals compared with control. In females mated in the first week post-exposure there was a small but statistically significant increase in the number of dead implants per pregnancy at 1,000 ppm (1.42 per pregnancy compared with 0.78 in control). Smaller increases at 200 and 5,000 ppm were not statistically significant compared with control. These increases were due to an increase in early deaths. In the second post-exposure week, there was a statistically significant increase in the number of dead implantations per pregnancy at 200 and 1,000 ppm, but not at 5,000 ppm. Again, the increase was due to an increase in early deaths. There were no other statistically significant changes in any of the measured parameters in weeks 3-8 post-exposure. There was no clear dose-relationship for the effects seen in weeks 1 and 2. The greatest response was seen in the 1,000 ppm exposure group. In conclusion, the results of this study are equivocal and no firm conclusions with regard to germ cell mutagenicity can be drawn.

A second dominant lethal assay in CD-1 mice is also available (Anderson et al., 1993; BIBRA, 1995). In this study, males were exposed either singly or repeatedly to butadiene. In the single exposure protocol, groups of 25 males were exposed to 0 or 1,250 ppm and 50 males were exposed to 6,250 ppm butadiene for 6 hours. After 5 days, the males were housed with 2 unexposed females for one week. In the repeated exposure regime, groups of 25 males were exposed to 0 or 12.5 ppm and 50 males were exposed to 1,250 ppm butadiene, 6 hours/day, 5 days/week for 10 weeks. Each male was mated with 2 unexposed females immediately post-exposure. Following mating, one female per pair was sacrificed on day 17 of gestation while the other was allowed to deliver and rear the litter. This surviving F1 generation is currently being studied for the incidence of tumours, and the results from this part of the study are not yet available. Females sacrificed on day 17 of gestation were examined for the number of implantations and post implantation deaths (early and late deaths, including dead fetuses).

There were 3 deaths at 6,250 ppm in the single exposure group and 2 deaths at 1,250 ppm in the repeated exposure group. It is not clear whether these were considered to be treatment-related. No effect of treatment on bodyweight in surviving animals was reported and no clinical observations of systemic toxicity were seen. Following single exposure to butadiene, there was no treatment-related effect on the pregnancy rate, the number of implantations nor on post-implantation deaths, and therefore no evidence of a dominant lethal effect. Following repeated exposure to butadiene, pregnancy rate was unaffected. There was no change in the total number of implantations per pregnancy at 12.5 ppm compared with control, while at 1,250 ppm there was a statistically significant reduction in this parameter, from a mean of 12.09 in controls to 10.68. At 1,250 ppm there was a statistically significant increase in post-implantation losses, mainly due to an increase in early deaths, which were increased from a control value of 4.7% (13/278) to 21.4% (87/406). Late post-implantation losses were statistically significantly

increased at both exposure concentrations, with the greatest effect seen at 12.5 ppm. Late deaths increased from a control value of 0% (0/278) to 2.3% (7/306) at 12.5 ppm and 1.5% (6/406) at 1,250 ppm. The increase in the incidence of early deaths at 1,250 ppm may have masked an increase in late deaths at this exposure concentration. The values for early and late deaths were also compared with historical control data for the laboratory, and were found to exceed these values (5.03% early deaths and 1.30% late deaths). Overall, these results indicate that repeated exposure of male mice to 12.5 or 1,250 ppm butadiene can induce dominant lethal mutations in the germ cells which lead to an increase in post-implantation losses.

As a follow-up to this study, the same group conducted another dominant lethal assay in CD-1 mice, to investigate the effect of shorter duration exposure to butadiene (BIBRA, 1996). Groups of 23-25 males were exposed to 0, 12.5, 65 and 130 ppm butadiene 6 hours/day, 5 days/week for 4 weeks. Each male was then mated with 2 females for up to one week beginning on day 4 post-exposure. Females were necropsied on day 17 of gestation and examined for the presence of live implantations, early and late deaths and dead fetuses. For a number of females, the start of pregnancy was unknown and day 17 of gestation was estimated from bodyweight gain. However, for many of these, it was clear that the gestation stage was underestimated and therefore necropsy was performed prior to day 17 of gestation.

There were no treatment-related mortalities, and no clinical signs nor any treatment-related effect on bodyweight. Fertility was unaffected by exposure. There was no statistically significant difference in the total number of implantations per pregnancy in treated groups compared with controls. However, a statistically significant increase in the number of early deaths per implantation per pregnancy was observed at 65 and 130 ppm, from 0.039 in controls to 0.083 and 0.082 respectively. The number of early deaths in the 12.5 ppm group was not increased. The numbers of late deaths, excluding or including dead fetuses, were not increased in any exposure group. One possible explanation for this is that a number of females were necropsied prior to gestation day 17, and therefore effects arising late in gestation were not detected. Overall, this study confirms the results of the previous study, namely that exposure to butadiene causes dominant lethal mutations in mice, as indicated by an increase in early deaths. This effect was evident following repeated exposure to 65 or 130 ppm, but not to 12.5 ppm butadiene.

The fourth mouse dominant lethal study was conducted in (102/E1xC3H/E1)F_1 mice (Adler et al., 1994). Groups of 20 males were exposed to 0 or 1,300 ppm butadiene 6 hours/day for 5 days. At 4 hours after the last exposure each male was mated with pairs of unexposed females for a period of 4 consecutive weeks. Pregnant females were sacrificed on days 14-16 of gestation and the uterus contents were examined for the presence of live and dead implants. No distinction was made between early and late deaths. There was no effect of exposure on pregnancy rate nor on the total number of implantations per pregnancy. However, a statistically significant increase in post-implantation losses was seen in the second week post-exposure, from 8.2% in week 2 controls to 15.4% at 1,300 ppm. Increased incidence in weeks 1 and 3 did not reach statistical significance. Overall, this study is positive for dominant lethal mutations induced in mice following exposure of males to 1,300 ppm butadiene.

The potential for butadiene to induce dominant lethal mutations in the Sprague-Dawley rat has been investigated by Anderson et al. (1996). Groups of 25 males were exposed to 0, 65, 400 or 1,250 ppm butadiene for 6 hours/day, 5 days/week for 10 weeks prior to mating. An additional group of 50 males was kept as an untreated control group. No positive control was used, on the basis that a positive result had been obtained in similar studies in mice, in the same laboratory. At 3 days after the last exposure, each male was allowed to mate with two untreated females, over a 10-day mating period. Females were sacrificed on day 20 of pregnancy and numbers of corpora lutea, live implantations, early deaths, late deaths and dead fetuses were counted. All

malformed fetuses were stored for further examination, along with one normal litter mate and one concurrent control fetus.

Exposure to butadiene had no effect on mating success nor on fertility. There was no effect of treatment on pre- or post-implantation losses, early or late deaths nor on the numbers of dead or abnormal fetuses. Overall, this study showed no evidence for a dominant lethal effect of butadiene in the rat.

The induction of micronuclei in the germ cells of mice was investigated by Xiao and Tates (1995). Two independent experiments were conducted. In the first, groups of 2-5 male F_1 (102 x C3H) mice were exposed to 0, 500 or 1,300 ppm butadiene, 6 hours/day for 5 days and sacrificed 2-15 days post-exposure; while in the second, 5 or 6 mice were exposed to 0, 200, 500 or 1,300 in the same regime and sacrificed 15 days post-exposure. Early spermatids were isolated and 2,000 – 10,000 spermatids per animal were examined for the presence of micronuclei. The ratio of testicular weight to bodyweight, measured at sacrifice, was used as an indicator of toxicity. Cytotoxicity was additionally evaluated by analysis of the relative frequency of early spermatids in Golgi and cap phases, from 500 cells per animal.

In both studies there was evidence of toxicity at 500 and/or 1,300 ppm, indicated by a statistically significant reduction in the ratio of testis to body weight and/or in the ratio of cells in each phase (Golgi/Golgi + cap). In the first experiment, a statistically significant increase in the incidence of micronucleated spermatids was seen at 500 and 1,300 ppm in animals sacrificed on day 15 post-exposure, from 0.4 per 1,000 cells in controls (sacrificed on days 2-5) to 3.7 per 1,000 cells at 500 ppm and 2.2 per 1,000 at 1,300 ppm. The second study confirmed this result at 15 days post-exposure, with statistically significant increases in the incidence of micronucleated cells at all three exposure levels, from a control value of 0.33 per 1,000 cells to 2.8 at 200 ppm, 3.4 at 500 ppm and 2.6 at 1,300 ppm butadiene. In both studies, the lower incidence of micronuclei at 1,300 ppm compared with 200 or 500 ppm may be explained by the severity of cytotoxicity at this exposure level. Overall, these data provide positive evidence for a genotoxic effect of butadiene in the germ cells of male mice.

As well as the investigation of dominant lethal effects in mice reported above in the studies by Anderson et al. (1993) and BIBRA (1996), these studies also included an investigation of the potential for butadiene to cause non-lethal germ cell mutations. This endpoint was assessed by examination of fetuses at term, to identify any male-mediated fetal malformations induced by exposure to butadiene. In the first study (Anderson et al., 1993) performed with the single exposure regime, there was no effect of exposure on the incidence of fetal abnormalities. In contrast, in the 10-week repeated exposure protocol, there was a statistically significant increase in the incidence of abnormal fetuses at both 12.5 and 1,250 ppm. The incidence was higher at 12.5 ppm (7/282; 2.5%) than at 1,250 ppm (3/312; 0.96%). This compares with 0% (0/263) in concurrent controls, and also exceeds values reported for historical control data from the same laboratory (0.74%). The fetal abnormalities reported at 1,250 ppm were 1 hydroencephaly and 2 fetuses with reduced bodyweight. At 12.5 ppm, 4 cases of exencephaly (3 in a single litter), 2 fetuses with reduced bodyweight and 1 with blood in the amniotic sac were reported. In the more recent study by this group, in which males were exposed for 4 weeks prior to mating, there was no increase in the numbers of dead or abnormal fetuses in exposed groups compared with controls, although it was noted that since a number of females were sacrificed earlier than gestation day 17, this may explain the lack of finding of any effects which occur late in gestation. In addition, karyotyping of fetuses showed no effect of treatment. Overall, whilst the results of one study suggests that repeated exposure of males to 12.5 or 1,250 ppm butadiene may be associated with the presence of abnormalities in the offspring, these findings are not clearly reproducible and the significance of these observations for human health is unclear.

4.1.2.7.4 Metabolites of butadiene

Epoxybutene and diepoxybutane have been studied in a number of *in vitro* and *in vivo* studies. The data are summarised in HSE (1985) and in IARC (1992). Positive results have been obtained for epoxybutene and diepoxybutane in the Ames test, in the absence of metabolic activation and for diepoxybutane which has also been tested in the presence of metabolic activation. Epoxybutene, epoxybutanediol and diepoxybutane induced an increase in mutation frequency at the *tk* and *hprt* locus in TK6 human lymphoblastoid cells, with diepoxybutane producing a response at concentrations ~40 to 100-fold lower than either epoxybutene or epoxybutanediol (Cochrane and Skopek, 1994a). There was no evidence that epoxybutene or diepoxybutane could induce UDS in rat or mouse hepatocytes *in vitro* (Arce et al., 1990; Vincent et al., 1986). Both epoxybutene and diepoxybutane are genotoxic agents in somatic cells *in vivo* in studies in the mouse and/or hamster (IARC, 1992) and in the somatic and germ cells of mice and rats *in vivo* (Xiao and Tates, 1995).

4.1.2.7.5 Studies in humans

Mutations at the *hprt* locus in blood lymphocytes have been investigated in a series of three studies of butadiene-exposed workers (Legator et al., 1993; Ward et al., 1994, 1996a). The first two studies investigated effects in workers employed at a butadiene production plant; preliminary results only are available for the third study, conducted in workers employed at a styrene-butadiene rubber (SBR) plant. Exposure groups were defined according to employment in areas of the plant with different exposure potential. The first study included a 'high' and 'low' exposure group, with 8 and 5 subjects respectively per group; a control group of 6 non-exposed subjects, not employed at the plant, was also included. All subjects were non-smokers. The second study was a follow-up to this first study, and included 7 subjects in an 'intermediate' exposure group, as well as groups of 7 'high' and 8 'low' exposure workers. No control group was included. It is not clear if any workers were included in both studies. The third study includes 16 workers in a 'high' exposure group and 9 in a 'low' exposure group, of which 5 and 3 subjects respectively are cigarette smokers. Blood and urine samples were taken from each subject post-shift. An autoradiographic method was used to determine *hprt* variant frequency (V_f) in blood lymphocytes. Urine was analysed for butadiene metabolites. Exposure estimates for the first study were determined by an exposure survey, conducted 3-9 months prior to the study; exposure estimates for the other two studies were determined from personal samplers worn in the breathing zone for 8 hours on the day of blood sampling.

Average 8-hour TWA exposures at the butadiene production plant in study I were 3.5 ± 7.25 and 0.03 ± 0.03 ppm in the 'high' and 'low' exposure groups respectively. The average value for the 'high' exposure group includes samples taken from areas of high exposure in which workers spent relatively little time; if these samples are omitted, the average exposure is about 1 ppm for the 'high' exposure group. In study II, average exposures of 0.30 ± 0.59, 0.21 ± 0.21 and 0.12 ± 0.27 ppm were measured for the 'high', 'intermediate' and 'low' exposure groups respectively. The only butadiene metabolite detected in the urine was dihydroxybutane mercapturate. The highest urinary concentrations of this metabolite were measured in the 'high' exposure groups, in both studies. In both studies, average V_f in the 'high' exposure groups was statistically significantly increased compared with all other exposure groups and controls. There were no other statistically significant differences between groups. Average V_f (expressed per 10^6 evaluatable cells) in the 'high' exposure groups was 3.99 and 5.33 in studies I and II respectively, compared with 1.20 in the 'low' exposure group and 1.03 in controls (study I) and

2.27 and 2.14 in the 'intermediate' and 'low' groups respectively in study II. V_f was correlated with urinary concentration of dihydroxybutane mercapturate only in study I.

Preliminary data only are available for the third study reported by this group, investigating workers at an SBR plant. Exposures measured in this plant were reported to be generally higher than those in the monomer plant. In the 'high' exposure group, 20 out of 40 personal samples obtained were above the detection limit of 0.25 ppm (8-hour TWA) and 11 were greater than 1 ppm. In the 'low' exposure group, none of the 26 samples obtained were above this detection limit. A 2-way statistical analysis was performed on the data to control for smoking in this study. The results of this analysis indicated a significant effect of butadiene exposure on *hprt* variant frequency, but did not provide any indication of an interaction between smoking and butadiene exposure. V_f (expressed per 10^6 evaluatable cells) was 7.47 in 'high' exposure non-smokers compared with 6.24 in 'high' exposure smokers; and 1.68 in 'low' exposure non-smokers compared with 3.42 in 'low' exposure smokers. In a separate study to investigate V_f in non-exposed subjects for comparative purposes, V_f values of 7.24 were reported for 11 smokers and 1.74 for 11 non-smokers. Overall, these results provide evidence for a consistent elevation in variant frequency at the *hprt* locus in blood lymphocytes of workers exposed to the highest concentrations of butadiene, around 0.3 – 1 ppm (8-hour TWA). No increase in variant frequency was seen in workers exposed to average concentrations of 0.2 ppm or less.

A second study to investigate mutations at the *hprt* locus in human lymphocytes has been conducted by Tates et al. (1996). Blood samples were taken from 19 workers and 19 non-exposed controls, at a butadiene production plant in the Czech republic. The non- exposed controls were employed at the same plant and were matched for age and smoking status. Samples were collected in 1993 and 1994, but for technical reasons, 1993 samples for only 5 exposed and 13 controls were available for analysis. Three subjects were included in both the 1993 and 1994 sample analyses. Personal sampling for butadiene was performed on the day of blood sampling. In 1993, personal butadiene exposure in exposed workers ranged from 0.05 to 1.47 ppm (mean 0.8 ppm) and from 0.01 to 0.14 ppm (mean 0.06 ppm) in controls; in 1994, personal exposures were <0.024-10.2 ppm butadiene (mean 1.7 ppm) in exposed workers and <0.009-0.12 ppm (mean 0.02 ppm) in controls. Cells were cloned and the cloning efficiency (CE) in the presence and absence of the selective agent, 6-thioguanine, was used to determine mutant frequency (MF). In addition, the comet assay was used for detection of DNA damage in blood samples taken in 1994 only.

No statistically significant differences in CE or MF were seen in exposed groups compared with controls. Results from the comet assay did not provide any evidence for an effect of butadiene exposure on DNA damage, although it is recognised that this is not a well-validated assay. Overall, therefore, this study provides no evidence of an effect of butadiene exposure on the frequency of *hprt* mutants. However, in view of the overlap between exposure levels measured for exposed workers compared with controls, this study will have limited potential to detect an effect of butadiene exposure.

A third study of mutant frequency at the *hprt* locus in lymphocytes, also utilised a clonal assay to investigate this endpoint (Hayes et al., 1996). This study investigated mutant frequency (Mf) at the *hprt* locus in lymphocytes of workers employed at a polybutadiene rubber plant in China. The study included 41 exposed workers, of whom 13 were smokers, and 38 controls matched for age, sex and smoking status. Personal exposure to butadiene was determined from personal samples collected in the breathing zone over a 6-hour working shift. Blood samples were collected post-shift. Exposure values for butadiene, measured for workers in 3 separate areas of the plant, were reported as 1.0, 3.5 and 1.1 ppm (median 6-hour TWA values). In the latter of these 3 areas, exposures of up to 45 ppm (median value) were reported to occur during particular

maintenance operations, and presumably related to short-term peak exposures rather than 6-hour TWA exposures, although this is not clearly stated. Mf was found to decrease with cloning efficiency (CE) and increase with age and was also slightly higher in females compared with males. The average Mf in exposed workers (expressed per 10^6 cells) was 21.6 compared with 20.2 in controls. After adjustment of Mf to account for age, sex and CE, the average Mf was 18.0 in the exposed groups compared with 13.6 in controls. This slight elevation in the exposed group did not reach statistical significance.

The findings of these latter two *hprt* clonal assays are in contrast to the results of the study reported by Ward et al. (1996a), in which a statistically significant increase in *hprt* mutant frequency in workers in the highest butadiene exposure groups was shown. It is possible that the different methodology used to detect *hprt* mutants in these latter two studies could explain the differences in the results obtained. The baseline variant frequency measured using the autoradiographic method appears to show less inter-individual variation, so that the statistical analysis may be more sensitive to small variations in V_f compared with the clonal assay. Other possible explanations for the different results are that the pattern of exposures may be different in the different studies; for example, the frequency and level of peak exposures could be important factors in induction of *hprt* variants.

In addition to the analysis of variant frequency reported above by Ward et al. (1994, 1996a), this group also reported the results of assays for chromosome aberrations and for DNA repair deficiency in lymphocytes taken from exposed workers included in study I of the Ward et al. (1996a) report (Au et al., 1995). Blood samples were taken from 10 non-smoking exposed workers from the 'high' exposure group, whose average butadiene exposure was 3.5 ppm, although the majority of exposures were of an average of 1 ppm. A control group of 10 non-smoking plant employees, matched for age and sex, worked in an area of the plant with an average butadiene exposure of 0.03 ppm. None of the subjects had any known confounding exposures to toxicants such as cytotoxic drugs, diagnostic radiation exposure or excessive alcohol consumption. Chromosome aberrations were determined from blood cultures treated with bromodeoxyuridine. Two cultures per individual were prepared. A total of 200 metaphases per individual were analysed for chromosome aberrations. The abililty of cells to repair DNA was evaluated using an *in vitro* challenge assay. Cells were exposed to γ–radiation in a single or split dose, to induce damage and bromodeoxyuridine added to the cultures immediately after exposure. Again, two blood cultures per individual were used in the assessment, one per irradiation dosing regime, and 100 metaphases per culture were analysed for chromosome aberrations. The ability to repair damage was evaluated; cytogenetic analyses were also conducted on lymphocytes from the exposed groups, to evaluate the frequency of chromosomal aberrations and thus evaluate DNA repair efficiency.

The results of the standard cytogenetics assay showed no statistically significant differences in the frequency of cells with chromosome aberrations (excluding gaps) between the exposed control groups, although there was a slightly higher aberrant frequency in the exposed groups compared with controls. However, the results of the γ-irradiation challenge assay showed that following both radiation exposure regimes, there was a slight but statistically significant increase in the exposed group compared with controls in the frequency of aberrant cells, in the number of chromatid breaks per 100 cells and in the number of dicentric chromosomes per 100 cells. A slight increase in the number of chromosome deletions per 100 cells in both radiation regimes did not reach statistical significance at the 5% level. The strongest association with exposure was found for the dicentric frequency. In the single exposure radiation regime, for example, the percentage of aberrant cells increased from 37.2% in controls to 42.9% in exposed workers, the number of chromatid breaks per 100 cells increased from 2.1 to 4.8 and the number of dicentrics

per 100 cells from 19.6 to 21.0. Comparison of the dicentric frequency with the concentration of the urinary metabolite of butadiene, for which data for these subjects was already available (Ward et al., 1994), showed a statistically significant correlation. This study provides some indication of a marginal increase in chromosome aberrations in workers exposed to about 3.5 ppm butadiene compared with controls and suggests that DNA repair efficiency is impaired in these exposed workers. These results, although they do not provide clear evidence of a cytogenetic effect in humans, may be biologically relevant and therefore cannot be dismissed.

