IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT

N° 30

1,3-Butadiene: Human Health Aspects

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

WORLD HEALTH ORGANIZATION

Concise International Chemical Assessment Document 30

1,3-BUTADIENE: HUMAN HEALTH ASPECTS

First draft prepared by K. Hughes, M.E. Meek, M. Walker, and R. Beauchamp,
Health Canada, Ottawa, Canada

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

World Health Organization
Geneva, 2001

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

1,3-Butadiene : human health aspects.

(Concise international chemical assessment document ; 30)

1.Butadienes - toxicity 2.Risk assessment 3.Environmental exposure
4.Occupational exposure I.International Programme on Chemical Safety
II.Series

ISBN 92 4 153030 8 (NLM Classification: QD 305.H7)
ISSN 1020-6167

The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

TABLE OF CONTENTS

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based tolerable intakes and guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