Following reports that genetic polymorphism may increase susceptibility to genetic damage induced by the diepoxide metabolite of butadiene, in individuals who the lack the GSTT1 gene (which codes for glutathione-S-transferase class theta, GST θ), Kelsey et al. (1995) investigated the induction of SCEs by butadiene diepoxide in workers from the same butadiene plant as previously reported by Legator et al. (1993) and Ward et al. (1994, 1996a). All of the 46 plant employees (38 male, 8 female) were invited to participate in the study, although blood cell cultures from only 40 workers were suitable for analysis. Each worker completed a questionnaire to assess medical and occupational history, smoking status, coffee consumption and alcohol and drug use. Blood and urine samples were obtained post-shift; personal sampling was performed during the shift. Urine samples were analysed for the presence of the metabolite 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane (M1). Blood lymphocytes were cultured in the absence or presence of butadiene diepoxide, to determine baseline and DEB-induced SCE frequency respectively.

Mean 8-hour TWA exposure to butadiene was less than 1 ppm (ranging from non-detectable to 8.53 ppm). The butadiene metabolite M1 was detected in the urine of all workers, including all those whose personal sampling results did not detect butadiene. Urinary M1 levels were reported not to correlate significantly with personal sampling measurements. Although actual data were not presented, analysis of SCEs was reported to indicate that 34 of the 40 subjects studied were relatively 'resistant' to induction of SCEs by butadiene diepoxide (median SCE frequency 67 per cell) while the remaining 6 subjects (15%) were 'DEB-sensitive' (median SCE frequency 102 per cell). In addition, all the 'DEB-sensitive' subjects were reported to lack the GSTT1 gene, although again, details of how this was determined were not given. Analysis of variance showed that baseline SCE frequency did not correlate with 8-hour TWA exposure to butadiene, nor with urinary excretion of the M1 metabolite, although there was a positive association with DEB-sensitivity and with smoking status. When only high SCE frequency cells, using the mean of the five highest-scoring cells, were included in the analysis, only smoking status was found to correlate with high SCE frequency; neither butadiene exposure nor DEB sensitivity were correlated with the high SCE frequency. Overall, this study found no effect of exposure to butadiene (< 1 ppm 8-hour TWA) on SCE induction in these workers, nor any evidence that increased sensitivity to DEB-induced cytogenetic damage confers increased susceptibility to cytogenetic damage arising from exposure to butadiene. The inability of this study to demonstrate a genetic effect is in contrast to that of the previous study, which demonstrated induction of *hprt* variants in workers at the same plant.

As a follow-up to the earlier study of mutant frequency in workers at a polybutadiene rubber plant in China, Hayes et al. (2000) reported the results of other analyses of genotoxic markers among the same workers. Whole blood samples taken from the 41 exposed workers and 38 controls studied in the original investigation were analysed for erythrocyte glycophorin A (GPA) mutations, SCEs (with and without treatment with BDE) aneuploidy (measured using fluorescence *in situ* hybridisation) and chromosome aberrations. Workers were also evaluated with respect to GSTT1 and GSTM1 genotype; the latter genotype was investigated on the basis that lack of the GSTM1 gene has been linked to sensitivity to butadiene monoepoxide.

As previously reported, exposure values for butadiene, measured for workers in three separate areas of the plant were 1.0, 3.5 and 1.1 ppm (median 6-hour TWA values). In the latter of these three areas, exposures of up to 45 ppm (median value) were reported to occur during particular maintenance operations. Short-term exposures to butadiene, for the same three groups were 54 ppm, 6.5 ppm and 7 ppm (median values), although the range of short-term peak exposures was very wide, with some measurements reported to exceed 12,000 ppm. Markers of internal exposure (N-(2,3,4-trihydroxybutyl) valine (THBVal) haemoglobin adducts and the urinary metabolite M1(mercapturic acid butanediol)) were measured for each worker and showed a moderate correlation with the air measurements. No M-2 (mercapturic acid butenol) was detected in urine, with the exception of one worker who was reported to be highly exposed and for whom there was 'equivocal' evidence of urinary M-2.

There was no evidence of any statistically significant differences between exposed workers and controls in any of the markers of genotoxicity evaluated (actual data for chromosome aberrations were not presented). In addition, there was no evidence that either GSTT1 or GSTM1 genotype was correlated with any markers of exposure or of genotoxic effect, with the exception of BDE-induced SCEs. Subjects (exposed workers and controls) lacking the GSTT1 gene showed a statistically significantly higher frequency of SCEs following treatment of lymphocytes with BDE. This is consistent with the results of Kelsey et al. (1995), reported above.

Overall, this study shows no evidence of an effect of exposure to butadiene on a variety of genotoxic markers in this group of exposed workers.

Sorsa et al. (1994) evaluated chromosome aberrations, SCEs and micronuclei in blood lymphocytes of workers from two separate European butadiene manufacturing plants, A and B. Blood samples were collected from 17 male and female workers exposed to butadiene at plant A, and from 10 male and female controls, who worked at the same plant but were not exposed to butadiene. At the second plant, blood samples were taken from 23 male employees and from 20 controls who were employed at the plant in jobs with no exposure. Of the 23 exposed workers, 10 were exposed only to butadiene while the remaining 13 were exposed to butadiene and styrene. Controls were roughly matched for age and smoking habits. Ambient exposure concentrations of butadiene at plant A were in the range 1-3 ppm, with 72% of samples < 1 ppm. The average exposure level at plant B was 1.8 ppm, with 43% of samples < 1 ppm. The control workers at both plants were exposed to 0.01-0.3 ppm butadiene, with a mean of 0.07 ppm. Although it is not stated, it is assumed that these values represent 8-hour TWAs. Blood cultures were prepared in triplicate for cytogenetic analysis, with 100 metaphases analysed for chromosomal aberrations, 50 second-division metaphases analysed for SCEs and 1,000 binucleate cells analysed for micronuclei. No statistically significant differences between control and exposed workers at either of the two plants were detected for any of the cytogenetic endpoints tested. Exposure to background levels of 3 ppm butadiene or less, did not induce chromosome damage in blood lymphocytes in these workers.

As a follow-up to the above study, the presence of *ras* oncoprotein in the plasma of the 23 workers and 15 of the controls from plant B has also been investigated (Anderson et al., 1996). The presence of *ras* oncoprotein as an indicator of the expression of the *ras* oncogene has been proposed as a suitable biomarker of exposure to chemical carcinogens. Gel electrophoresis was used to separate plasma proteins, and a monoclonal antibody was used to detect the presence of *ras* proteins. No statistically significant differences in the presence of *ras* oncoprotein levels were found for either the group of 10 butadiene-exposed workers or the group of 13 styrene-butadiene exposed workers, compared with 15 controls. Whilst this study gave a negative result for this endpoint, the significance of this endpoint for human health is currently unvalidated. It

does, however, support the lack of a cytogenetic effect in these workers, as indicated by more the more conventional and validated cytogenetic investigations reported by the same group.

Three genotoxic endpoints, chromosome aberrations, SCEs and micronuclei, were investigated in lymphocytes from 23 exposed workers at a butadiene manufacturing plant (Ahlberg et al., 1992). A control group of 24 workers from the transport department of an oil refinery was included for comparison. Air monitoring at the butadiene plant was conducted with both stationary and personal samplers. Ambient air concentrations of butadiene, measured over a mean sampling time of 5.3 hours, were generally < 10 ppm. During certain operations, occasional exposures up to 300 ppm were measured using personal samplers. However, protective clothing and respirators were worn during these operations. No statistically significant differences between employees and controls were found for any of the cytogenetic parameters evaluated.

Chromosome aberrations (CA), sister chromatid exchanges (SCE) and proliferation indices (PI) in lymphocytes of 21 workers in the styrene-butadiene rubber industry was investigated by Sasiadek (1992). The mean age of the subjects was 42 years with a mean duration of occupational exposure of 14 years (range 2-35 years). A control group of 14 non-exposed office workers with a mean age of 39 years (30-52) was used for comparison. Statistically significant changes in all three parameters were observed in the exposed workers compared with non-exposed controls, with Cas (including gaps) measured as 2.2% in workers, compared with 0.9% in controls; mean SCEs per cell 16.1 in workers, 10.0 in controls; and mean PI 1.76 in workers, 2.13 in controls. These changes did not correlate with age or exposure duration, but the result for SCEs was apparently affected by smoking habits. Analysis of the work atmosphere revealed the presence of polycyclic aromatic hydrocarbons, nitrosamines, carbon monoxide and sulphur dioxide. No exposure data were presented. Overall, no conclusions can be drawn from this study because of the mixed exposures.

4.1.2.7.6 Summary of mutagenicity

Potential for genotoxic activity is indicated from the metabolic profile of butadiene, with the formation of reactive epoxide metabolites demonstrated in animal and human tissue *in vitro* and in animal studies *in vivo*.

Butadiene has been shown to be genotoxic to bacterial cells *in vitro*, in the presence of metabolic activation. There is a lack of good quality studies that investigate the genotoxic potential of butadiene in mammalian cells *in vitro*. There is some evidence that it has genotoxic potential *in vitro* from a poorly reported mouse lymphoma cell mutagenicity assay, in which positive results were seen in the presence of metabolic activation. Conflicting results have been obtained in SCE tests.

There are a number of studies that demonstrate the genotoxic potential of butadiene *in vivo* in mice. Butadiene was shown to induce micronuclei in the bone marrow and peripheral blood of mice. Chromosome aberrations have also been demonstrated in the bone marrow of mice exposed to butadiene. Positive results have been obtained in a number of other *in vivo* assays in mice, for SCEs, DNA strand breaks and crosslinks. Evidence of mutagenic potential *in vivo* was also demonstrated in transgenic mice, in two *hprt* mutation assays and in the mouse spot test. These data provide additional supporting evidence for the genotoxic potential of butadiene to mammalian cells *in vivo* in the mouse. Positive results in a number of dominant lethal studies and in two studies that investigated the induction of micronuclei in germ cells, indicate that butadiene is also a germ cell mutagen in mice.

Evidence from a limited number of studies in the rat indicates that butadiene is not genotoxic in this species. A clear negative result is reported in one well-conducted bone marrow micronucleus assay, and a negative result in an *in vivo*/*in vitro* liver UDS assay has been reported, as well as a negative result in a dominant lethal assay. Overall the evidence indicates that butadiene is not genotoxic to somatic cells or germ cells in the rat *in vivo*.

The epoxide metabolites of butadiene, epoxybutene and diepoxybutane, have been shown to be genotoxic to bacterial and mammalian cells *in vitro*, to somatic cells of the mouse, rat and/or hamster *in vivo* and to the germ cells of mouse and rat *in vivo*.

The genotoxic potential of butadiene in humans has been evaluated in a number of studies in exposed workers. Results from one of these studies are suggestive that exposure to butadiene at an average 8-hour TWA concentration of the order of 0.3-1 ppm may lead to an increase in mutation frequency at the *hprt* locus, but not chromosome damage in blood lymphocytes. However, this finding of an increase in mutation frequency at the *hprt* locus has not been clearly supported by other studies that have investigated this endpoint. There is no clear explanation for this discrepancy in the data, although differences in the methodology as well as differences in exposure pattern or in the statistical sensitivity of the assay could be important and therefore the results from this single positive study cannot be discounted. In addition, a marginal increase in chromosome aberrations and evidence for an impairment of DNA repair efficiency was also reported in the same workers at these exposure levels. However, other studies that have investigated a variety of genotoxic endpoints, including chromosome aberrations, have found no effects in workers exposed to average butadiene levels of the order of 3-3.5 ppm. No effect on mutation frequency, chromosome aberrations or DNA repair efficiency was reported at exposures at or below about 0.2 ppm (8-hour TWA). Overall, there is some suggestion of concern for mutagenicity in humans from two studies. However the data are inconsistent and not reproducible, although the importance of factors such as exposure pattern is not clear. Overall, given the clear evidence for mutagenicity in mice, these positive findings in humans cannot be dismissed.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

The carcinogenicity of butadiene has been studied in the rat and mouse in a number of studies. The data have been reviewed in various publications, including reviews by DECOS (1990), ECETOC (1992), IARC (1992) and Melnick et al. (1993). Inhalation carcinogenicity studies in mice have been conducted on behalf of the US Government's National Toxicology Program (NTP) and a study in the rat has been conducted on behalf of the International Institute of Synthetic Rubber Producers (IISRP).

Studies in mice

An NTP study was conducted in which B6C3F1 mice were exposed to 0, 6.25, 20, 62.5, 200 or 625 ppm butadiene, 6 hours/day, 5 days/week for up to 2 years (Melnick et al., 1990a,b; NTP, 1993). There were 70 mice per sex per group except at 625 ppm, which had 90 mice per sex. Up to 10 animals per group were sacrificed for examination at 40 and 65 weeks. A full gross necropsy and histopathological examination was carried out on each animal sacrificed during or at the end of the study. In addition, the study included a series of stop-exposure studies, in which

male mice were exposed to butadiene for a limited period and the animals were then kept in control chambers for the remainder of a 2-year period. In these stop-exposure experiments, groups of 50 male mice were exposed to one of the following exposure regimens: 625 ppm for 13 weeks; 200 ppm for 40 weeks; 625 ppm for 26 weeks; or 312 ppm for 52 weeks. All tumour incidences quoted are adjusted for mortality.

In the main 2-year exposure study, survival in animals exposed to 20 ppm butadiene or greater was statistically significantly reduced and at the highest concentration, 625 ppm, there was 100% mortality by week 65 of the study. Survival was reduced due mainly to the development of treatment-related malignant tumours. The major cause of death in the 625 ppm exposure group was lymphocytic lymphoma of thymic origin which developed in 91% of animals (mortality adjusted tumour incidence) compared with 4% incidence in controls. These tumours appeared from week 23 onwards. The incidence of lymphocytic lymphoma was also statistically significantly increased in females at 200 ppm (41% incidence). Haemangiosarcoma of the heart occurred with statistically significantly increased incidence in males exposed to 62.5 ppm and higher and in females at 200 and 625 ppm. At 625 ppm this tumour was seen in 6 males (53%) and 26 females (84%) compared with zero incidence in controls. The appearance of this tumour is considered to be important since it is a very rare tumour in the mouse. The historical control incidence is 1 in 2,500 animals. Other tumours which occurred with a statistically increased incidence in treated animals compared with controls and which included malignant neoplasms, were alveolar-bronchiolar neoplasms of the lung, squamous cell neoplasm of the forestomach, Harderian gland adenoma or carcinoma and hepatocellular neoplasm. In males there was also a significantly increased incidence of preputial gland adenoma or carcinoma, while in females, there was increased incidence of adenocarcinoma of the mammary gland and ovarian neoplasms. In general, at each of these sites, there was evidence of increases in the incidence of related non-neoplastic proliferative lesions. In females, only benign neoplasms of the lung, forestomach, Harderian gland and ovary were seen in control animals but malignant neoplasms were seen in these organs in exposed animals. In males, progression from alveolar-bronchiolar adenoma to carcinoma was seen at 200 ppm.

In most cases there was evidence of a dose-relationship in the tumour incidence, with increased incidence beginning at 62.5 or 200 ppm. However, it was observed that for some tumours, the incidence was higher in the lower exposure groups compared with the highest exposure group and statistical significance was lost at 625 ppm. This pattern of the tumour incidence is attributed to the high mortality in the 625 ppm group and the high incidence of the early developing lethal tumour, lymphocytic lymphoma, in these animals. At lower butadiene concentrations, the lymphomas do not occur, which allows the development of tumours in other tissues in the low exposure groups. In females, the incidence of hepatocellular neoplasm was increased from 20 ppm and above and appeared to be mainly due to an increase in hepatocellular carcinomas. Lung neoplasms, including malignant neoplasms, were increased in females at 6.25 ppm and above.

The results and tumour profile in the stop-exposure groups were similar to those in the main study. Survival in all groups was markedly reduced, again due to the development of malignant tumours. For example, even after only 13 weeks exposure to 625 ppm butadiene, there was a statistically significant increase in the incidence of lymphocytic lymphoma, haemangiosarcoma of the heart, alveolar-bronchiolar adenoma and carcinoma, squamous cell benign and malignant neoplasm of the forestomach, Harderian gland adenoma or adenocarcinoma and preputial gland carcinoma. The development of tumours other than the lymphomas (which require high butadiene concentrations) appeared to show a concentration x time dependency.

Overall, this study demonstrates butadiene to cause malignant tumours at multiple sites in mice. A statistically significantly increased incidence of malignant lung tumours was seen at the lowest

concentration tested, 6.25 ppm. The evidence indicates that butadiene is a genotoxic carcinogen in the mouse and that the risk of carcinogenicity in mice is high even at low exposure concentrations. From stop-exposure studies it appears that butadiene can elicit a carcinogenic response in the mouse even after a short exposure of 13 weeks to 625 ppm.

In an earlier study using B6C3F1 mice, conducted by the NTP, groups of 50 animals per sex were exposed to 0, 625 or 1,250 ppm butadiene, 6 hours/day, 5 days/week (Huff et al., 1985; NTP, 1984). The study was scheduled to last 2 years but was terminated at 60 weeks (males) or 61 weeks (females) because of the high mortality in both exposure groups. Survival was markedly reduced in exposed animals, due primarily to malignant tumours. A statistically significantly increased incidence of a wide range of tumours, including haemangiosarcoma of the heart, a very rare tumour type in this strain, was found in both exposure groups. The tumour pattern was similar to that in the study described above. The results are summarised in HSE (1985) and IARC (1992).

A detailed analysis of the tumour pathology in the animals from these NTP studies has been reported (Goodrow et al., 1990; Miller and Boorman, 1990; Solleveld et al., 1988; Wiseman et al., 1994). Goodrow et al. (1990) examined lymphomas, lung and liver tumours from the butadiene exposed mice for the presence of activated protooncogenes and showed K-ras activation in some of the tumours. Since activation of the K-ras gene has not been found in spontaneous tumours from untreated B6C3F1 mice, this provides additional evidence for a genotoxic mechanism for butadiene-induced carcinogenicity. Wiseman et al. (1994) characterised allelic losses in DNA from butadiene-induced mouse lung and mammary tumours and found frequent losses of heterzygosity at, or at loci surrounding, known or postulated tumour suppressor genes.

In a study to explore the contribution of endogenous retrovirus (MuLV) in the development of thymic lymphoma/leukaemia (TL) in B6C3F1 mice, Irons et al. (1989) exposed groups of 60 male B6C3F1 mice and male NIH Swiss mice to 0 or 1,250 ppm butadiene. Exposure was for 6 hours/day, 5 days/week for 1 year. In addition, 50 male B6C3F1 mice were exposed to 1,250 ppm for 12 weeks and sacrificed at 52 weeks. No statistical analysis of the results was performed.

TL developed in 34/60 (57%) B6C3F1 mice exposed to butadiene for 1 year compared with a control incidence of 1% in controls. NIH Swiss mice had a lower incidence of TL (8/57 mice; 14%) after the 1-year exposure. However, the control incidence of this tumour in Swiss mice was not given. The development of tumours was also increased in B6C3F1 mice exposed for 12 weeks, with TL reported in 10/48 (21%) mice. Endothelial cardiac haemangiosarcoma was reported in both strains of mice after 1-year exposure (8% B6C3F1; 2% Swiss). The control incidence of this tumour was not reported. In addition, B6C3F1 mice were reported to have bronchial-alveolar neoplasms and neoplasms of the glandular and non-glandular stomach, although no incidence values nor comparisons with control were given. In Swiss mice, an increased incidence of bronchial-alveolar carcinoma (27%) and adenoma (38%) was reported, although a high control incidence of bronchial-alveolar adenoma was also recorded in this strain (19%). Swiss mice also developed adenocarcinoma of the harderian gland and the thyroglossal duct. It is not stated by how much these tumour incidences were increased over control.

In conclusion, this study shows that exposure to butadiene for 1 year causes multi-organ tumours in two strains of mouse. Tumour development can occur after a short exposure, but the tumour incidence is greater when the exposure period is longer. There is a suggestion that B6C3F1 mice are more susceptible to the development of TL tumours than are NIH Swiss mice, but lack of reporting of control data prevents any firm conclusion from being drawn. However, further study

by Irons et al., (1987b) indicates that repeated butadiene exposure increases the expression of endogenous ecotropic retrovirus in the bone marrow, thymus and spleen of B6C3F1 mice but does not affect virus expression in NIH Swiss mice. This difference in viral expression may play a role in the greater susceptibility of B6C3F1 mice to butadiene-induced thymic lymphomas.

In a very briefly reported study B6C3F1 mice were exposed to high concentrations of butadiene for very short periods, in order to assess cancer risk arising from a single exposure (Bucher et al., 1993). Groups of 60 mice per sex were exposed for a single 2-hour period to 0, 1,000, 5,000 or 10,000 ppm butadiene and maintained without further exposure until sacrifice at 2 years. There was no effect on survival or on bodyweight. There was no exposure-related increase in tumour incidence in a wide range of tissues examined.

Studies in rats

One study is available, sponsored by the IISRP. Three groups of 110 Sprague-Dawley rats per sex, were exposed to 0, 1,000 or 8,000 ppm butadiene, 6 hours/day, 5 days/week for 105 weeks (females) or 111 weeks (males); 10 males and 10 females from each group were killed after 52 weeks (Owen, 1981; Owen and Glaister, 1990; Owen et al., 1987). The study was well-conducted and conforms to current regulatory guidelines.

There was a slight but statistically significant transient reduction in bodyweight gain in both sexes at 8,000 ppm and in males at 1,000 ppm during the initial 12 weeks of the study. In the second year of the study there was a concentration-related statistically significant increase in mortality, mainly due to tumours in both sexes. There was an increase in the incidence of a number of tumours, which were considered to be treatment-related. Females in both exposure groups had a statistically significantly increased incidence of mammary tumours, mainly benign, with a total tumour incidence of 79% and 81% in the 1,000 and 8,000 ppm groups respectively compared with 50% in controls. The incidence of malignant mammary tumours was 15% and 26% in the 1,000 and 8,000 ppm groups compared with 18% in controls. The mammary tumours appeared earlier in exposed animals than in controls. Also in females, there was a statistically significant concentration-related positive trend in the incidence of follicular thyroid adenoma (2% and 10% at 1,000 and 8,000 ppm; 0% in controls). In males, there was a statistically significant, concentration-related increase in Leydig cell tumours (3% and 8% at 1,000 and 8,000 ppm, 0% in controls). The incidence at the top dose is close to the historical control incidence for the laboratory (0-6%), but is considered to be treatment-related. Also in males, an increase in pancreatic exocrine adenoma at 8,000 ppm was seen (10% cf 3% in controls). However, distinguishing between hyperplastic lesions and adenomas in the exocrine pancreas is difficult. The more severe classification was given, but because of this doubt over classification, the significance of the result is not clear and cannot be taken as evidence of a carcinogenic effect of butadiene. Other tumours which developed, namely sarcoma of the uterus in females at 1,000 and 8,000 ppm and Zymbal gland carcinomas in both sexes at 8,000 ppm, were within historical control values and are not considered to be treatment related.

The study shows an increased incidence of mainly benign tumours, which occur spontaneously in the rat. The tumour profile suggests that butadiene may act by a non-genotoxic mechanism, and that tumour formation occurs indirectly via the endocrine system, rather than by a direct effect of reactive metabolites.

Metabolites of butadiene

Limited animal carcinogenicity experiments have been conducted with the metabolites, 1,2-epoxy-3-butene and diepoxybutane. It is not possible to evaluate the carcinogenic potential of

epoxybutene, from the information available (Van Duuren et al., 1963). Several isomers of diepoxybutane have been examined in rat and mouse carcinogenicity studies. Many of these studies are inadequately conducted or poorly reported, and no conclusions can be drawn from them (Hendry et al., 1951; Kotin and Falk, 1963; McCammon et al., 1957; Van Duuren, 1965; Weil et al., 1963). However, skin-painting experiments with mice have shown diepoxybutane to be carcinogenic (Van Duuren et al., 1963, 1965).

4.1.2.8.2 Studies in humans

Mortality studies

Mortality studies have been conducted on workers employed in butadiene manufacturing facilities, where exposure is to butadiene monomer alone. Other studies have investigated workers exposed to butadiene during styrene-butadiene rubber (SBR) production. In these plants, multiple chemical exposures are common and this makes interpretation of the results more difficult. An additional complication in these studies is that many employees move between plants, and have worked in both the butadiene manufacturing industry and in the SBR industry. Initial studies suggested a link between exposure to butadiene and an excess of cancers of the lymphohematopoietic system and for this reason many of the studies focused on cancers of this type in particular.

Although there is a relatively large number of studies reported, a number of these update previously reported findings and thus relate to the same or overlapping cohort populations. Thus, only the most recently reported mortality experience of a particular cohort is summarised in detail in this section. It is indicated in the text where the information presented updates earlier reports of the same cohort. The two major studies of mortality experience among butadiene exposed workers, which incorporate all or part of previously studied cohorts, are those of Divine and Hartman (1996), which investigates mortality in the monomer production industry and Delzell et al. (1995, 1996, 2000), which investigate mortality among SBR workers.

Butadiene manufacturing plants

Cause-specific mortality in a cohort of male workers at a butadiene manufacturing plant was first reported by Downs et al. (1987) and updated by Divine (1990), Divine et al. (1993) and most recently by Divine and Hartman (1996). The findings of the updated study essentially confirm those reported in the earlier studies, which investigated mortality among workers employed at the plant for at least 6 months since it opened in 1942, until 1990. The earlier studies reported a statistically significant excess of deaths from lymphosarcoma among workers first employed during World War II, employed for less than 10 years and in jobs which involved routine daily exposure to butadiene. However, there was no evidence for an increase in SMR with increasing duration of employment, and SMRs were found to be highest for men with the shortest latency and employment.

The most recent update of this cohort (Divine and Hartman, 1996) added an additional four years of follow-up, to the end of 1994. The study population, which encompassed those workers included in the earlier studies, was selected from male workers who had at least 6 months of regular employment between the start of plant operations in 1942 and the end of 1994. Death certificates were classified according to the 8th revision of the International Classification of Diseases (ICD8). The work history for each cohort member was used to allocate a score based on the potential for butadiene exposure, in terms of exposure frequency and intensity. This score,

along with exposure data from sampling conducted from 1980 onwards, was used to group jobs with similar exposure potential. Three exposure categories were defined: 1) the background exposure group included workers in jobs with only background exposure to butadiene, such as office staff and warehouse employees; 2) the low exposure group included workers whose jobs involved some potential exposure, but who also spent time in areas with only background exposure; 3) the varied exposure group included workers whose jobs involved routine exposure. Workers included in the latter two groups may have been employed for some time in more than one category; workers in the background exposure group were exclusively employed in this group.

Standardised Mortality Ratios (SMRs) for the complete cohort were calculated with reference to the US white male population. For this analysis, all individuals in the study cohort were assumed to be white; however, there were 211 non-whites in the cohort and 45 for whom race was unknown. The data were analysed in relation to employment duration, time of first employment and exposure category. In addition, estimates of relative risk were derived for all lymphohematopoietic cancer (LHC) and sub-categories, with cumulative exposure and age at hire as variables. Cumulative exposure estimates were weighted by calendar time, in five-year periods, based on anecdotal historical plant operating information. Three different models were used for this analysis, as a means of cross-checking for reliability: a Cox proportional hazard model, a person-time logistic regression model and a nested case-control model. .

The final study cohort comprised 2,795 male workers who met the eligibility criteria, with a total of 89,581 person-years of follow-up. The mean duration of employment was 12.2 years and the mean duration of survival from entry into the cohort was 32.1 years. A total of 546 workers were lost to follow-up, of whom 518 were known to be alive at the end of 1993. There were 1,222 deaths in the cohort, for whom death certificates were available for 1,202 (98%). In terms of the three exposure categories, 344 workers had background exposure, 996 had low exposure and 1,874 had varied exposure. This gives a total of 3,214 workers compared with the 2,795 in the total cohort; this discrepancy reflects the situation that some workers could have been employed for some time in different jobs, with the potential for different exposure potential and thus be allocated to more than one exposure category.

Deficits were found for deaths from all causes and all cancers among the total cohort, with SMRs of 88 (95% CI: 83-93) and 92 (95% CI: 82-104) respectively. The only cause of death for which the SMR was statistically significantly elevated was for all lymphatic and hematopoietic cancer (LHC) for which an SMR of 147 (95% CI: 106-198) was found, based on 42 observed deaths. This increase was due to increases in the SMRs for lymphosarcoma and reticulosarcoma (SMR = 191; 95% CI: 87-364, 9 deaths), Hodgkin's disease (SMR = 166; 95% CI:45-424,4 deaths), leukaemia (SMR = 113; 95% CI:60-193,13 deaths) and cancers of other lymphatic tissue (SMR = 152; 95% CI:85-250,15 deaths); however none of these SMRs reached statistical significance. The deaths in the category of other lymphatic tissue were reported to be eight lymphomas, six multiple myelomas and one polycythemia vera. The authors suggested that it might be more appropriate to combine lymphoma and lymphosarcoma deaths into one category, non-Hodgkin's lymphoma (NHL), for analysis, since the diagnosis of lymphoma may now be used in preference to that of lymphosarcoma; this approach is considered to be reasonable. Thus, based on 17 deaths from NHL (and using the assumption that 50% of expected deaths in the category of cancer of the other lymphatic tissue are lymphomas), an SMR of 176 (95% CI: 103-282) was calculated.

Analysis of the data on the basis of employment duration (less than 5 years, 5-19 years or $\geq$ 20 years employment) indicated that the excess for all LHC was due primarily to a statistically significant excess among workers employed for less than 5 years (SMR = 162; 95% CI: 101-245, 22 deaths). None of the other SMRs, either for all LHC or for specific lymphatic cancer types

reached statistical significance when analysed in relation to duration of employment. In relation to lymphosarcoma and reticulosarcoma, for which a statistically significantly elevated SMR had been found in the previous analyses of this cohort, six of the nine deaths were in workers employed for less than 5 years (SMR = 261; 95% CI: 95-568). Based on the category of NHL, six of the 17 decedents were employed for more than 5 years.

When the data were analysed in relation to time of first employment (first hired before 1946, 1946-1949 and after 1950), the SMR for all LHC was increased, although not statistically significantly, for workers first employed before 1950; thus for workers employed pre-1946, the SMR for LHC was 148 (95% CI: 96-219, 25 deaths) and for workers first hired 1946-1949, the SMR was 174 (95% CI: 95-292, 14 deaths). Only three LHC deaths were among workers first hired after 1950, one lymphasarcoma and reticulosarcoma, one Hodgkin's disease, and one cancer of the other lymphatic tissue; no leukaemia decedents were in the group first hired after 1950. Again, there were no statistically significantly elevated SMRs for any specific LHC cancer types; a non-statistically significant excess of lymphosarcoma and reticulosarcoma was seen among workers first hired pre-1946 (SMR = 241, 95% CI: 97-497, 7 of the 9 deaths) of whom four had been employed for less than 5 years. Similarly, of seven leukaemia deaths which occurred in workers first hired pre-1946, four of these were in workers employed for less than 5 years. Using the category of NHL, 16 of the 17 decedents were first employed before 1950.

In relation to the defined exposure categories, analyses of selected causes of death were performed for all workers ever employed in each category and for workers employed for 10 years or more in each category. For the background exposure group, there were no statistically significant increases in SMRs for any of the causes of death, although elevated SMRs were found for cancer of the large intestine (SMR = 175, 95% CI: 70-960, 7 deaths), LHC (SMR = 156, 95% CI: 57-339, 6 deaths), Hodgkin's disease (SMR = 626, 95% CI: 70-2260, 2 deaths) and for other lymphatic cancers (SMR = 229, 95% CI: 46-669, 3 deaths). In all cases, other than for Hodgkin's disease, these SMRs were lower among workers employed for more than 10 years; in the case of Hodgkin's disease, although the SMR increased, this was based on only 1 death and therefore cannot be viewed with reliability. In the low exposure category, the only statistically significantly elevated SMR was for pneumonia, an isolated finding which is unlikely to be evidence of a real association with butadiene exposure. Non-statistically significantly elevated SMRs were found for kidney cancer (SMR = 214, 95% CI: 78-465, 6 deaths), lung cancer (SMR = 120, 95% CI: 88-160, 46 deaths) and other lymphatic cancers (SMR = 161, 95% CI: 59-351, 6 deaths); of these, only the SMRs for kidney cancer and pneumonia increased in workers employed for more than 10 years. Among workers in the varied exposure category, the category with the potential for the highest exposure to butadiene, a statistically significantly elevated SMR was obtained for all LHC (SMR = 172, 95% CI: 117-244, 31 deaths), mainly attributable to an elevated SMR for lymphosarcoma and reticulosarcoma (SMR = 249, 95% CI: 100-513, 7 deaths), but with increased SMRs also for Hodgkin's disease (SMR = 128, 95% CI: 14-464, 2 deaths), leukaemia (SMR = 154, 95% CI: 77-275, 11 deaths) and cancers of other lymphatic tissue (SMR = 156, 95% CI: 75-287, 10 deaths). In addition, elevated SMRs in this group were also found for kidney cancer (SMR = 194, 95% CI: 88-368, 9 deaths) and pneumonia (SMR = 136, 95% CI: 90-197, 28 deaths). In workers with varied exposure employed for more than 10 years, only the SMRs for kidney cancer, Hodgkins' disease and other lymphatic cancers showed a further increase, although none reached statistical significance.

Additionally, the mortality data for the 211 non-white males in the cohort were analysed separately, with SMRs calculated with reference to US rates for non-white males. This analysis showed a different pattern of results to those for the whole cohort, with a statistically

significantly increased SMR for death from all causes (SMR = 128, 95% CI: 106-153). A number of SMRs for specific causes of death were elevated, although none reached statistical significance, including the SMRs for all infectious disease, cancer of the large intestine, lung cancer, lymphosarcoma and reticulosarcoma, arteriosclerotic heart disease, stroke and pneumonia. The SMR for lymphosarcoma and reticulosarcoma was based on only one death, in an employee in the low exposure group, who had worked for only a short time in the 1940s and had a short latency between exposure and death.

The estimates of relative risk for LHC and its sub-categories, derived using three independent methods, did not indicate any association between increased cancer risk and estimated cumulative exposure to butadiene.

Overall, this study extends and confirms the findings from earlier reports of this worker cohort, namely that there is an excess of LHC, mainly due to excesses for lymphosarcomas and cancers of other lymphatic tissue. The excess for lymphosarcoma is concentrated among workers first hired pre-1946, employed for less than 5 years and in jobs which involved the potential for highest exposure to butadiene. Production of butadiene increased during World War II and therefore exposure would be expected to have been greater during this pre-1946 period. An elevated SMR for cancer of other lymphatic tissue was also found among workers in the varied exposure category, which has the potential for highest exposures, and tended to increase with increased employment duration. An alternative grouping of the LHC sub-categories into a category for NHL revealed a statistically significant excess of deaths in this category, concentrated among workers first employed before 1950, in jobs with varied exposure and often employed for more than five years. However, although this pattern of results supports the possibility that exposure to high levels of butadiene, which occurred during the earlier years of the plant's operation, are associated with an excess of LHC, and specifically with NHL, the authors reported that high peak exposures continued to occur after 1950, whereas no excess LHC is seen in workers first employed after 1950. In addition, the study found no evidence of an association between increased risk of NHL and estimated cumulative exposure to butadiene. Thus, whilst this study clearly demonstrates an excess of LHC among this cohort of butadiene monomer workers, the pattern of results does not clearly support an association with occupational exposure to butadiene.

A small cohort mortality study has been conducted in male workers employed at three butadiene production units at three chemical plants in the US (Ward et al., 1995, 1996b). The workers included in this study formed part of a larger cohort of 29,139 male employees at these chemical plants, which had previously been the subject of a mortality study conducted by Rinsky et al. (1988). This larger, earlier study had found a statistically significant excess of deaths from lymphosarcoma and reticulosarcoma; however, the data had not been analysed in relation to any specific chemical exposure. The hypothesis addressed by Ward et al. was that exposure to butadiene in these chemical plants is associated with an excess of LHC and also with an excess of mortality from other neoplastic effects.

Employment records were obtained for 29,139 male workers employed at the three chemical plants from 1940-1979. Of a total of 527 workers identified as having ever worked in a unit where butadiene was the main product, only 364 were included in the final study cohort, on the basis of having worked in a unit during a period when it was active in the production of butadiene. The workers had no co-exposure to benzene or ethylene oxide but were exposed to the potential carcinogens bis(2-chloroethyl) ether and acetaldehyde. Vital status was established for the cohort members up to the end of 1990 and cause of death was established from death certificates. SMRs were calculated with reference to national and local death rates, with similar

results, and only national referent SMRs are reported below. Race was unknown for 28% of the cohort, and for these cases, race was assumed to be white.

At the end of December 1990, 176 (48.3%) of the 364 cohort members were alive, 185 (50.8%) were deceased and vital status was unknown for 3 (0.8%). The SMR for death from all causes was 91 (95% CI: 79-106), while that from all cancers was 105 (95% CI: 78-140). The only category for which there was a statistically significantly elevated SMR was for lymphosarcoma and reticulosarcoma (SMR = 577; 95% CI: 157-148, 4 deaths). Of these 4 deaths, 3 were workers with 2 or more years of employment in a butadiene production unit and had worked for 30 or more years since first employment. An influence of concurrent exposure to acetaldehyde was ruled out as a possible confounding factor in this group. No exposure data for this butadiene production unit were available; in addition, this unit was in operation for a period of only 4 years. Overall, although this study demonstrates a statistically significantly elevated incidence of lymphosarcoma and reticulosarcoma among a cohort of workers exposed to butadiene, it is limited in terms of size, lack of exposure data, and, since the excess deaths were concentrated among workers employed in a unit which was operational for only 4 years, it does not address the effects of long-term exposure to butadiene. Therefore, whilst this study cannot in itself provide reliable evidence for a carcinogenic effect of butadiene, it does support the findings of the other, larger study of butadiene monomer workers reported above, in which an excess of lymphohematopoietic cancer has been found.

A study on the health of butadiene workers at the Shell Deer Park Manufacturing Complex was conducted by Cowles et al. (1994). The plant was active in the manufacture of butadiene monomer from 1941 to the end of 1948 and from 1970 onwards. The final study cohort included 614 male workers. These were all the male employees at the Complex who had a minimum of 5 years employment in jobs with potential exposure to butadiene or had worked for at least half of their total employment in jobs with potential exposure to butadiene, with a minimum of 3 months in such jobs. The average age at entry was 31 years and average duration of employment in jobs involving potential exposure to butadiene was 7.6 years. There were 24 deaths in the cohort, 12 of which were among employees hired before 1949. Death certificates were obtained for all decedents. SMRs adjusted for age, race and calendar year were calculated with reference to the local regional population. Exposures to butadiene measured in the period 1979-1992 were found to be in the range < 0.1-143 ppm (8-hour TWA), with a mean of 3.5 ppm. Exposure levels prior to 1979 were not available.

All-causes SMR was 48 (CI: 31-72) and all cancers SMR was 34 (CI: 9-87). There were no deaths from lymphohematopoietic cancers (1.2 expected). Lung cancer was identified as the cause of death in 2 workers (SMR = 42, CI: 5-151). Overall, this study indicates no excess of cancers and in particular, no excess of lymphohematopoietic cancers, in butadiene workers at this manufacturing plant. However, the power of this study to detect an excess of cancers is reduced because of the relatively small cohort size and the small number of deaths. As such, any small excess of cancer associated with butadiene exposure is unlikely to be detected. Therefore although a negative result is indicated, the possibility of an association between butadiene exposure and an excess risk of cancer cannot be ruled out by these results.

Styrene-butadiene rubber manufacturing plants

A number of cohort mortality studies of workers employed in the SBR industry within the USA and Canada have been reported. However, the cohorts for these investigations are drawn from a limited number of SBR plants, and therefore there is considerable overlap between the study populations reported for different studies. Additionally, as is the case for studies of monomer workers, there have been a number of updates of the cohorts.

Two large cohorts of SBR workers have been studied. The first cohort is drawn from workers employed at two plants at Port Neches, USA, first reported by Meinhardt et al. (1978) and updated in 1982 (Meinhardt et al., 1982). The second cohort is drawn from eight SBR plants excluding those at Port Neches, within USA and Canada, first reported by Matanoski et al. (1987) and subsequently updated (Matanoski et al., 1990). The most recent and by far the biggest study largely combines these two cohorts, although it excludes workers at one of the eight plants studied by Matanoski et al. (Delzell et al., 1996). Although the overlap with the two previous study cohorts is not known exactly, it is expected to be large.

Meinhardt et al. (1978, 1982) investigated the mortality experience of a cohort of workers employed at two styrene-butadiene rubber production plants at Port Neches, Texas. Data for each plant were considered separately. Butadiene (mean concentration 1.24 ppm, range 0.11-4.17 ppm), styrene (mean 0.94 ppm, range 0.03-6.46 ppm) and benzene (mean 0.10 ppm, range 0.08-0.14 ppm) were present in the atmosphere of the first plant (plant A) in 1976. Exposure levels previous to this were not available. In this plant, employment records were available from 1943, the date when the plant opened. A total of 3,494 people had been employed, 1,662 of whom were white males with at least six months' employment. Vital status of the 1,662 workers was determined at 31 March 1976; 1,356 (81.6%) were identified as alive, 252 (15.2%) as dead and 54 (3.3%) could not be definitely identified, and were assumed to be alive. Deaths were classified in accordance with the International Lists of Disease and Causes of Death current at the time of death, and the classification was converted to that of the 7th revision. Age, calendar year and cause-specific mortality rates for the white male US population were used to calculate the expected number of deaths.

The SMR for all causes of death at plant A was 80. An elevated SMR value was obtained for malignant neoplasms of the lymphatic and haemopoietic systems (SMR = 155, 95% CI: 71-294, 9 deaths), due to increased numbers of deaths from lymphosarcomas and reticulosarcomas (SMR = 181, 95% CI: 37-529, 3 deaths) and leukaemia (SMR = 203, 95% CI: 66-474, 5 deaths). One of these excesses was statistically significant, although this may be due to the small numbers involved.

All of the deaths from leukaemia occurred in employees who had at least six months' experience between January 1943 and December 1945, a period in which a hot-temperature batch process, subsequently discarded, but which would possibly have resulted in higher exposures, was used in the plant. When the mortality of a sub-group of workers employed for at least six months between January 1943 and end of December 1945 was examined, overall mortality was still low (SMR = 83, 95% CI: 72-95, 201 deaths). However, mortality due to malignant neoplasms of the lymphatic and haemopoietic tissues (SMR = 212, 95% CI: 97-402, 9 deaths) and leukaemia (SMR = 278, 95% CI: 90-649, 5 deaths) was increased.

Only butadiene and styrene levels were measured at plant B. Butadiene levels (mean 13.5 ppm, range 0.34-175 ppm) were proportionately higher than styrene levels (mean 1.99 ppm, range 0.05-12.3 ppm). Employee records were available only from 1950; the plant was previously operated by a different company (1943-1947) and was shut down from 1947 to 1950. Of a total of 2,015 employees, 1,094 were white males with at least six months' employment; 980 (89.6%) were alive at the end of March 1976, 80 (7.3 %) were known to have died and the vital status of 34 (3.1 %) was unknown. The data for cause of death were analysed in the same way as for plant A. Overall mortality was low (SMR = 66, 95% CI: 52-82, 80 deaths, healthy worker effect). High SMR values were seen for malignant neoplasms of the testis (SMR = 215, 95% CI: 26-777, 2 deaths) and for lymphosarcoma and reticulosarcoma (SMR = 132, 95% CI: 3-736, 1 death). Clearly, because of the small numbers of deaths none of these results reached statistical significance. No useful conclusions can be drawn from these data for plant B.

In conclusion, there is an indication of an excess of lymphohematopoietic cancers in workers at one of the two SBR facilities studied (plant A). This excess was highest in a subgroup of employees with possibly the highest exposures to butadiene and styrene. Although there is mixed exposure in this case, the study supports a possible link between exposure to butadiene and the incidence of lymphohematopoietic cancer.

A large mortality study, conducted on behalf of the International Institute of Synthetic Rubber Producers, was performed using data from eight butadiene-styrene rubber production plants, seven in the USA and one in Canada (Matanoski et al., 1982; Matanoski and Schwartz, 1987) and a follow-up was subsequently published (Matanoski et al., 1990, 1993). No exposure data were available but a qualitative estimate of exposure was made from consideration of job type.

Production at seven of the plants first started in 1943; production at the eighth plant started in 1957. However, record keeping at several plants was inadequate in earlier years, thus only individuals present at the time of the start of complete record keeping were entered into the study cohort i.e. 1943 for four plants and 1953, 1958, 1964 and 1970 respectively for the other four plants. In total, 13,422 workers were included in the final study. The study cohort comprised all male employees who had worked for at least 1 year and were hired after the start of production in the plant or who had worked at any time after record keeping was complete, up until the end of 1976. Death certificates were obtained for 97.2% of the 2,441 decedents. All deaths were classified in accordance with ICD8. Workers whose vital status could not be traced were assumed to be alive. Standardised mortality ratios were calculated with reference to the US male population. The data were corrected for age, race and calendar year of death. No quantitative exposure data were available. Job categories were defined and workers were coded according to these, but no attempt was made to group the jobs according to predicted exposure.

All-cause mortality was low (SMR = 81, 95% CI: 78-85), as was all-cancer mortality (SMR = 85, 95% CI: 78-93). A statistically significant excess of arteriosclerotic heart disease was observed in black workers (SMR = 148, 95% CI: 123-176, 125 deaths). There was no statistically significant increase of any specific cancer type. The SMR for cancers of the lymphohematopoietic system was 97 (95% CI: 73-126, 55 deaths). Within this cancer group, slightly elevated SMRs were recorded for Hodgkin's lymphoma, (SMR = 120, 95% CI: 52-237, 8 deaths) and for other lymphatic cancers excluding leukemia or lymphosarcoma (SMR = 111, 95% CI: 64-177, 17 deaths). Again, these figures were not statistically significant. There was no trend indicative of an association between length of employment and cancer mortality.

The authors related specific causes of death to job category. In production workers, who might be assumed to have had greater exposure to the styrene and butadiene monomers, a slight excess of lymphohematopoietic cancers was found (SMR = 146, 95% CI: 88-227, 19 deaths), but this was not statistically significant. This excess was mainly due to a particularly high incidence among black production workers (SMR = 507, 95% CI: 187-1107, 6 deaths), which was statistically significant. The only lymphohematopoietic cancer type that was statistically significantly higher in all production workers was for 'other' lymphatic cancers – Non-Hodgkin's lymphoma and multiple myeloma (SMR = 260, 95% CI: 119-494, 9 deaths). Black production workers had a statistically significant excess of leukemias (SMR = 656, 95% CI: 135-1906, 3 deaths). In comparison, maintenance workers, who are expected to have some incidental exposure to styrene-butadiene, showed no excess of lymphohemato- poietic cancers or of any other specific cancer. It is possible, however, that at least up to the late 1960s, black production workers may have higher average exposures to butadiene than white production workers due to job segregation by race (Landrigan, 1993).

Overall, this study provides some evidence for an excess of lymphohematopoietic cancers in styrene-butadiene workers at these plants. The only significant excess of these cancers appears in a sub-group of workers involved in production jobs. Production workers are predicted to have had the greatest exposure to the styrene and butadiene monomers. However, the excess was concentrated among black workers, and not distributed evenly among the population. This may represent an artefact, particularly since when racial status was unknown for any worker, the worker was assumed to be white. This could artificially elevate the incidence of a particular cancer in the black population by dilution of the total population size. However, it is also possible that the excess in black workers could be due to job segregation by race, which may lead to higher average exposures for black workers.

In a more recent report of this cohort, measured exposure data were available for seven of the eight plants (Matanoski et al., 1993). The data were obtained by sampling exposures for particular jobs, and the jobs sampled varied between plants; thus, there may be differences in the measured levels for each plant dependent on the jobs sampled in each. These exposure data indicated that geometric mean exposure was higher in three of the seven plants (1.25-1.90 ppm) compared with the others and so the cohort mortality data were re-analysed for workers at these three plants only; this analysis was restricted to workers hired before 1960 and with 10 or more years employment duration, a total of 3,429 employees.

Mortality from all causes and all cancers was slightly reduced compared with expected values, with SMRs of 86 (95% CI: 80-92) and 96 (95% CI: 83-109) respectively. However, there was a statistically significantly elevated SMR for all lymphohematopoietic cancer (SMR = 163; 95% CI: 113-227, 34 deaths), which was mainly attributable to a statistically significant excess of leukemia and aleukemia (SMR = 181; 95% CI: 101-299, 15 deaths). Although elevated SMRs were found for the other specific lymphohematopoietic cancer types, none of these reached statistical significance. Thus, increased SMRs of 116 (95% CI: 37-270, 5 deaths), 243 (95% CI: 78-568, 5 deaths) and 149 (95% CI: 68-282, 9 deaths) were found for lymphosarcoma and reticulosarcoma, Hodgkin's disease and cancers of other lymphatic tissue, respectively. This further analysis therefore supports the findings for the overall cohort and is suggestive of an excess of lymphohematopoietic cancer amongst longer-term workers who would be expected to have the highest butadiene exposures. However, given that the exposure data relate to general levels in each plant, and are not necessarily reliable indicators by which to compare exposures between plants, nor can they be related to individual exposure levels, it is not possible to use these data to establish any dose-response relationship for this finding.

A very large cohort mortality study conducted in workers in the US and Canada has very recently been completed (Delzell et al., 1995, 1996; Macaluso et al., 1996). This study combines the mortality experience of previously studied SBR worker cohorts, from workers at seven of the eight SBR plants in the US and Canada previously reported by Matanoski and Schwarz (1987) and Matanoski et al. (1990, 1993) and from the US SBR two-plant complex previously reported by Meinhardt et al. (1982). Only male workers who had worked at any plant for at least one year within the period of the study, 1943-1992 were included in the study cohort. In order to identify those eligible for inclusion, records were reviewed for 25,500 employees from the seven US plants and 6,994 employees from the Canadian plant. Of the 25,500 US plant employees, a total of 12,605 were included in the study, with most of the exclusions on the grounds of less than 1 year of employment. In the Canadian plant, 5,359 subjects met the eligibility criteria. Thus a total of 17,964 employees were eligible for entry into the study. In the Canadian plant, of the 5,359 eligible subjects, 3,044 were identified as having worked in styrene-butadiene rubber (SBR) and related operations. The remainder were classed as having worked in non-SBR-related operations, although some may have worked in SBR or related operations. The results presented

below are for the total of 15,649 workers who were known to have worked in SBR and related operations, a large number of whom are likely to have been included in the earlier epidemiological studies.

Payroll status (hourly-paid, salaried or mixed), year of hire, duration of employment, race and vital status was established for each cohort member. Cause of death was established from death certificates and classified according to ICD8. SMRs were calculated with reference to national US rates for the 7 US plants and to Ontario rates for the Canadian plant. An attempt was made to estimate exposures to butadiene, styrene and benzene, using work histories from about 97% of the study cohort. Analyses of process and job types were used in conjunction with an exposure model to estimate 8-hour TWAs and the number of exposure peaks, defined as an average exposure concentration of > 100 ppm butadiene or > 50 ppm styrene in any 15 minute period.

Vital status information indicated that as of 1st January 1992, of the 15,649 subjects in SBR and related processes, 10,939 (70%) were alive, 3,976 (25%) were deceased and 734 (5%) were lost to follow-up. The average period of follow-up was 24.7 years per person with a total of 386,172 person-years of follow-up. The median year of hire was 1960 and 44% of the cohort had $\geq$ 10 years employment since hire. The SMR for death from all causes was 87 (95% CI: 85-90; 3976 deaths) and for all cancers was 93 (95% CI: 87-99; 950 deaths). The only cause of death for which an elevated SMR was found was for leukaemia, with an SMR of 131 (95% CI: 97-174; 48 deaths). All other SMRs were close to or below 100. The cohort was subdivided according to duration of employment and number of years since hire. The subgroup with relatively long duration of employment ($\geq$ 10 years) and long period since hire ($\geq$ 20 years) were found to have SMRs for all deaths and all cancers similar to that for the total cohort (all mortality SMR = 94, 95% CI: 90-99; 1,678 deaths; all cancer SMR = 95, 95% CI: 86-104; 426 deaths). There was a statistically significantly elevated SMR for all lymphopoietic cancer in this subgroup (SMR = 139, 95% CI 104-183; 52 deaths). This was due mainly to an excess of mortality from leukaemia, for which an SMR of 201 (95% CI: 134-288; 29 deaths) was obtained. Also in this subgroup, elevated SMRs were recorded for laryngeal cancer (SMR = 141, 95% CI: 65-268; 9 deaths) and cancer of the CNS (SMR = 135, 95% CI: 72-230; 13 deaths), although neither of these were statistically significant. All the deaths from laryngeal and CNS cancer were among white workers in this group.

Further analysis indicated that the SMRs for 'ever hourly' subjects i.e. hourly-paid subjects, in jobs most likely to involve exposure to butadiene, were similar to those for the overall cohort, with again, a statistically significantly elevated SMR for leukaemia (SMR = 143, 95% CI: 104-191; 45 deaths). In particular, ever hourly workers with $\geq$ 10 years employment and $\geq$ 20 years since hire had an excess of leukaemia (SMR = 224, 95% CI: 149-323; 28 deaths). The SMRs for never hourly subjects were, in general, lower than those for ever hourly workers, and the SMR for leukaemia was below 100 in this group. Among ever hourly workers, the SMR for leukaemia increased with duration of employment (from 95 in subjects with < 10 years employment, to 170 in subjects employed between 10 and 19 years, and 240 for employment $\geq$ 20 years) and number of years since hire (SMRs of 50, 251 and 140 for < 20, 20-29 and $\geq$ 30 years since hire respectively). The leukaemia excess in ever hourly workers was concentrated among workers hired in or after 1950, and with $\geq$ 10 years employment and 20-29 years since hire (SMR = 353, 95% CI: 176-631; 11 deaths). No excess of leukaemia was observed in ever-hourly workers hired pre-1950; this group also had significantly low all-cause mortality. For all ever-hourly leukaemia decedents, median values of 58 years for age at death, 17.1 years employment duration, 28.2 years since hire and 1951 for year of hire were obtained.

When race was taken into consideration in the analyses, the leukaemia SMR was elevated for both white and black workers, and again, the excess was concentrated among ever-hourly

workers with ≥ 10 years employment and ≥ 20 years since hire. The leukaemia excess in this group was higher in black workers (SMR = 436, 95% CI: 176-901; 7 deaths) compared with whites (SMR = 192, 95% CI: 119-294; 21 deaths).

Work history data for 13 713 subjects were used to identify 5 main process groups – production (50% of subjects), maintenance (32%), labour (35%), laboratories (13%) and other operations (21%). These categories were not mutually exclusive. In general, although not always, SMRs were lowest for laboratory workers and highest for maintenance workers. Statistically significant excesses were found for lung cancer among maintenance workers (SMR = 124, 95% CI: 104-146; 141 deaths) and for leukaemia among production workers (SMR = 159, 95% CI: 100-241; 22 deaths), labourers (SMR = 195, 95% CI: 112-317; 16 deaths; concentrated among black workers), laboratory workers (SMR = 462, 95% CI: 238-806; 12 deaths; all white workers) and among black workers in other operations (SMR = 680, 95% CI: 137-1986; 3 deaths). The two job categories with the highest SMRs for leukaemia, laboratory workers and maintenance labourers, involved intermittent exposures to high levels of butadiene.

Estimated exposure to butadiene monomer, styrene and benzene were based on data from six of the eight plants. Of the subjects included in this analysis, 75% were exposed to butadiene, 83% to styrene and 25% to benzene. Cumulative median 8-hour TWAs estimated for all exposed workers were 11.2 ppm-years for butadiene, 7.4 ppm-years for styrene and 2.9 ppm-years for benzene. Leukaemia decedents had around two-fold higher median cumulative exposures to butadiene and styrene (36.4 ppm-years butadiene; 22.4 ppm-years styrene) in comparison with all decedents (19.0 ppm-years butadiene, 9.7 ppm-years styrene) and around three-fold higher than all exposed workers (11.3 ppm-years butadiene, 7.4 ppm-years styrene). Amongst exposed workers, there was a moderate correlation between butadiene and styrene exposures (correlation coefficient = 0.53). Benzene exposures were low and infrequent for all groups and showed no association with leukaemia mortality rates and were therefore excluded as a potential confounding factor. Regression analysis was performed to evaluate the association between cumulative exposure to butadiene and styrene separately, based on a series of different exposure categories. The exposure categories were defined such that each category included a reasonable number of leukaemia deaths. A positive association was found between cumulative exposure to butadiene and leukaemia mortality, after controlling for styrene exposure, age, years since hire, calendar period and race, for butadiene cumulative exposure categories based on cut-off values of 20, 100 and 200 ppm-years. Thus, relative risk (RR) values for leukaemia of 1.0, 1.1, 1.8, 2.1 and 3.6 were obtained for butadiene exposure categories 0, > 0-19, 20-99, 100-199 and ≥ 200 ppm-years respectively. The association between styrene exposure and leukaemia, corrected for butadiene exposure and the covariables listed above did not show a consistent trend for any of the exposure category cut-off values used, with RRs of 1.0, 1.0, 1.2, 1.8 and 1.3 for exposures of 0, > 0-19, 20-39, 40-59 and ≥ 60 ppm-years styrene respectively. These analyses were carried out for various different cumulative exposure categories and showed a consistent correlation between cumulative butadiene exposure and leukaemia mortality; the correlation between cumulative styrene exposure and leukaemia was weaker and less consistent when alternative categories were used. Macaluso et al. (1996) presented an analysis based on butadiene exposure cut-off categories of 1, 20 and 80 (the rationale behind the cut-off values for these categories was not stated), which again showed a statistically significant association between cumulative exposure and leukaemia mortality for butadiene but not for styrene. The RRs for leukaemia mortality were 1, 2.0, 2.1, 2.4 and 4.5 for butadiene cumulative exposure categories of 0, <1, 1-19, 20-79 and 80+ respectively. This trend of increased RR with increasing cumulative butadiene exposure remained statistically significant after exclusion of all workers with zero cumulative exposure to both butadiene and styrene. The association between leukaemia mortality and cumulative styrene exposure was inconsistent and not statistically significant.

The association between butadiene exposure and leukaemia was present in ever-hourly workers while no relationship with styrene exposure was found in this group. There was limited evidence for an association between leukaemia and peak exposure to butadiene, but not with peak exposure to styrene. RR values of 1.0, 2.6 and 0.8 were obtained for butadiene exposures of 0, > 0-199 and $\geq$ 200 peak-years respectively. However, the authors noted that the analysis of peak exposures was subject to some degree of error, and it is possible that there was an underestimation of peak exposures, particularly among laboratory workers for whom there was insufficient information to accurately identify peak exposures. An additional analysis of the peak exposure data was therefore subsequently undertaken (Delzell et al., 1996; unpublished report). In addition, more recently, in the light of concerns raised about the overall accuracy of the exposure estimates for the study and possible misclassification of exposures, a reanalysis of the exposure assessment (peak and non-peak exposures) was conducted (Macaluso et al., 2000). This reanalysis involved the collection of new, additional information on the operating conditions of the plants involved in the study, in many cases leading to the replacement of default assumptions with actual data to refine the exposure assessment. In addition, the exposure assessment included an evaluation of exposure to another substance used in the SBR manufacturing process and to which workers would potentially have been exposed. This substance, dimethyldithiocarbamate (DMDTC) has been putatively proposed as a possible confounder in relation to the positive cancer findings in the SBR industry (Irons and Pyatt, 1998). The revised exposure assessment and the reanalysis of the mortality data based on it, are described below.

An attempt was made to subdivide the leukaemia cases into specific forms of leukaemia. While there was some indication of an increased in relative risk for acute forms of leukaemia with increasing butadiene exposure, overall no convincing associations were found when the leukaemia cases were subclassified into specific forms. This is probably due to the small numbers of cases involved for each subtype, as well as probable misclassification of leukaemia type, so that overall, no clear conclusions can be drawn from this analysis.

In addition to the mortality analysis, a cancer incidence analysis for the period 1965-1992 was conducted for the Canadian plant, using the Ontario Cancer Registry for comparative incidence data. This incidence analysis involved 5,184 subjects, of whom 3,017 had worked in SBR or related operations. No statistically significant excesses were found overall, in SBR workers or in non-SBR subjects, nor in a subgroup of ever-hourly workers. However, an excess of leukaemia cases was reported in the period pre-1980 (6 observed versus 3.0 expected for the total cohort; 6 observed/2.9 expected for ever-hourly workers).

Following the initial publication of this study, a further analysis of the exposure data which had been derived for six of the eight plants was performed, because of concerns that in the original analysis there may have been some misclassification of exposures (Macaluso et al., 2000). This reanalysis is unpublished, although the full report has been made available to the rapporteur. The analysis was based on a detailed review of operations and the prevailing conditions at the time of exposure (such as the ventilation systems in place, layout of the plant, air flow in open or semi-open buildings). The information was used to develop exposure models, which were used to determine 8-hour TWA exposures for butadiene, styrene and DMDTC, and peak exposures for butadiene ($\geq$ 100 ppm) and styrene ($\geq$ 50 ppm); peak exposures were analysed in terms of number of peaks and cumulative exposure above and below the peak value. The revised exposure assessment found that the exposure estimates originally derived were likely to have underestimated exposures to butadiene and styrene. Based on these revised exposure estimates, the relationship between exposure to butadiene, styrene and DMDTC and lymphohematopoietic cancers was (re)investigated.

The analysis using the revised exposure estimates included 13 130 of the original 17,964 eligible workers at the eight SBR plants. As before, inadequate information was available for two of the plants to allow a reliable estimate of exposure to be derived and therefore all eligible workers (1,354) from these two plants were excluded. Additional exclusions were made on the basis of duplicate records (12) or because subjects had died or were lost to follow-up before reaching 40 years old or more than 10 years since hire. The re-evaluation did not include exposure to benzene, as exposures were low and there was no association with lymphohematopoietic cancer in the previous analyses. Relative rates (RRs) were determined by regression analysis, for exposed workers compared with unexposed or low exposed workers. Account was taken of exposure level, age and years since hire. Vital status was determined for $\geq$ 99% of the cohort and information from death certificates and from medical records where available, was used to confirm cause of death from lymphohematopoietic cancer. Of all lymphohematopoietic cancer deaths, 59 were leukaemia, 38 were non-Hodgkin's lymphoma (NHL), 21 were multiple myeloma and 9 were Hodgkin's disease.

Exposures to the three substances were highly correlated. The proportion of the total workforce exposed to butadiene was 79%; 85% of all workers were exposed to styrene; and 62% to DMDTC. The median cumulative exposures for all workers were 71 ppm-years for butadiene and 17 ppm-years for styrene; exposure to DMDTC was by the dermal route only, and cumulative exposure was estimated to be 374 mg-years.cm^{-1}. For all decedents, median cumulative exposures were 90 ppm-years for butadiene, 18 ppm-years for styrene and 836 mg-years.cm^{-1} for DMDTC. Compared with all decedents, leukaemia and NHL decedents had higher median exposures to butadiene, styrene and DMDTC: by 2.3-fold, 2.2-fold and 2.6-fold respectively for leukaemia decedents and by 1.5-fold, 2-fold and 1.3-fold respectively for NHL decedents. Multiple myeloma and Hodgkin's disease decedents had generally similar or lower butadiene, styrene and DMDTC exposures compared with all decedents.

Regression analysis indicated a positive association between cumulative exposure to butadiene and leukaemia. Exposure categories were selected on the basis of tertiles among leukaemia decedents. RRs (adjusted for age and years since hire) were 1.0, 1.2, 2.0 and 3.8 for butadiene exposures of 0, >0-<86.3, 86.3-<362.2 and $\geq$362.2 ppm-years, respectively. A positive association with leukaemia was also found for cumulative exposure to styrene, with adjusted RRs of 1.0, 1.2, 2.3 and 3.2 for exposures to 0, >0-<20.6, 20.6-<60.4 and $\geq$60.4 ppm-years, respectively. In each case, the RRs reached statistical significance only for the highest exposure category. For DMDTC exposure, there was no clear exposure-related trend, with RRs of 1.0, 2.3, 4.9 and 2.9 for exposures to 0, >0-<566.6, 566.6-<1,395.1 and $\geq$1,395.1 mg-years.cm^{-1}, although the RR for each exposure category was statistically significantly increased.

Analyses performed in relation to peak exposures, controlling for age and years since hire, indicated that the total number of butadiene peaks (any exposure $\geq$100 ppm) and styrene peaks (any exposure $\geq$50 ppm) were positively associated with leukaemia.

The analyses were then performed for each exposure, adjusting for the other two exposures (in addition to adjustment for age and years since hire). For butadiene, after adjustment for exposure to styrene and DMDTC, a positive association between cumulative exposure and leukaemia remained, although the relationship was weak, and the RRs did not reach statistical significance; adjusted RRs of 1.0, 1.3, 1.3 and 2.3 were obtained for exposures to 0, >0-<86.3, 86.3-<362.2 and >362.2 ppm-years, respectively. No association between styrene exposure and leukaemia was found after adjustment for butadiene and DMDTC exposure. For DMDTC, although the RRs were elevated for all exposure categories, after adjustment for butadiene and styrene exposure there was no clear exposure-related trend and the RR reached statistical significance only in the intermediate exposure category (RRs of 1.0, 2.2, 4.1 and 2.1 for exposures to 0, >0-

<566.6, 566.6-<1,395.1 and ≥1,395.1 mg-years.cm^{-1}). Similar patterns were also obtained when these analyses were repeated using alternative exposure categories, based on quartiles or quintiles among leukaemia decedents.

When the number of peak exposures was considered, there were no clear exposure-related trends for any of the individual exposures after adjustment for the other two exposures, age and year since hire. However, there was a positive association with intensity of exposure and leukaemia. Thus, when cumulative butadiene exposures accrued by exposures above 100 ppm (ppm-years due to exposures ≥ 100 ppm) were considered, RRs of 1.0, 2.3, 2.2 and 4.3 were obtained for 0, >0-<46.5, 46.5-<234.3 and ≥234.3 ppm-years due to exposure intensities ≥ 100 ppm; only the RR for the highest exposure category reached statistical significance. The relationship was weak when cumulative exposures accrued by exposures < 100 ppm were considered. However, the relative contribution of exposures above and below 100 ppm could not be examined because of the absence of leukaemia decedents with cumulative exposures below 100 ppm and no or minimal contribution from exposures above 100 ppm.

Finally, to investigate any possible interaction between cumulative butadiene exposure and DMDTC exposure, an analysis was performed to look at the relationship between leukaemia and exposure to both butadiene and DMDTC. Three exposure categories were defined for each substance, based on the quintiles of the exposed decedents (the lowest exposure category comprised the unexposed and lowest quintile of exposed; the middle exposure category was the second and third quintiles combined; the highest exposure category was the fourth and fifth quintiles combined). There was a high correlation between butadiene and DMDTC exposure, thus there were limited numbers of subjects with exposure to butadiene but low DMDTC exposure and vice versa, which limited the power of the analysis to separate out the effect of each exposure. This analysis indicated increasing RRs with increasing cumulative exposure to both butadiene and DMDTC, with no clear association between leukaemia and cumulative butadiene exposure amongst workers who had the lowest DMDTC exposure (RRs 1.0, 0.7, 1.2 for cumulative butadiene exposures of 0-<38.7, 38.7-<287.3 and ≥287.3 ppm-years respectively and exposure to 0-<342.4 mg-years.cm^{-1} DMDTC). Statistically significantly elevated RRs were obtained for leukaemia decedents with medium or high exposure to butadiene (38.7->287.3 ppm-years or ≥ 287.3 ppm-years) and medium or high cumulative exposure to DMDTC. For the category with the highest butadiene and highest DMDTC exposures (butadiene ≥ 287.3 ppm-years and DMDTC ≥ 1222.6 mg-years.cm^{-1}), the RR was statistically significantly elevated to 4.4.

No meaningful analyses could be performed based on sub-groups of leukaemia, because of the small numbers involved.

Overall, this large cohort-mortality study shows a clear excess of leukaemia among workers in the styrene-butadiene rubber industry. Detailed analyses of exposures to butadiene, styrene and DMDTC, based on exposure estimates using job-exposure matrices, are available. There is a high correlation between exposures to the three substances and this makes it difficult to clearly separate out any effect of each individual substance. However, overall, the evidence suggests that exposure to styrene is not associated with the leukaemia excess. A positive association between exposure to butadiene and leukaemia was consistently found, even after correction for the other two exposures, although the association was weakened by this adjustment. There is also some indication that exposure to butadiene at levels ≥ 100 ppm may be of greater importance in the development of leukaemia than exposures below 100 ppm. However, uncertainties in the estimates of peak exposure and the limited numbers of subjects with no peak exposures preclude a definitive conclusion. The results also suggest that leukaemia rates were highest in subjects with the highest exposures to both butadiene and DMDTC. This raises the possibility that

exposure to DMDTC may be a confounding factor in the SBR industry. However, exposures to butadiene and DMDTC were highly correlated, making it difficult to separate the contribution of each individual exposure. Although a positive correlation was consistently found between exposure to DMDTC and leukaemia, there was no evidence for a dose-response relationship and there is no evidence currently available in animals or humans that exposure to DMDTC causes leukaemia.

While this exposure analysis provides the most useful exposure assessment to date in relation to carcinogenicity in humans, and provides some indication of a dose-response in relation to leukaemia mortality, the exposure data are not considered sufficiently robust to use as a reliable basis for determination of a dose-response relationship for carcinogenicity. In addition, whilst there is some indication that exposures accrued by exposure to butadiene peaks may be important in the development of leukaemia, there is insufficient data to clarify this, nor to exclude the possibility that non-peak exposures may also be of concern. Therefore, while this study demonstrates clear evidence for carcinogenicity in humans, associated with exposure to butadiene, and raises the possibility that a theoretical threshold for the excess risk of cancer may exist, no reliable conclusion can be reached in relation to the quantitative dose-response relationship for this effect.

The combined data from three previously reported of the cohort mortality studies described above (Divine, 1990; Matanoski et al., 1990; Meinhardt et al., 1982) was evaluated to assess the overall evidence for a link between butadiene exposure and the occurrence of lympho-hematopoietic cancers (Cole et al., 1993). This combined cohort included 17,448 male workers in the butadiene manufacturing and styrene-butadiene rubber industries. In the overall population, there were no statistically significant excesses of any cancers of the lymphohematopoietic system (SMR = 108, 95% CI: 87-133, 91 deaths). Specifically, the SMR for leukaemia was 105 (95% CI: 74-146, 36 deaths) and for lymphosarcoma SMR = 112 (95% CI: 68-173, 20 deaths). All other lymphohematopoietic cancers had an SMR of 109 (95% CI: 76-151, 35 deaths). There is no evidence from this combined cohort for an association between exposure in these industries and occurrence of lymphohematopoietic cancers.

In a mortality study at one tyre-manufacturing plant in Akron, Ohio, at which SBR manufacture was one of a range of processes, all 6,678 male workers and retirees aged 40 or over on 1 January 1964 were entered into the study (McMichael et al., 1974, 1975, 1976). A total of 1,783 deaths were recorded, all those occurring between 1964 and 1973; death certificates for all but nine were obtained, classified in accordance with ICD8 and compared with age-specific US national mortality data.

The number of deaths from all causes was similar to that expected (SMR = 99). However, among specific cancer types, there was a statistically significant excess mortality due to lymphosarcoma (SMR = 226, 95% CI: 124-379, 14 deaths), cancer of the stomach (SMR = 187, 95% CI: 133-256, 39 deaths) and cancer of the prostate (SMR = 142, 95% CI: 105-188, 49 deaths). Deaths among those aged 40-64 were also analysed separately. The number of deaths from all causes was similar to that expected (SMR = 93), but there was statistically significantly elevated mortality from leukaemia (SMR = 315, 95% CI: 157-564, 11 deaths) and cancer of the stomach (SMR = 219, 95% CI: 113-382, 12 deaths), with an excess of lymphosarcoma also seen, although this did not reach statistical significance (SMR = 251, 95% CI: 92-546, 6 deaths). Further analysis showed that an employment record including at least 5 years in the synthetic plant (where predominantly butadiene-styrene rubber was manufactured) was 5.6 times as common among decedents from lymphatic and haemopoietic cancer than in a representative sample of about one quarter of the workforce.

This study appears to show an excess of lymphohematopoietic cancers among workers, with evidence of an association between leukaemia and lymphosarcoma and exposure to styrene-butadiene in an older subgroup of the population.

Other investigators have also reported an increase in deaths from leukaemia in workers in the rubber tyre industry at Akron, Ohio (Andjelkovic et al., 1976, 1977; Monson and Nakano, 1976). Although butadiene was used in these plants, it is not possible to identify butadiene as the causative agent.

The importance of exposure to several chemicals, including butadiene, in contributing to deaths from angiosarcoma of the liver among workers at a vinyl chloride polymerisation plant has been investigated by applying a serially additive exposure dose model (Smith et al., 1980; Waxweiller, 1981). No association was found between butadiene exposure and mortality from angiosarcoma. However, insufficient information was given on the source of the data for the result to be evaluated properly.

Case-control studies

The cohort from eight SBR facilities reported in a mortality study in the previous section (Matanoski et al., 1990) was investigated further in a nested case-control study (Santos-Burgoa et al., 1992). This study considered specifically the association between exposure to butadiene and/or styrene and the incidence of lymphohematopoietic cancer. A total of 59 cases were identified from the cohort, with cause of death from lymphohematopoietic cancer confirmed from death certificates. A total of 193 controls were selected from workers in the cohort who were alive or who had died from causes other than cancer and who had survived at least as long as the case. Controls and cases were matched for age, year of first employment, duration of employment and plant. Job history was defined for each subject and an exposure estimate was made by a panel of 4 chemical engineers with practical experience of the industry, and an environmental engineer. This ranked jobs according to the extent of exposure to butadiene, styrene and to other potentially toxic chemicals. However, as exposure to other chemicals was a rare event, these exposures were considered negligible. Ranked exposures to styrene and butadiene were given a score of 1-10 with 10 representing the highest exposure, and an exposure index was calculated as the product of the exposure score for each job held and number of months spent in that job. Each matched case-control set was classified to two exposure classes according to whether the case exposure score was greater or less than the geometric mean of the exposure scores of the controls. Odds ratios (OR) were calculated for all lymphohematopoietic cancers and for four lymphohematopoietic cancer subgroups.

Of the 59 cases, there were 6 lymphosarcomas, 8 Hodgkin's disease, 26 leukaemias and 18 other lymphatic neoplasms. On the basis of the exposure indices, cases of leukaemia had considerably higher scores for butadiene and styrene exposure than did controls, or the other cancer subgroups. Odds ratios were calculated for workers ever/never exposed to butadiene and styrene, in an unmatched analysis. Only in the case of leukaemia was there a significant increase in the OR for both butadiene (6.82, 95% CI: 1.10-42.2) and styrene (4.25, 95% CI: 1.02-17.8). Analysis of the matched pairs using the dichotomised exposure scores resulted in an increase in the OR for butadiene (OR = 9.36, 95% CI: 2.05-22.9), whereas the OR for styrene was reduced by this method and was no longer statistically significant. The only other association that reached statistical significance was between butadiene exposure and risk of all lymphohematopoietic cancers (OR = 2.3, 95% CI: 1.13-4.71).

Conditional logistic regression models were used to calculate the odds ratios for exposure to butadiene adjusted for styrene exposure as a confounding variable. Separate exposures to either

butadiene or styrene occurred infrequently, so that the reliability of such an analysis is reduced. However, for all lymphohematopoietic cancers, the odds ratio for butadiene exposure alone was 2.42 (95% CI: 1.12-5.23). A very strong association was found between exposure to butadiene alone and cases of leukaemia (OR = 7.61, 95% CI: 1.62-35.6, $p<0.002$). In comparison, the OR for styrene exposure alone was not statistically significantly increased for any cancer category.

Overall, this study demonstrates a strong association between exposure to butadiene and incidence of lymphohematopoietic cancer, particularly leukaemia. This association is increased when the potential effect of co-exposure to styrene is taken into account and therefore strongly implicates butadiene as the chemical of concern. Exposure to styrene alone was not associated with any significant excess cancer risk.

A re-analysis of this data was conducted in order to address the possibility that effects in the most highly exposed workers were underestimated because of inclusion of large numbers of unexposed workers in the overall cohort (Matanoski et al., 1993). It was noted that for most areas of the plant, the range of exposures included zero exposure, so that effects on workers with high exposures could potentially be diluted by inclusion of workers with little or no exposure. In addition, measured butadiene exposure data from some of the plants were compared with the rank exposure scores used in the model and a reasonable correlation was found. The same cohort was used in this analysis, and again, conditional logistic regression models were used to calculate odds ratios for butadiene exposure adjusted for different confounding variables. Specific work areas were defined and data on each area were evaluated separately to establish any differences between cases and controls. It was found that there was an excess risk for leukaemia associated with 3 particular work areas, operation services, laboratory and utility. In these 3 areas, jointly referred to as mixed jobs, the OR for leukaemia was 3.8 (CI: 95% 1.2-11.9). In a joint model, which included factors for mixed jobs and butadiene, both factors were statistically significant (mixed jobs OR = 13.3, 95% CI: 2.2-78.5; butadiene OR = 3.8, 95% CI: 1.2-11.9). Thus, the two factors appear to be independent correlates of risk.

Since it is possible that the elevated OR for leukaemia is a reflection of incorrect classification of jobs with butadiene exposure, a new model was constructed with butadiene exposure included as a continuous variable. In this model, the OR for area of work adjusted for butadiene exposure was no longer significant (OR = 5.6, 95% CI 0.5-18.1) while that for butadiene exposure adjusted for job area remained statistically significant (OR = 1.5, 95% CI: 1.1-2.0). Thus there appears to be an independent effect of butadiene exposure but no independent effect of job area, on the risk for leukaemia. The authors also considered separately the mortality data for 3 of the 8 plants, which were found to have higher measured butadiene levels than the others. A cohort of 3,429 workers hired before 1960 and with $\geq$10 years of employment was identified. Cohort analysis of mortality for these workers showed a significantly elevated excess of all lymphohematopoietic cancers (SMR = 1.63, 95% CI: 1.13-2.27, 34 deaths), and in particular excesses of leukaemia and aleukaemia (SMR = 1.81, 95% CI: 1.01-2.99, 15 deaths). Although elevated SMRs were observed for other lymphohematopoietic cancer subgroups, none were statistically significant. Overall, these data support the findings of the original case-control study and are suggestive that the lack of a statistically significant overall effect in that study could have been due to dilution of the exposed cohort by large numbers of unexposed workers.

Linet et al. (1987) report the results of a population-based case-control study which looked for a possible link between cases of chronic lymphocytic leukaemia (CLL) and lifetime occupation. Cases of CLL in the Baltimore area of the US were identified from hospital records. A total of 342 cases were included in the study. Control cases were chosen from the same hospitals and matched for age, race, sex and year of discharge, with a diagnosis other than cancer. A lifetime occupational history was obtained for each subject in the study, with specific details obtained

about occupational exposures associated with CLL, including the rubber manufacturing industry. Two different methods were then used to link exposure with occupation.

There was no evidence for an association between occupation in the rubber manufacturing industry and incidence of CLL. Workers in the rubber manufacturing industry accounted for 1.8% of cases and 2.1% of controls, giving a matched relative odds ratio of 0.85 (95% CI: 0.28-2.55). There was no association between exposure to butadiene specifically and cases of CLL. However, there are a number of difficulties with this type of study, which reduce the power of the study to identify statistically significant associations. These include small study size, errors in reporting and low prevalence of the occupations of interest in the population under study, as well as possible inaccuracies in the methods used to link exposures with occupation and the choice of a single type of leukaemia which may not be associated with butadiene exposure while other types are. Overall therefore, although no statistically significant association was found between CLL and exposure to butadiene or employment in the rubber manufacturing industry, it is not considered to be reliable evidence for an absence of carcinogenicity.

There was no clear evidence of an excess of lymphohematopoietic cancers in association with butadiene exposure in a study of workers employed at three chemical plants in the US (Ott et al., 1989). This nested case-control study was initiated after an excess of lymphohematopoietic cancer mortality was revealed in a cohort study at these facilities (Rinsky et al., 1988). A smaller sub-set of this cohort was subsequently studied by Ward et al., 1995, 1996b, who found a statistically significantly elevated incidence of lymphosarcoma and reticulosarcoma among a cohort of workers exposed to butadiene. These two cohort mortality studies have been described in the section on butadiene manufacturing facilities, above. A large number of chemicals was used within the sites and the study attempted to relate cancer incidence to work area or to specific chemicals or chemical groups. The study evaluated the incidence of four subcategories of lymphohematopoietic cancers, identified as being of interest from the results of the study by Rinsky et al. (1988)- non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukaemia and non-lymphocytic leukaemia. The cases were taken from the original study cohort of 29,139 male employees. Cause of death was identified from death certificates. Controls were randomly selected and matched for decade of first employment and survival time. Workers were excluded from the study if the time of death was less than five years after first exposure, since the authors considered it unlikely that in these cases death would be related to exposure. Exposure information was based on work category. Crude odds ratios were calculated for a number of chemicals considered to be potentially associated with carcinogenicity and for each cancer category.

For butadiene, the odds ratios for associations between each disease category and exposure were 0.7 for non-Hodgkin's lymphoma (based on 3 cases); 1.4 for both multiple myeloma and nonlymphocytic leukaemia (each based on 3 cases); and 1.5 for lymphocytic leukaemia (2 cases). Given the very small number of cases, it is not possible to draw any firm conclusions from these data.

4.1.2.8.3 Summary of carcinogenicity

In relation to investigations in experimental animals, the carcinogenicity of butadiene has been studied in rats and mice. There is a marked species difference in the susceptibility of rodents to the carcinogenic properties of butadiene. In the mouse, butadiene is a potent, multi-organ carcinogen. The carcinogenic response is typified by early onset of tumours and the development of rare tumour types. Tumour development occurs at relatively low exposure concentrations and is also seen following a relatively short exposure to higher butadiene concentrations. All the

evidence indicates that a genotoxic mechanism is involved. In comparison, in the rat, the one available study shows a lower tumour frequency, fewer tumour types, mainly of a benign nature, with effects seen at exposure concentrations 2-3 orders of magnitude higher than in the mouse. The tumour type in the rat suggests that hormonal influences may play a role in the carcinogenic response, and thus a non-genotoxic mechanism may underlie the tumour formation in this species.

It is not possible to evaluate the carcinogenic potential of the metabolite epoxybutene from the information available. Skin-painting experiments with mice have shown diepoxybutane to be carcinogenic.

It is apparent from the animal data that there is a marked species difference in carcinogenicity and in the mechanism which underlies the carcinogenic response. In relation to human health hazard, there are insufficient mechanistic data to exclude the possibility that butadiene has the potential to be carcinogenic in humans. Information from toxicokinetic studies indicate that in rodents and in humans, butadiene is metabolised to the reactive epoxide metabolite, epoxybutene. In addition, the metabolite diepoxybutane is detectable in the mouse and rat. Both metabolites are mutagenic in animal assays. Overall, on the basis of the available evidence, it is considered that butadiene has the potential to form genotoxic metabolites and therefore to act as a genotoxic carcinogen in humans.

A number of major epidemiological studies have been conducted with workers from the butadiene manufacturing and styrene-butadiene rubber industries. The largest of these, conducted among styrene-butadiene rubber workers in the USA and Canada, demonstrates a clear excess of mortality from leukaemia, which is associated with occupational exposure to butadiene monomer. The excess is concentrated among workers with the potential for highest cumulative exposures to butadiene, with long duration of employment and long time since hire. In addition, there is some indication that exposures accrued due to peaks (defined as $\geq$ 100 ppm) are more important in the development of leukaemia than exposures below 100 ppm. However, there are insufficient data to confirm this, nor to exclude the possibility that non-peak exposures may also be of concern. There was no evidence that exposure to styrene was related to the finding of excess leukaemia. A nested case-control study of workers in the SBR industry also found an association between butadiene exposure and the incidence of lymphohematopoietic cancer, particularly leukaemia.

The results of studies in workers in the butadiene monomer industry indicate a small, but statistically significant excess of lymphohematopoietic cancers among workers exposed to butadiene alone, from two independent cohort mortality studies. The evidence from these studies indicates that in the butadiene manufacturing industry, although the excess of these cancers is greater among workers estimated to have the highest butadiene exposures, there is no clear association with cumulative butadiene exposure. Overall, in the butadiene manufacturing industry, the pattern of results does not clearly indicate an association between butadiene exposure and excess cancer mortality, nor is there any clear evidence for excess leukaemia mortality, as in the SBR industry. However, it must be noted that the cohorts studied in the butadiene monomer industry are considerably smaller than those investigated in the SBR industry and thus have a lower statistical power to detect any excess cancer mortality risk; nor are quantitative exposure data available for these studies.

Although a number of studies have also been reported in which no excess of cancers attributable to butadiene exposure were observed, these do not provide sufficient evidence that butadiene has not caused cancer in exposed workers.

Overall therefore, a clear association between butadiene exposure and leukaemia in humans has been demonstrated from one large, good quality cohort-mortality study. It is concluded on the basis of this evidence, that butadiene should be regarded as carcinogenic in humans.

Although the most recent study has undertaken a sophisticated occupational exposure modelling assessment, based on expert judgement of historical exposure conditions, overall these modelled data cannot be viewed as of sufficient reliability on which to base an estimate of the dose-response relationship for the carcinogenic effect. However, some authors have derived an estimate of human cancer risk on the basis of the exposure data from this most recent study (Environment Canada/Health Canada, 2000; Stayner et al., 2000). In both analyses, the authors used a variety of models to derive human cancer risk estimates. The range of risk estimates were found to be generally comparable with risk estimates derived on the basis of the rodent carcinogenicity data. However, it should be noted that the human cancer risk estimates were based on the original exposure analysis for the epidemiological study, and do not take account of the revised exposure estimates. The extent and quality of exposure data from other studies are limited. Overall, therefore, it is not possible to offer a reliable estimate of the dose-response relationship for the carcinogenic effect in humans.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Effects on fertility

There are no adequate studies which assess the effect of butadiene on fertility. An early study is available but was poorly reported and used small numbers of animals (Carpenter et al., 1944). Rats, guinea pigs and rabbits were exposed to 0, 600, 2,300 or 6,700 ppm butadiene, 7.5 hours/day, 6 days/weeks for 8 months. In rats, the number of litters per female was reported to be slightly reduced in the exposed groups but because of inadequacies in the study, no conclusions can be drawn from these data.

No effect on fertility has been seen in three dominant lethal studies in mice, reported in the section on mutagenicity. In the first of these studies, groups of 20 males were exposed to 0, 200, 1,000 or 5,000 ppm butadiene 6 hours/day for 5 days and then mated with unexposed females (Hackett et al., 1988b, summarised by Morissey et al., 1990). There was an indication from effects seen in the first 2 weeks post-exposure that butadiene may result in damage to the more mature sperm cells, spermatozoa and spermatids. However, the results were not conclusive.

Similarly, no evidence for an effect on fertility was seen in a second dominant lethal study in mice, in which animals were exposed to butadiene either as a single exposure or in a repeated exposure regime (Anderson et al., 1993). In the single exposure protocol, groups of 25 male mice were exposed to 0 or 1,250 ppm while 50 male mice were exposed to 6,250 ppm butadiene for 6 hours. Animals were mated with unexposed females 5 days post-exposure. In the repeated exposure method, 25 males were exposed to 0 or 12.5 ppm while 50 mice were exposed to 1,250 ppm butadiene, 6 hours/day, 5 days/week for 10 weeks and then mated immediately with unexposed females.

In the third study, conducted in (102/E1xC3H/E1)F1 mice, groups of 20 males were exposed to 0 or 1,300 ppm butadiene 6 hours/day for 5 days (Adler et al., 1994). At 4 hours after the last

exposure each male was mated with pairs of unexposed females for a period of 4 weeks. There was no evidence to indicate an effect of exposure on fertility.

Developmental studies

The developmental toxicity of butadiene has been investigated in mice and rats by the NTP. An overview of the studies is provided by Morissey et al. (1990).

Groups of 31-33 pregnant Swiss CD-1 mice and 30 pregnant Sprague-Dawley rats were exposed to 0, 40, 200 or 1,000 ppm butadiene for 6 hours/day on days 6-15 of gestation (Hackett et al., 1987a,b). Mice were sacrificed on day 18 of gestation and rats on day 20. Implantation sites were recorded. Live fetuses were weighed and gross, visceral and skeletal examination made.

Maternal toxicity was elicited at the highest exposure level in rats, observed as a statistically significant, 31% reduction in bodyweight gain during gestation. Exposure to butadiene had no effect on developmental parameters at any exposure concentration. In the mouse study, a statistically significant reduction in maternal bodyweight gain during gestation was seen at 200 ppm (14% reduction) and 1,000 ppm (20% reduction). Fetal weight was statistically significantly lower at 200 ppm (16% less than control) and 1,000 ppm (22% less than control). There were no statistically significant increases in percentage resorptions or malformations per litter although there was a slight, statistically significant increase in minor skeletal abnormalities at 200 and/or 1,000 ppm, indicative of growth retardation (supernumerary ribs, reduced sternebral ossification and misaligned, scrambled or cleft sternebrae). These studies demonstrate that butadiene is not a developmental toxicant to the rat following inhalation exposure. However, in the mouse, butadiene appears to have a minor effect on development, with retardation in fetal bodyweight and skeletal development seen at 200 and 1,000 ppm, concentrations which also produced evidence of maternal toxicity.

In a study conducted on behalf of the IISRP, female rats were exposed to 0, 200, 1,000 or 8,000 ppm for 6 hours/day on days 6-15 of gestation and sacrificed on day 20 (Irvine, 1981). There were 40 negative controls, 24 females in each test group and 26 females in a positive control group dosed with aspirin. There was a statistically significant concentration-related reduction (14-45%) in maternal bodyweight gain at all exposure levels. There was a marginal concentration-related lowering of fetal weight and size (crown/rump length) which reached statistical significance at 8,000 ppm (mean fetal weight 6% less than control; crown/rump length 5% less than control). It was noted that the values of these parameters were low in all groups, compared with historical controls. Statistically significantly increased incidences of marked and severe forms of wavy ribs, irregular rib ossification and incomplete ossification were noted at 8,000 ppm. These effects are considered to be indicative of delayed development. There was a statistically significantly increased incidence of bipartite thoracic centra in all exposure groups. An appropriate response was seen in the positive control group. This study demonstrates that butadiene has a minor effect on fetal development at concentrations which are toxic to the dam. These effects can be attributed to delayed development, secondary to maternal toxicity and are therefore of low concern for human health.

Other studies

A sperm-head morphology assay was conducted in mice (Hackett et al., 1988a). Details of the study are provided by Morissey et al. (1990). Groups of 20 male mice were exposed to 0, 200, 1,000 or 5,000 ppm butadiene 6 hours/day for 5 days and sacrificed in the fifth week post-exposure. Mice were examined for lesions of the reproductive tract and for gross tissue abnormalities. At least 500 sperm heads per mouse were examined for morphological

abnormalities. Transient signs of toxicity, piloerection and dyspnea, were observed immediately following exposure to 5,000 ppm butadiene, but there were no mortalities and no effect on bodyweight in any groups compared with control. There was a concentration- related increase in the percentage of abnormal sperm in exposed mice, with an increase of 21% in abnormal sperm at 200 ppm, 73% at 1,000 ppm and 129% at 5,000 ppm, relative to controls. The increases at 1,000 and 5,000 ppm were statistically significant.

Information on the effects of butadiene on reproductive organs is available from NTP and IISRP toxicity and carcinogenicity studies (Maronpot, 1987). In one NTP study, ovarian atrophy, hyperplasia and neoplasia in female mice and testicular atrophy in male mice were reported following exposure to 625 or 1,250 ppm butadiene for 60-61 weeks (Huff et al., 1985). A NOAEL for these effects was not identified from this study. In the second NTP bioassay, mice were exposed to 0, 6.25, 20, 62.5, 200 or 625 ppm butadiene 6 hours/day, 5 days/week for up to 2 years (NTP, 1993). Interim sacrifices of 10 animals per sex per group were performed at 9 and 15 months, except at 625 ppm, when the reduction in survival was such that 2-8 animals were examined. In females, a statistically significantly increased incidence of ovarian atrophy was seen at 200 and 625 ppm at the 9-month sacrifice and at 62.5 ppm and above at the 15-month interim sacrifice. After 2 years, the incidence of ovarian atrophy showed a dose-related statistically significantly increase in all exposure groups, from 6.25 ppm upwards and it was reported that affected females had no evidence of oocytes, follicles or corpora lutea. After 2 years, the incidence of ovarian atrophy was 4/49 in controls compared with 19/49, 32/48, 42/50, 43/50 and 69/79 at 6.25, 20, 62.5, 200 and 625 ppm butadiene respectively. Uterine atrophy also occurred with increased incidence at 200 and 625 ppm, compared with controls, at 9 and 15 months and after 2 years of exposure. The incidence at 2 years was 1/50 in controls, compared with 8/50 and 41/78 at 200 and 625 ppm respectively. In males, there was an increased incidence of testicular atrophy at 625 ppm exposure groups at both the 9 and 15-month interim sacrifices and at 2 years. At 2 years the incidence was 53/72 compared with 1/50 in controls. In view of the reduction in survival in both sexes at 20 ppm and above and the severity of the neoplastic response in both sexes at 20 ppm and above and also in females at 6.25 ppm, it is possible that the gonadal effects seen in this study are a secondary consequence of severe generalised toxicity, rather than a direct effect of butadiene on the reproductive system. No significant ovarian effects were seen in females following either 15 days or 14 weeks of exposure to 625, 1,250, 2,500, 5,000 or 8,000 ppm butadiene (Maronpot, 1987). Leydig cell tumours were observed in the IISRP bioassay in rats, at 1,000 and 8,000 ppm (Owen, 1981; Owen and Glaister, 1990; Owen et al., 1987).

4.1.2.9.2 Studies in humans

No data are available.

4.1.2.9.3 Summary of toxicity for reproduction

There are no adequate fertility studies available for butadiene. However, no evidence for an adverse effect on male fertility was seen in three dominant lethal assays in the mouse. In developmental studies in the rat and mouse, butadiene caused developmental toxicity, manifested as a retardation in fetal development. However, these effects were seen at concentrations which resulted in significant maternal toxicity and are considered to be secondary to the effect on the dam. The data do not indicate specific toxicity to the reproductive system. The available evidence suggests that these effects on development are of low concern for human health.

Butadiene has an adverse effect on the germ cells in mice, with a dose-related increase in abnormal sperm morphology following exposure of males to 200-5,000 ppm and positive results in three dominant lethal assays in the mouse. The results of long-term toxicity and carcinogenicity studies indicate that the ovaries and testes are a target organ for butadiene toxicity in mice, with the testes also a target organ in the rat. A dose-related increase in the incidence of ovarian atrophy occurred in mice exposed to 6.25 ppm and above for 2 years in one study, while testicular atrophy developed in mice after exposure to 625 ppm butadiene for 9 months. In male rats, Leydig cell tumours were seen following chronic 2-year exposure to 1,000 and 8,000 ppm butadiene. In view of the severity of effects on survival and tumour development in the mouse studies, from 6.25 ppm and above in females, and 20 ppm and above in males, it is not clear whether or not the effects on the gonads are a direct effect on fertility or a secondary consequence of the severe generalised systemic toxicity. Overall, there is no clear evidence for a direct effect of butadiene on fertility, in the absence of severe systemic toxicity.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Butadiene is absorbed via the lungs in humans and animals and this is considered to be the main route of exposure and uptake. There are no data in relation to the potential for absorption via the oral and dermal routes of exposure. However, given the physicochemical properties of butadiene, it is considered unlikely that significant uptake via these two routes would occur. Once absorbed, butadiene is widely distributed throughout the body. The first step in the metabolic pathway is the formation of epoxybutene. Further metabolism of epoxybutene can proceed by a number of different pathways, with possible conjugation with glutathione, hydrolysis to butenediol, or further epoxidation to diepoxybutane. Further epoxidation and/or hydrolysis reactions can then take place, ultimately leading to erythritol formation. CO_2 is also produced at some stage during metabolism. The main route of elimination of butadiene and its metabolites in rodents and primates is urinary excretion or exhalation in the breath. Minor faecal excretion also occurs.

Assessment of the available animal and human toxicology data indicates that butadiene is of low acute toxicity in animals and in humans. There is no evidence that butadiene is irritant to the skin. Eye irritation is reported in humans only at very high exposure concentrations. Butadiene is not corrosive to the skin or eyes. Although there are no data on skin or respiratory sensitisation to butadiene in animals or in humans, it is significant that no such effects have been reported in humans and overall, it is considered that butadiene would not have the potential to cause sensitisation in humans. There is very little useful information on the health effects in humans of repeated exposure to butadiene, although no excesses of morbidity nor haematological changes were observed in workers employed for a minimum of 5 years, exposed to an estimated 8-hour TWA concentration of 3.5 ppm butadiene, in one modern study. However, it is noted that this study was limited in terms of cohort size and availability of exposure data for the period of the study. Butadiene has been well investigated for repeated dose toxicity in rats and mice, and the evidence from these studies shows marked species differences. Butadiene is generally of low toxicity following repeated exposure in rats, with some evidence of toxicity occurring at 8,000 ppm following 2-years of exposure. In contrast, in mice increased mortality occurs in both sexes at 20 ppm and above, and tumour development and ovarian toxicity also occurs in females at 6.25 ppm, the lowest exposure concentration tested. Limited information suggests that butadiene is also of low toxicity in several other animal species (guinea-pig, rabbit, dog) and supports the conclusion that the mouse is particularly susceptible to butadiene-induced toxicity. Consideration

of the available human data, although limited in terms of well-documented information on exposure levels, indicates that humans are not as susceptible as mice to the effects of repeated exposure to butadiene.

In experimental studies, butadiene and its two epoxide metabolites, epoxybutene and diepoxybutane, are mutagenic *in vitro* and in somatic cells and germ cells *in vivo*. The *in vivo* mutagenicity data indicate that butadiene is mutagenic in somatic and germ cells in the mouse but not in the rat, while epoxybutene and diepoxybutane are mutagenic in somatic cells in the mouse, rat and/or hamster *in vivo* and in the germ cells of mice and rats *in vivo*. In addition, the results of rodent bioassays demonstrate butadiene to be a potent multi-site carcinogen in the mouse. The tumour profile in this species suggests that a genotoxic mechanism is involved. The carcinogenic response in the rat is somewhat different; in this species the tumour profile suggests that a non-genotoxic mechanism may underlie the response, and tumour formation occurs at much higher dose levels than in the mouse. Diepoxybutane has been shown to be carcinogenic in the mouse; no studies in the rat are available. The data for epoxybutene are of insufficient quality to assess the carcinogenic potential of this metabolite in animals. Overall, therefore, the lead health effects of concern for butadiene are mutagenicity and carcinogenicity. Butadiene is a genotoxic carcinogen in at least one rodent species, the mouse. This effect may be mediated by the production of reactive epoxide metabolites.

There is evidence for species differences in the toxicology of butadiene and therefore the relevance of the animal data for human health requires particular consideration. Studies on the toxicokinetics of butadiene have demonstrated quantitative species differences. The mouse absorbs and retains approximately 4 to 7-fold higher concentrations of butadiene per kg bodyweight than the rat and also produces around 2 to 20-fold higher concentrations of epoxybutene than the rat, for equivalent exposures. Although detectable blood levels of the metabolite diepoxybutane have been found in both the mouse and rat, the evidence suggests that diepoxybutane levels in the mouse exceed those in the rat, by up to about 160-fold in some tissues, for equivalent butadiene exposure concentrations. The known quantitative species differences in the metabolism of butadiene may explain in part the very marked difference in toxicity of butadiene between rats and mice.

In humans, evidence from a limited number of studies indicates that butadiene is metabolised to epoxybutene with subsequent hydrolysis to butenediol. There are no data on the formation of diepoxybutane in humans *in vivo*. *In vitro* studies indicate that human liver, lung and bone marrow can metabolise butadiene to epoxybutene. The only study which investigated the ability of human liver and lung tissue to metabolise epoxybutene to the diepoxide, found no detectable levels of diepoxybutane. However, *in vitro* studies have also demonstrated considerable inter-individual variation in the capacity of human liver tissue to metabolise butadiene to epoxybutene *in vitro* and the available *in vitro* data raise the possibility that some humans may be quantitatively comparable to the mouse in the production of epoxybutene. The involvement of specific P450 isozymes in metabolism of butadiene to the monoepoxide has been demonstrated, and raises the possibility that differences in expression of P450 isozymes may explain some of the inter-individual variability which has been seen in human tissue *in vitro*.

There are data available in relation to the mutagenicity of butadiene in humans and a number of epidemiology studies which investigate carcinogenicity in workers exposed to butadiene. Although the mutagenicity data do not allow a firm conclusion to be drawn, there are at least some suggestions that butadiene may be mutagenic in humans, at exposure concentrations of the order of 0.3 – 1 ppm (8-hour TWA). There is clear evidence from one recent, large epidemiology study in SBR workers, that occupational exposure to butadiene, but not styrene, is associated with an excess of leukaemia. Further analysis of the data from this study also raises the

possibility that peak exposures could be an important factor in relation to the excess of leukaemia. However, the data do not allow a clear distinction to be drawn between the relative importance of cumulative versus peak exposure as the critical factor. Among workers exposed to butadiene alone in the manufacturing industry, although an excess of lymphohematopoietic cancers has been found, where qualitative exposure estimates are available, the pattern of results does not clearly indicate an association between butadiene exposure and excess cancer mortality, nor is there any clear evidence for excess leukaemia mortality, as in the SBR industry. However, no quantitative exposure data are available and the cohorts studied in the butadiene monomer industry are considerably smaller than those investigated in the SBR industry, and thus have a lower statistical power to detect any excess cancer mortality risk.

Although the most recent study has undertaken a sophisticated occupational exposure modelling assessment, based on expert judgement of historical exposure conditions, overall these modelled data cannot be viewed as of sufficient reliability on which to base an estimate of the dose-response relationship for the carcinogenic effect. The extent and quality of exposure data from other studies are limited. Overall, therefore, and it is not possible to offer a reliable estimate of the dose-response relationship for the carcinogenic effect in humans.

There are no human data available in relation to reproductive parameters. In relation to animal reproductive toxicity data, there are no adequate fertility studies available, although no evidence for an adverse effect on male fertility was seen in three dominant lethal assays in the mouse. The results of long-term toxicity studies and bioassays in rodents suggest that the ovaries and/or testes are a target organ for butadiene toxicity. Ovarian atrophy was seen in a 2-year study in the mouse, at the lowest exposure concentration tested, 6.25 ppm, and uterine atrophy developed after 9 months exposure to 200 ppm and above. The effects on the ovary at 6.25 ppm were seen only towards the end of the 2-year exposure period, when there would be general senescence of the reproductive system. In mice sacrificed after 9 or 15 months of exposure to butadiene, NOAELs for ovarian atrophy were identified at 62.5 and 6.25 ppm respectively. Atrophy of the testes has been reported following exposure to 625 ppm and above, for several months. A NOAEL for testicular atrophy can be identified at 200 ppm for 2 years. However, it should be noted that other severe effects, including increased mortality rates and/or tumour development also occurred at the exposure levels causing gonadal atrophy in mice. When considering the implications of the butadiene-induced gonadal effects in mice for human health, it is noted that both the toxicokinetic and the epidemiological data suggest that quantitatively, humans are less susceptible than mice to the toxic effects of butadiene. There is no indication that humans respond in a manner which is quantitatively similar to the marked responses seen in mice, although it is acknowledged that reliable quantitative human exposure data in relation to the epidemiology studies are limited. In relation to effects on development, the results of developmental studies in the rat and mouse suggest that any effects are secondary to maternal toxicity and therefore are of lesser concern for human health.

Overall, the critical health concerns are for mutagenicity and carcinogenicity. There is clear evidence for carcinogenicity in butadiene-exposed workers, although the associated occupational exposure data are not of sufficient quality to allow a dose-response relationship for this effect to be identified, nor to identify a level of exposure at which there would be no excess risk of cancer. There are also data available which are suggestive of mutagenicity in humans at current occupational exposure levels. In addition, positive results have been obtained in animal studies for somatic and germ cell mutagenicity and carcinogenicity, for butadiene and/or its epoxide metabolites. It is therefore concluded that butadiene should be regarded as a potential genotoxic carcinogen in humans. It is not currently possible to identify a threshold for the mutagenic or carcinogenic effects of butadiene.

4.1.3.2 Workers

4.1.3.2.1 Introduction

The main route of occupational exposure to 1,3-butadiene, a gas, is by inhalation. The potential for oral or dermal exposure cannot be entirely excluded, but is considered to represent a very minor potential route of exposure.

Occupational exposure data obtained from companies across the EU indicate that the majority of personal 8-hour TWA airborne exposures to butadiene during monomer and polymer production are very low, with more than 90% of the data collected over the period 1984-1996 showing exposures in these industries to be below 5 ppm (8-hour TWA). In monomer production, 90% of exposures are below 1 ppm, with 70% of results in polymer production less than 1 ppm. Exposures in excess of 10 ppm (8-hour TWA) are likely to be rare, and will arise as a result of unplanned releases. There is the potential for short-term exposures of the order of about 30 – 70 ppm (15-minute reference period) to occur during certain specific operations, particularly during sampling and loading/unloading operations. Where there is the potential for high exposure, EU industry indicates that exposures can be adequately controlled with LEV, changes in work practices or the wearing of appropriate respiratory protective equipment during specific operations. Personal exposure in situations such as sampling and loading/unloading will be mitigated by the use of appropriate respiratory protective equipment.

The extent to which exposure during breaches of closed systems can be controlled during manufacture of the monomer and polymers, will depend on the technology adopted. For example, tanker filling could typically range from the use of traditional couplings (i.e. no dry-break connection) to the use of dry-break coupling systems, the latter providing a greater degree of control. Similarly for product sampling or maintenance there are a variety of different ways of carrying out the activity, each with a different exposure profile. The extent to which a manufacturer of the monomer or polymers can be considered to have reduced exposure as far as is reasonably practicable will depend on the extent to which high standards of control have been adopted. For carcinogens, best practice would be considered to include, as far as is reasonably practicable, the use of systems that minimise release of butadiene during a breach of the system, for example, dry-break coupling systems for tanker loading and off loading, or the use of closed or ventilated sampling points.

The concentration of butadiene in end-use products is low. Therefore, airborne exposure during the handling and use of such products will be minimal, with the majority of exposures below the limit of detection.

4.1.3.2.2 Comparison of exposure and effects

<u>Manufacture of monomer and production of polymer</u>

When considering the risks to human health arising from occupational exposure to butadiene, the key areas of concern are for mutagenicity and carcinogenicity. It is apparent from the animal data that there is a marked species difference in mutagenicity and carcinogenicity between rats and mice and in the mechanism that underlies the carcinogenic response in each species. Mice are clearly more susceptible to the toxicity of butadiene compared with rats. There is a relatively extensive human database for butadiene, which provides evidence of concern for both mutagenicity and carcinogenicity. It is clear from the available human data that neither the rat

nor the mouse is an appropriate animal model for use in quantitative comparisons between exposure levels and the levels at which the health effects of concern occur in animals, and therefore calculations of margins of safety based on animal data are not appropriate for butadiene. Overall, the available data do not allow the identification of a threshold level of exposure below which there would be no risk for the development of mutagenic or carcinogenic effects in humans. In view of this, there are potential health concerns at all exposure levels and consequently conclusion (iii) is reached. Although high standards of control are available in these industry sectors, representing best practice for a substance with these properties, there is no evidence that these standards are currently applied consistently across all EU industry. Thus, there is no evidence that the appropriate equipment is in place in all EU workplaces and that it is used and maintained in the correct manner. Therefore it is considered that risk reduction measures are required, and conclusion (iiib) applies.

The results of repeated exposure studies in animals reflect the marked species difference in the toxicological response to butadiene between rats and mice, referred to above. As before, it is clear from the available human data that neither species is an appropriate model for use in quantitative comparisons and thus the calculation of margins of safety is not appropriate. The mouse is the most susceptible species in relation to repeated exposure toxicity. However, no useful information on the dose-response relationship for non-neoplastic effects can be derived from the available long-term studies in this species, as tumour formation and tumour-related mortality dominated the response at all exposure levels in these studies (6.25 ppm and above). The only useful information in relation to repeated dose toxicity in the mouse comes from short-term repeated exposure studies, in which non-neoplastic effects of concern occur only at very high exposure concentrations, which are three orders of magnitude above contemporary occupational exposure levels (1-5 ppm). Overall, therefore, concerns for repeated exposure toxicity are overridden by the concerns for genotoxicity and carcinogenicity and conclusion (ii) is reached.

Although ovarian atrophy has also been identified in mice following long-term repeated exposure to concentrations as low as 6.25 ppm, the concentrations producing such damage also produced other severe signs of systemic toxicity in this species. As previously noted, mice appear to be particularly susceptible to butadiene-induced toxicity, and there are no indications that humans respond in a similar fashion to mice in quantitative terms. For testicular atrophy, a NOAEL of 200 ppm for 2 years has been identified in mice; this is two orders of magnitude above contemporary occupational exposure levels. Overall, it is considered that the risk of gonadal damage in workers exposed to butadiene under contemporary exposure conditions is extremely low and conclusion (ii) is reached for this endpoint.

In relation to irritation, slight irritation of the eyes, nose and mouth have been reported in humans exposed to very high concentrations of butadiene, of the order of thousands of ppm. This is two orders of magnitude higher than the peak exposures which occur in the occupational setting and thus there is negligible risk of local irritation effects under contemporary occupational exposure conditions. Conclusion (ii) is therefore reached for this endpoint.

Overall, **in view of the concerns for mutagenicity and carcinogenicity**, it is considered that conclusion (iiib) applies:

Conclusion (iiib) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.

For all other endpoints, conclusion (ii) applies:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4.1.3.3 Consumers

1,3-Butadiene is not supplied for use directly in consumer products. The only consumer exposure is to items manufactured from synthetic butadiene-based polymers, which may contain residual free monomer. There is the potential for exposure to any free monomer that is released from the polymer. In addition, adventitious sources of consumer exposure have been identified. Estimates of exposures arising from two of these adventitious sources – exposure from motor fuel vapour and from cigarette smoke – have been derived for information only, to provide a relevant context within which to consider the other sources of exposure included in this assessment. They are not included for the purposes of risk characterisation.

In this section, dose levels have been calculated per kg bodyweight, based on a 70 kg adult or a 14.5 kg toddler (aged 1.4-4.5 years), with 100% absorption of butadiene following both inhalation and oral exposure. Bodyweight values for adults and young children are based on UK data (HMSO, 1990, 1992, 1995)

By far the greatest source of consumer exposure to butadiene monomer is from cigarette smoke. The average yield of butadiene is 0.4 mg per cigarette. As a reasonable worst-case, someone who smokes 40 cigarettes per day will inhale 16 mg butadiene per day, equivalent to a dose of 0.23 mg/kg/day. In relation to passive smokers, it is predicted that a person in a smoke-filled room would inhale approximately 13 µg/hour of butadiene, equivalent to 0.19 µg/kg/hour, or a dose of 2.2 µg/kg/day if daily exposure is for 12 hours.

Exposure to butadiene may arise as a result of inhalation of petrol vapour during filling of a car fuel tank. This source is estimated to result in inhalation of butadiene of approximately 69 µg/event, equivalent to a dose of approximately 1 µg/kg/event.

Consumer exposure may occur as a result of release of free monomer from polymeric consumer products. The two main sources are from indoor air and from butadiene-based food packaging materials.

The only available measured data for the presence of monomer in indoor air suggest that indoor levels are generally below 2.2 $\mu g/m^3$ (equivalent to 0.001 ppm). If the average lung ventilation for an adult is assumed to be approximately 11.5 l/min, and exposure is assumed to last for 24 hours/day, this would equate to a daily dose of about 5×10^{-4} mg/kg/day (0.5 µg/kg/day). For a toddler, with a breathing rate of 3.5 l/min, the daily dose would be about $7 \cdot 10^{-4}$ mg/kg/day (0.7 µg/kg/day) for a 24-hour exposure.

The predicted reasonable worst-case oral intake as a result of free butadiene monomer leaching out of packaging into foodstuffs is 0.015 mg/day for an adult, equivalent to a dose of about $2.1 \cdot 10^{-4}$ mg/kg/day (0.2 µg/kg/day); and 0.017 mg/day for a toddler, equivalent to a dose of about $1.2 \cdot 10^{-3}$ mg/kg/day (1.2 µg/kg/day).

Although some consumer exposure could potentially arise as a result of thermal degradation of polymer, such exposure is predicted to be infrequent, with resultant exposures of the order of µg/m^3. There are no measured exposure data to confirm this prediction. Overall, exposure from this source is likely to be negligible, and will not be considered further.

The combined exposure from indoor air and leaching from packaging into foodstuffs amounts to a predicted reasonable worst-case dose of $7 \cdot 10^{-4}$ mg/kg/day (0.7 µg/kg/day) for an adult and $1.9 \cdot 10^{-3}$ mg/kg/day (1.9 µg/kg/day) for a toddler. If the contribution from cigarette smoke during passive smoking is included, the combined exposure for an adult could increase to 2.9 µg/kg/day. The additional exposure during filling of a petrol tank is 1 µg/kg/event. In comparison, the exposure due to cigarette smoking far exceeds the combined value, such that additional exposures are negligible in comparison with cigarette smoking.

Overall, excluding adventitious sources, consumer exposure to butadiene can potentially occur as a result of exposure to residual monomer in consumer products manufactured from synthetic butadiene-based polymers. The two main sources are from indoor air (primarily due to release from carpet backings) and from food packaging materials. The most recent information indicates that the release of free monomer from carpet backings is not detectable. The release of free monomer from food contact materials is currently regulated by Directive 90/128/EEC and amendments. This Directive stipulates that there should be no detectable migration of 1,3-butadiene into foods or food simulants, using an analytical method with a detection limit of 0.02 mg/kg (20 ppb).

In view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. For these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The level of risk to human health under current levels of consumer exposure in the EU is uncertain, but in view of the very low estimated exposure levels, it is predicted that there would be negligible residual risk.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

4.1.3.4 Humans exposed via the environment

The greatest predicted exposures to butadiene via the environment are from butadiene in air. Therefore, only airborne exposure estimates are considered in this part of the risk assessment. The local predicted environmental concentration ($PEC_{local(air)}$) is 222 µg/m^3 (0.1 ppm), due to release from butadiene plant. If a ventilation rate of 11.5 l/min is assumed, this exposure could lead to a daily dose of 0.05 mg/kg/day (70 kg person, 100% absorption). The predicted regional environmental concentration (PECregional) in air, from all known sources, is considerably lower, 1.5 µg/m^3 (0.00068 ppm). This exposure would give rise to a daily dose of $3.5 \cdot 10^{-4}$ mg/kg/day (0.35 µg/kg/day). While it is recognised that these exposures are based on model predictions (but from real emissions data), it is noted that some measured data are available from the US, and in general, the measured data support the model predictions.

In view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. In relation to these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The risks to human health under contemporary environmental exposure conditions in the EU are uncertain. However, given that the exposure levels are very low, it is concluded that there would be a negligible residual risk. Conclusion (iiia) is reached.

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

4.1.3.5 Combined exposure

Exposure to butadiene may reasonably be predicted to arise as a result of combined exposure from workplace, consumer and environmental sources. As an example someone who works in and lives locally to a butadiene plant, is a heavy smoker (40 cigarettes/day) and is exposed via indoor air and monomer leaching from packaging into foodstuffs, could have a very approximate combined exposure/intake (dose in brackets) of 12 – 60 mg/day (0.17 – 0.86 mg/kg/day) from an 8-hour shift in the workplace, 16 mg/day (0.23 mg/kg/day) from cigarettes, and between 7 µg/day (0.10 µg/kg/day) (exposure inside the home) and 2.45 mg/day (0.03 mg/kg/day) (exposure outside the home local to the factory). The in-home and outside-home figures are based upon a 16-hour day. If remote from local emissions, the environmental exposure is calculated to be 0.3 µg/kg/day. Clearly, the exact contribution from each source is almost impossible to state, depending upon a considerable range of local and individual factors. Equally clearly, for smokers, cigarettes make a major contribution to butadiene dose.

In relation to mutagenicity and carcinogenicity, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The risks to human health under conditions of combined exposure to butadiene are uncertain. Setting aside exposure from smoking, the combined exposure is dominated by the occupational exposure. Therefore, the conclusions reached for the occupational setting will apply.

Conclusion (iiib) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.

4.2 HUMAN HEALTH (PHYSICOCHEMICAL PROPERTIES)

There are hazards associated with the extremely low flash point, high vapour pressure and flammability of this substance. Butadiene has been classified as R12 extremely flammable and F+, extremely flammable (substances with a flash point less than 0°C). Butadiene has a flash point of –76°C and autoignition temperature of 420°C. It is noted that butadiene should be used stored, transported and handled under the correct conditions. Cylinders should be stored in dry, well-ventilated areas and the temperature should not be allowed to exceed 52 °C (125 °F), outside or detached storage is preferred, there should also be no sources of ignition in areas of storage or use. Butadiene is incompatible with oxidisers and should not be stored near compounds of this type. 1,3-Butadiene should be shipped and stored with an inhibitor/antioxidant to prevent polymerisation, with a recommended maximum storage time for inhibited product of 12 months. General warnings to this effect are recommended, and are currently in practice. If the appropriate handling and storage measures are applied, there are no concerns for risks to human health arising from the physicochemical properties and thus conclusion (ii) is reached.

Conclusion (ii) There is no need for further information and/or testing with regard to physicochemical properties.

5 RESULTS

There are 22 EU producers of 1,3-butadiene reported in IUCLID. The total production capacity reported is between 1,202,000 and 4,960,000 tonnes/year. Recent data shows that Western European 1,3-butadiene production was 1,742,000 tonnes/year in 1993 and 1,892,000 tonnes in 1994 (ECN, 1995).

Virtually all of this (96%) is used as a monomer in the manufacture of a variety of synthetic rubber and plastics, or as an intermediate in the production of several other compounds (4%).

5.1 ENVIRONMENT

5.1.1 Aquatic compartment

It is expected that any 1,3-butadiene present in surface water will volatilise rapidly. Therefore, even if 1,3-butadiene is released to surface water from point sources, the concentration would be expected to decrease markedly with increasing distance from the source. Thus, any potential problems are likely to be associated with the area immediately downstream of a point source discharge.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.2 Terrestrial compartment

There is no toxicity information available for terrestrial organisms exposed via soil. Given the physical properties of 1,3-butadiene, soil is not thought to be a significant route of exposure.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.3 Atmosphere

5.1.3.1 Plants

The risk to plants exposed to 1,3-butadiene via the atmosphere is small.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.3.2 Other effects

1,3-Butadiene may play a role in photochemical smog and low-level (tropospheric) ozone formation. A major source of atmospheric 1,3-butadiene is from vehicle exhausts. However, vehicles fitted with catalysts are thought to emit much less 1,3-butadiene than non-catalyst vehicles. Therefore, the increasing use of catalyst equipped vehicles in future will reduce these effects.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.1.4 Secondary poisoning

1,3-Butadiene has a low bioaccumulation potential and so is of low concern with regard to secondary poisoning. The main source of exposure of higher animals to 1,3-butadiene is likely to be via inhalation and the predicted levels of 1,3-butadiene at the regional level are unlikely to be of concern in this respect. The highest predicted local air concentrations provide a margin of safety of approximately 20 for effects seen towards the end of a 2-year study in the most sensitive mammalian species. Thus, 1,3-butadiene is unlikely to be of concern with regard to secondary poisoning.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

The main route of occupational exposure to 1,3-butadiene is by inhalation of the vapour. While the potential for oral and dermal exposure cannot be ruled out, this is considered to represent a very minor route of exposure, particularly if good occupational hygiene practice is assumed.

When considering the risks to human health arising from occupational exposure to butadiene during the manufacture of monomer and polymers, the key areas of concern are for mutagenicity and carcinogenicity. In relation to worker exposure, the available mutagenicity and carcinogenicity data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. In view of this, there are potential health concerns at all exposure levels and consequently conclusion (iii) is reached. Although high standards of control are available in these industry sectors, representing best practice for a substance with these properties, there is no evidence that these standards are currently applied consistently across all EU industry. Thus, there is no evidence that the appropriate equipment is in place in all EU workplaces and that it is used and maintained in the

correct manner. Therefore, it is considered that risk reduction measures are required, and conclusion (iiib) applies.

Result

Conclusion (iiib) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iiib) is reached for manufacture of butadiene monomer and for production of polymers, in view of the carcinogenic and genotoxic nature of 1,3-butadiene.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is reached for all occupational exposure scenarios for all other endpoints of potential concern.

5.2.1.2 Consumers

Although butadiene is not added to consumer products as such, consumer exposure arises as a result of cigarette smoking, including passive smoking, and exposure to residual monomer in products manufacture from synthetic polymers. The main source of consumer exposure is from cigarette smoke, and in comparison, exposure from synthetic polymer products is minimal and considered to be of very low concern. In view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. For these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. It is recognised that the highest potential exposure arises as a result of cigarette smoking, with the next highest exposures as a consequence of passive smoking. In relation to the contribution from these adventitious sources, the exposures arising as a result of potential release of monomeric 1,3-butadiene from consumer products give rise to very low doses. The risks to human health under current consumer exposure levels are uncertain, but in view of the very low estimated exposure levels, it is predicted that there would be negligible residual risk.

Result

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Estimations indicate that consumer exposure is very low. Although thresholds cannot be reliably identified, the risk of mutagenicity and/or carcinogenicity is considered to be very low.

5.2.1.3 Humans exposed via the environment

Indirect exposure to butadiene via the environment occurs mainly as a result of emissions to the air from butadiene plant. The other potential source of exposure is from vehicle exhaust

emissions. However, the latter exposures are low compared with the local exposures to the predicted airborne emissions from butadiene plant. However, in view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. In relation to these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The risks to human health under current environmental exposure levels are uncertain. However, given that the exposure levels are very low, it is concluded that there would be a negligible residual risk.

Result

Conclusion (iiia) Risks cannot be excluded for all other exposure scenarios, as the substance is identified as a non-threshold carcinogen. The adequacy of existing controls and the feasibility and practicability of further specific measures should be considered. However, the risk assessment indicates that risks are already low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Conclusion (iiia) is reached for all exposure scenarios because exposures are very low and although thresholds cannot be reliably identified, the risk of mutagenicity and/or carcinogenicity is considered to be very low.

5.2.1.4 Combined exposure

Accurate predictions of the contributions made by individual sources to combined exposure and dose are always imprecise. However, such exposures could occur, comprising the workplace, smoking, the local environment and consumer exposures from polymeric materials, with intermittent exposures derived from filling petrol tanks. In view of the very low exposure levels which occur, the only potential concern for health effects is for mutagenicity and carcinogenicity. In relation to these endpoints, the available data for butadiene do not allow the identification of a threshold level of exposure below which there would be no risk for the development of these effects. The risks to human health under current environmental exposure levels are uncertain. Setting aside exposure from smoking, the combined exposure is dominated by the occupational exposure. Therefore, the conclusions reached for the occupational setting will apply.

Result

Conclusion (iiib) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account.

5.2.2 Human health (risks from physicochemical properties)

There are no significant risks to humans from the physicochemical properties of butadiene.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ABS	Acrylonitrile-butadiebe-styrene copolymers
ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATBN	Amine-terminated acrylonitrile-butadiene polymers
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
CTBN	Carboxyl-terminated acrylonitrile-butadiene polymers
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon

DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
FTP	Federal Test Procedure
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission –Baltic Marine Environment Protection Commission
HFET	Highway Fuel Economy Test
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1,000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration

ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
LPG	Liquefied Petroleum Gas
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MBS	Methylmethacrylate-butadiene-styrene resins
MC	Main Category
MFTP	Modified Version of the Federal Test Procedure
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NBR	Nitrile-butyl rubber
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)

NYCC	New York City Cycle
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
PFI	Port Fuel Injection
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POCP	Photochemical Ozone Creation Potential
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SBR	Styrene-butadiene rubber
SBS	Styrene-butadiene triblock copolymer
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry

SML	Specific Migration Limit
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDDS	Urban Dynamometer Driving Schedule
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
XNBR	Carboxylated nitrile rubber
XSBR	Carboxylated styrene-butadiene copolymers

Annex A Quantitative risk assessment for 1,3-butadiene

A submission by the Netherlands and Norway

CA Name:	1,3-Butadiene
CAS No:	106-99-0
EINECS No:	203-450-8
EU classification:	Carcinogenicity Category 1, mutagenicity Category 2
Conversion:	1 ppm = 2.21 mg/m^3
	CH_2=CH-CH=CH_2
	C_4H_6 Mol.weight: 54.1

Exposure levels and route of exposure

Human exposure for butadiene according to the Risk Assessment of Butadiene (February 2001). Only exposure by inhalation is considered in the quantitative risk assessment. Dermal route of exposure is also relevant for workers.

Workers:*

Monomer production 5 ppm = (5 x 2.21 x 13.9/70) Inhalation 2.2 mg/kg/d

It is stated in monomer production, 90% of exposures are below 1 ppm.

*"Light work" used in calculation. The inhalation volume for light work: 13.9 m^3 /8h (default)

Consumers:

Combined exposure from indoor air and leaching from packaging into foodstuffs (worst case) $7x10^{-4}$ mg/kg/d.

[Exposure to adventitious sources:
petrol filling: $1x10^{-3}$ mg/kg/event, equivalent 2.8×10^{-4} mg/kg/d assuming 2 events/week
passive smoking: 2.2×10^{-3} mg/kg/d
smoking: 0.23 – 0.46 mg/kg/d]

Man via environment:

Environmental level (local): 0.05 mg/kg/day.
Environmental level (regional): 3.5 x 10-4 mg/kg/day.

Effective dose level in humans.

The Canadian Environmental Protection Act (1) and Stayner and coworkers (2) have recently calculated cancer potency estimates for 1,3-butadiene on the basis of epidemiological studies conducted by Delzell and coworkers (the references are cited in refs 1 and 2). The epidemiological study included 17,964 men employed for at least 1 year between 1943 and 1991 at 8 North American plants that made styrene-butadiene rubber and 48 deaths due to leukaemia. Different functional forms for the relationship between the relative rate and measures of exposure were evaluated. The square root model was identified as the "best model". However,

the difference in deviance between the various models was slight (171.5 for the square root model compared to 174.7 for the linear model). Fig 1 shows the observed rate ratios and fitted curves for leukaemia. It is apparent that the observed rate ratios deviate considerably from the curves. Since the variations in the data are not indicated, it is difficult to assess the uncertainties in the lifetime risk levels.

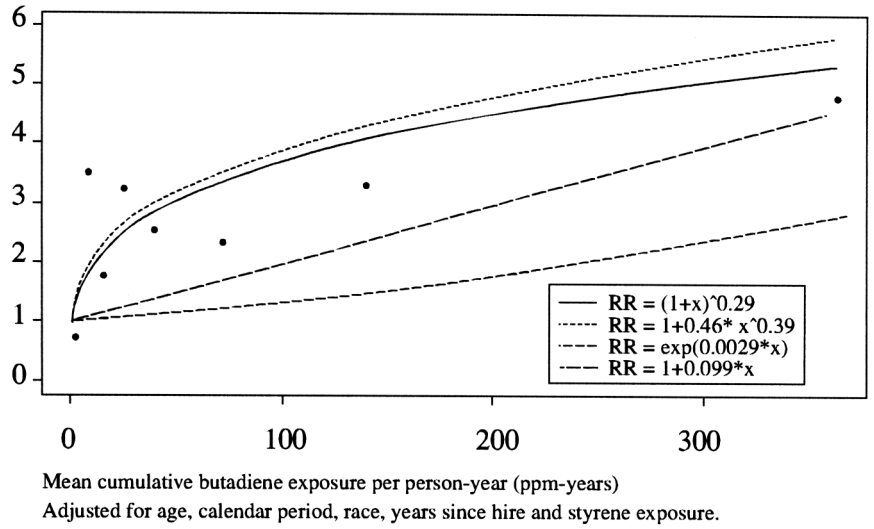

Fig 1. Observed rate ratios and fitted curves for leukemia in Delzell et al. (3) study. Taken from ref 1.

TC_{01} (concentration in mg/m^3 for lifetime exposure associated with an 1% increase in mortality due to leukaemia) was calculated for occupational exposure on the basis of observed rate ratios and estimated cumulative exposure. The results for the square root and linear approximation are shown in **Table A**.1 for exposure levels of 5 ppm and 0.5 ppm 1,3-butadiene.

Table A.1 Carcinogenic potency estimates.

Model	Occupational TC_{01} (mg/m^3)	Lifetime risk level at 5 ppm	Lifetime risk level at 0.5 ppm
Square root	7.8 (8.8)	$1.5x10^{-2}$ ($1.3x10^{-2}$)	$4.8x10^{-3}$ ($4.3x10^{-3}$)
Linear	13.8 (15.5)	$0.85x10^{-2}$ ($0.76x10^{-2}$)	$0.56x10^{-3}$ ($0.50x10^{-3}$)

The number in parenthesis represents the data recalculated according to defaults values used in the EU (occupational exposure 40 yrs versus 45 yrs) (Data taken from (1 and 2)

Since the square root model represent a supralinear dose response curve, it follows that the ratio between risk levels calculated by the square root model and the linear model increases at lower doses as is apparent from the table. Thus, while the ratio is only 1.8 at 5 ppm it is 8.6 at 0.5 ppm. Since the parameters for calculation of the risk levels at the much lower environmental exposure are not easily available from the two publications, the epidemiological data has not been used for calculation of the risks for consumers and man exposed via the environment.

Effective dose level in animals.

Butadiene has been studied in long-term experiments with mice and rats. The studies will be briefly summarised below.

MICE: B6C3F1 mice (4) were exposed to 6.25 to 625 ppm butadiene in air for 6 hours per day on five days per week for 2 years. Results for the two lowest doses used are shown in **Table A.2**.

Table A.2 Tumour frequency in mice after inhalation exposure for 1,3-butadiene for up to 2 years.

Tumour type	0 ppm		6.25 ppm		20 ppm	
	Males	Females	Males	Females	Males	Females
Alveolar/bron-chiolar adenoma or carcinoma	22/70 (31%)	4/70 (6%)	23/60 (38%)	15/60* (25%)	20/60 (33%)	19/60* (32%)
Lymphoma, all malignant	4/70 (6%)	10/70 (14%)	3/70 (4%)	14/70 (20%)	8/70 (11%)	18/49* (26%)
Haemangiosarcoma, heart	0/70 (0%)	0/70 (0%)	0/70 (0%)	0/70 (0%)	1/70 (1%)	0/70 (0%)
Papilloma or carcinoma of the fore-stomach	1/70 (1%)	2/70 (3%)	0/70 (0%)	2/70 (3%)	1/70 (1%)	3/70 (4%)

P<0.01, Fisher's Exact Test

Remarks on study:

species, strain: mouse, B6C3F1
route: inhalation
tumour: various tumours (lymphoid tissue, lung), lung (alveolar and bronchial) tumours chosen for calculation.

Lowest dose with a significant increased tumour incidence.

females, lung tumours at 6.25 ppm:
Control: 4/70 (6%)
6.25 ppm: 15/60 (25%)
net%: $[15 \cdot (100/60) - 4 \cdot (100/70)]/[100 - 4 \cdot (100/70)] = 20\%$

Daily dose per mouse during the exposure period.

6 hours · inhalation volume · mg 1,3-butadiene/m^3 · (5/7) (for 7 days a week)
6h · 2.5 l/h (def.) · 6.25 · 2.21 · 1/1,000 · (5/7) = 0.148 mg/mouse/day.

Daily dose per kg bodyweight during the exposure period.

Bodyweight is specified: . 39 gram
i.e. 1,000/39 · 0.148 = 3.8 mg butadiene/kg bodyweight per day.

T25 after 24 months.

T25 = 25/20 x 3.8 mg/kg/day = 4.8 mg/kg/day.

HT25 dose descriptor for human based on the mice study is: 4.8 mg/kg/d

RATS: Sprague Dawley female rats (the study was carried out at Hazleton Lab and has not been published, reported in ref 5) were exposed to 0, 1,000 or 8,000 ppm 1,3-butadiene in air for 6 hours per day on five days per week for 2 years. The treatment induced tumours both in male and female rats. The incidences of carcinomas in the mammary gland were 8/100 (8%) in the control females and in 42/100 (42%) of the low-dose females.

Remarks on study:

species, strain: rat, Sprague-Dawley (Charles River CD)
route: inhalation
tumour: mammary tumours

Lowest dose with a significant increased tumour-incidence.

females, mammary tumours at 1,000 ppm:
Control: 8/100 (8%)
1,000 ppm: 42/100 (42%)
net %: (42 - 8)/(100 - 8) = 37%

Daily dose per rat during the exposure period.

6 hours · inhalation volume · mg 1,3-butadiene/m^3 · (5/7) (for 7 days a week)
6h · 15.7 l/h (def.) · 2.21 · (5/7) = 148.7 mg/rat/day.

Daily dose per kg bodyweight during the exposure period.

Bodyweight is not specified: Mean bodyweight low-dose females = 350 gram (def.),
i.e. 1,000/350 · 148.7 = 424.9 mg butadiene/kg bodyweight per day.

T25 after 24 months.

T25 = 25/37 · 424.9 mg/kg/day = 287 mg/kg/day.

HT25 dose descriptor for human based on the rat study is: *287 mg/kg/d*

Elements that may influence the calculated lifetime cancer risks

Data-sets available:	One data-set from mice and one from rats available.
Epidemiological studies:	A clear association between butadiene exposure and leukaemia in humans has been demonstrated.
Dose-response relationships:	----
Site/species/strain/gender activity:	Tumour at different sites in both male and females rats and mice.
Mechanistic relevance to humans:	---
Toxicokinetics:	---
Other elements:	The potency of butadiene to induce tumours in mice and rats differ significantly. Risk assessments have been carried out on the basis of the mice study, as mice are the most sensitive species.

Lifetime increased cancer risk levels

*Workers:**

HT25: 4.8 mg/kg/d
Exposure level 5 ppm: 2.2 mg/kg/d
Lifetime cancer risk level: ([2.2/2.8]/[(4.8/0.25]) $\boldsymbol{4.1 \cdot 10^{-2}}$
Lifetime cancer risk level based on epidemiological studies $\mathbf{1.3 \cdot 10^{-2}}$ (from **Table A.1**)

Exposure level 0.5 ppm: 0.22 mg/kg/d
Lifetime cancer risk level: ([0.22/2.8]/[4.8/0.25]) $\boldsymbol{4.1 \cdot 10^{-3}}$
Lifetime cancer risk level based on epidemiological studies $\mathbf{4.3 \cdot 10^{-3}}$ (from **Table A.1**)

*Calculation based on the higher exposure scenario given (5 ppm). It is stated earlier that the exposures are in most cases less than 1 ppm, hence risk estimate for 0.5 ppm has been included.

Consumers:

HT25: 4.8 mg/kg/d
Exposure level: $7 \cdot 10^{-4}$ mg/kg bw/d
Lifetime cancer risk level: ($7 \cdot 10^{-4}$ /[(4.8/0.25]) $\boldsymbol{3.6 \cdot 10^{-5}}$

[Lifetime cancer risk level for adventitious sources

petrol filling:	$2.8 \cdot 10^{-4}$ mg/kg/d	($2.8 \cdot 10^{-4}$/[4.8/025])	$\boldsymbol{1.5 \cdot 10^{-5}}$
passive smoking:	$2.2 \cdot 10^{-3}$ mg/kg/d	($2.2 \cdot 10^{-3}$/[4.8/0.25])	$\boldsymbol{1.1 \cdot 10^{-4}}$
smoking:	0.23 – 0.46 mg/kg/d	(0.24-0.46/4.8/0.25])	$\boldsymbol{1.3\text{-}2.4 \cdot 10^{-2}}$

Humans exposed via environment

HT25:	4.8 (mice), 287 (rat) mg/kg bw/d	
Exposure level (local):	0.05 mg/kg/d	
Lifetime cancer risk level:	(0.05/[4.8/0.25])	$\boldsymbol{2.6 \cdot 10^{-3}}$
Exposure level (regional):	$3.5 \cdot 10^{-4}$ mg/kg bw/d	
Lifetime cancer risk level:	($3.5 \cdot 10^{-4}$ /[4.8/0.25])	$\boldsymbol{1.8 \cdot 10^{-5}}$

Comments: The potency of butadiene to induce tumours in mice and rats differ significantly. Risk assessments have been estimated from the mice study since mice is the most sensitive species. Quantitative risk estimates based on an epidemiological study have been published. The authors concluded that the data fits best to a supralinear dose response curve. If these data is used, the risk estimates based on mice are for an occupational exposure of 5 ppm about 3 times greater than based on the epidemiological study, while at 0.5 ppm the risk estimates are similar. If the epidemiological date is fitted to a linear dose response curve, the risk estimates from the mice study are about 7 times greater than from the epidemiological study. It is likely that the actual human risks are not greater than the risks based on the mice study.

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Annex B Possible confounding factors in the aetiology of leukaemias in styrene-butadiene rubber industry workers

A submission by industry

A large, well-conducted retrospective study of workers in the US SBR industry has demonstrated a correlation between butadiene exposure and incidence of leukaemia mortality (Delzell et al., 1995; Macaluso et al., 1996.) However, leukaemia deaths were not increased among 1,3-butadiene monomer production workers who are exposed to butadiene but not other chemicals present in SBR production (Cowles et al., 1994; Divine and Hartman, 1996; Ward et al., 1996).

There are plausible explanations for this divergence in the epidemiology database. Firstly, differences in the size of the cohorts studied in the SBR and monomer industries may affect their statistical power, and hence sensitivity to changes in the incidence of cancer mortality. Secondly, exposures (either peak or time-weighted) to butadiene are believed to have been higher in the SBR industry, compared to the monomer production industry, although there is no reliable exposure data from the early years to either confirm this or establish the extent of any difference. Finally, the potential for confounding exposures is greater in the SBR industry than during monomer production, and hence it is plausible that SBR leukaemia may be related to exposure other than to butadiene alone (either exposure to other agents together with butadiene, or to other agents alone but exposure to which correlates with that of butadiene.)

The aspects of cohort size and exposure to butadiene are addressed elsewhere in the review of the epidemiology data.

Confounding exposures in the SBR industry

SMRs for leukaemia in SBR workers increased with latency and duration of employment (all ever hourly workers SMR=143; 95% CI=104-191, ever hourly workers with 10+ years worked and 20+ years since hire SMR=224; 95% CI=149-323; Delzell et al. 1996, 1995). Regression analyses suggest a dose-response relationship between cumulative butadiene exposure and leukaemia (for exposures less than 80 ppm-yr the RR was approximately 2, and over 80 ppm-yr the RR rose to 4.5). The majority of the leukaemia excess occurred among workers hired in the period 1950-1959, with no increased risk for workers hired before 1950 (Delzell et al. 1995, 1996; Macaluso et al., 1996).

In the 1950s, the process technology used in the production of SBR was changed. Prior to this time, SBR was manufactured using a hot emulsion/persulphate process. By 1952, this was largely replaced by a cold emulsion/redox polymerisation technique that used dimethyl dithiocarbamate (DMDTC) as a reaction stopping agent. The use of DMDTC in the US rubber industry was for the most part phased out around 1965 due to concerns over emissions of carbon disulphide. Revised personal protection in the early 1970s essentially prevented exposure where DMDTC was still in use for specialised purposes. Irons and Pyatt (1998) have observed that leukaemia risk in the study of Delzell et al. (1995, 1996) not only correlates temporally with the use of DMDTC in the SBR industry, but also with the opportunity for exposure to DMDTC during SBR production (i.e. polymerisation, coagulation, maintenance and laboratory activities).

Biological fate and interactions of dithiocarbamates

Dithiocarbamates (DTCs) represent a class of thiono-sulphur compounds which are chemically related to the thiurams (thiuram disulphides are the oxidised form of the DTCs). These

compounds have complex biological properties, including inhibition of several enzymes, toxicity to the haematopoietic and immune systems, and mutagenicity.

Interaction of dithiocarbamates with metabolism

DTCs and thiurams are potent inhibitors of cytochrome P450 2E1 and aldehyde dehydrogenase (tetraethylthiuram disulphide, or Antabuse, which is the dimer of diethyldithiocarbamate, has been used in the behavioural treatment of alcoholism and exerts its action through the inhibtion of aldehyde metabolism and clearance). DMDTC may interact with the metabolism of butadiene in a number of ways, and the most obvious possibility is for it to inhibit the oxidation of butadiene to the toxic mono- and diepoxides (Irons and Pyatt, 1998).

However, 3-butenal and crotonaldehyde have been identified as minor metabolites of butadiene by mouse liver microsomes and human myeloperoxidase (Deuscher and Elfarra, 1992, 1993; Elfarra et al., 1991; Sharer et al., 1992). Therefore, an alternative possibility is that DMDTC may inhibit the further metabolism of these intermediates. In fact, DMDTC has recently been shown to increase the level of aldehyde substances in the livers of B6C3F1 mice exposed to butadiene monoepoxide, possibly as a result of inhibiting the further metabolism of butadiene-derived aldehydes. This elevation of protein carbonyls did not occur with either the epoxide or DMDTC alone, indicating modulation of butadiene metabolism by DMDTC (Witz, 1998).

Mutagenicity

DMDTC is the structural basis of two DTC fungicides, thiram and ziram (DMDTC disulphide and zinc complex respectively), which have been evaluated for mutagenic potential *in vitro* and *in vivo*. Both compounds caused an increase in revertants of *Salmonella typhimurium* (strains TA1535 and TA100) and *Escherichia coli* (strain WP2*uvrA*), in the presence and absence of a metabolic activation fraction (Crebelli et al., 1992; Hedenstedt et al., 1979).

In one micronucleus study, both DMDTC disulphide (12.5-50 mg/kg, i.p.) and zinc DMDTC (2.5-10 mg/kg i.p. in males, 5-20 mg/kg i.p. in females) caused a significant decrease in the incidence of polychromatic erythrocytes (PCEs) in the bone marrow of male and female B6C3F1 mice after 48 hours at the highest dose. However, only the disulphide caused a significant increase in micronucleated polychromatic erythrocytes, and only in males at 25, 37.5 and 50 mg/kg. Zinc DMDTC was tested at lower doses than the disulphide, due to its greater acute toxicity, and at these doses did not increase the incidence of micronuclei (Crebelli et al., 1992). However, in another study, zinc DMDTC (350-1050 mg/kg p.o., administered as two doses 24 hours apart) significantly increased micronuclei in the bone marrow of male Swiss albino mice (Hemavathy and Krishnamurthy, 1988).

Further evidence of DMDTC activity in the bone marrow was reported recently in a study into the interaction of butadiene and DMDTC in male and female B6C3F1 mice. DMDTC (sodium salt, 300 mg/kg, p.c.), both alone and in conjunction with butadiene, increased the incidence of PCEs in the bone marrow and blood, whereas butadiene alone was without effect. Butadiene increased the incidence of micronucleated PCEs in the bone marrow and blood, whereas DMDTC alone was without effect. However, when DMDTC was administered prior to butadiene exposure, the incidence of micronuclei was lower than that induced by butadiene alone (ECC, 1998). This study indicates that DMDTC is absorbed through the skin and affects the bone marrow, as well as interacting systemically with butadiene.

The variance in results from micronucleus assays may lie in the different protocols used (e.g. strain of mouse, route of exposure (oral, dermal, intraperitoneal), form of DMDTC (disulphide,

zinc complex, sodium salt)). However, it does appear that DMDTC is toxic to the mouse bone marrow and, under appropriate conditions, mutagenic also.

Immunotoxicity

T lymphocyte maturation, signalling and activation is mediated by nuclear factor kB (NF-κB), which is a member of the Rel family of transcription factors. Disassociation of NF-κB from its inhibitory protein and translocation to the cell nucleus activates a number of genes, including interleukin-2, involved in immune function and inflammation.

DMDTC disrupts intercellular signalling between primary human $CD4^+$ T lymphocytes *in vitro*, as evidenced by inhibition of TNF-α-mediated NF-κB activation (Pyatt et al., 1998). Studies with butadiene mono- and diepoxides showed them not to inhibit T lymphocyte activation (Irons and Pyatt, 1998.)

Exposure to DMDTC in the SBR industry

There are no quantitative exposure data for exposure to DMDTC in the SBR industry. However, there is circumstantial evidence suggesting that opportunities for exposure did exist.

Some experimental work conducted into the biological fate of DMDTC *in vivo* has used the dermal route of exposure, and shows that DMDTC is systemically available following exposure via the skin (ECC, 1998). As such, exposure may result from manual handling of DMDTC, or polymerisation products containing residual DMDTC, as well as by inhalation (Irons and Pyatt, 1998).

Exposure to DMDTC might occur during the unloading of DMDTC on receipt at the plant, or during processing or analysis of SBR polymer. Particular opportunities for exposure include polymerisation, coagulation and maintenance activities, and in the laboratory. There is also anecdotal evidence that systemic exposure to DMDTC did occur in the SBR industry. Occupational exposure to DMDTC was associated with alcohol intolerance in SBR workers, and DMDTC, structurally related to the drug disulfirm (Antabuse), is a potent aldehyde dehydrogenase inhibitor (Irons and Pyatt, 1998).

Summary

DMDTC has been shown to modify the metabolism of butadiene *in vivo*, changing the path or rate of metabolism from that which would be favoured in its absence. Furthermore, DMDTC (or structurally-related compounds) has been shown to be active within the target tissues for suspected leukaemogenic effects.

The use of DMDTC coincided temporally with the induction of leukaemia in SBR workers, and occupations with the greatest opportunity for exposure to DMDTC are the same as those which demonstrate the highest risk of leukaemia in the study of Delzell et al. (1995, 1996). Therefore, it is plausible that butadiene may not be the (sole) causative agent in the aetiology of leukaemia found in studies of SBR workers. The use of DMDTC coincided temporally with the induction of leukaemia in SBR workers, and this agent may modify the toxicokinetics or toxicodynamics of butadiene and its metabolites in the body.

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European Commission

EUR 20420 EN **European Union Risk Assessment Report**
1,3-butadiene, Volume 20

Editors: B.G. Hansen, S.J. Munn, M.Luotamo, C. Musset, J. de Bruijn, S. Pakalin
F. Berthault, S. Vegro, G. Pellegrini, R. Allanou, S. Scheer.

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Environment and quality of life series

The report provides the comprehensive risk assessment of the substance 1,3-butadiene. It has been prepared by the UK in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for 1,3-butadiene concludes that there is at present concern for workers. For consumers and human exposed via the environment the risk assessment concludes that a risk cannot be excluded as the substance is identified as a non-threshold carcinogen. The risks though are low and this should be taken into account when considering the feasibility and practicability of further specific risk reduction measures. The risk assessment for the environment concludes that there is at present no concern for the atmosphere, aquatic ecosystem, terrestrial ecosystem or for microorganisms in the sewage treatment plant from sources of 1,3-butadiene covered by Regulation 793/93.

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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

1,3-butadiene

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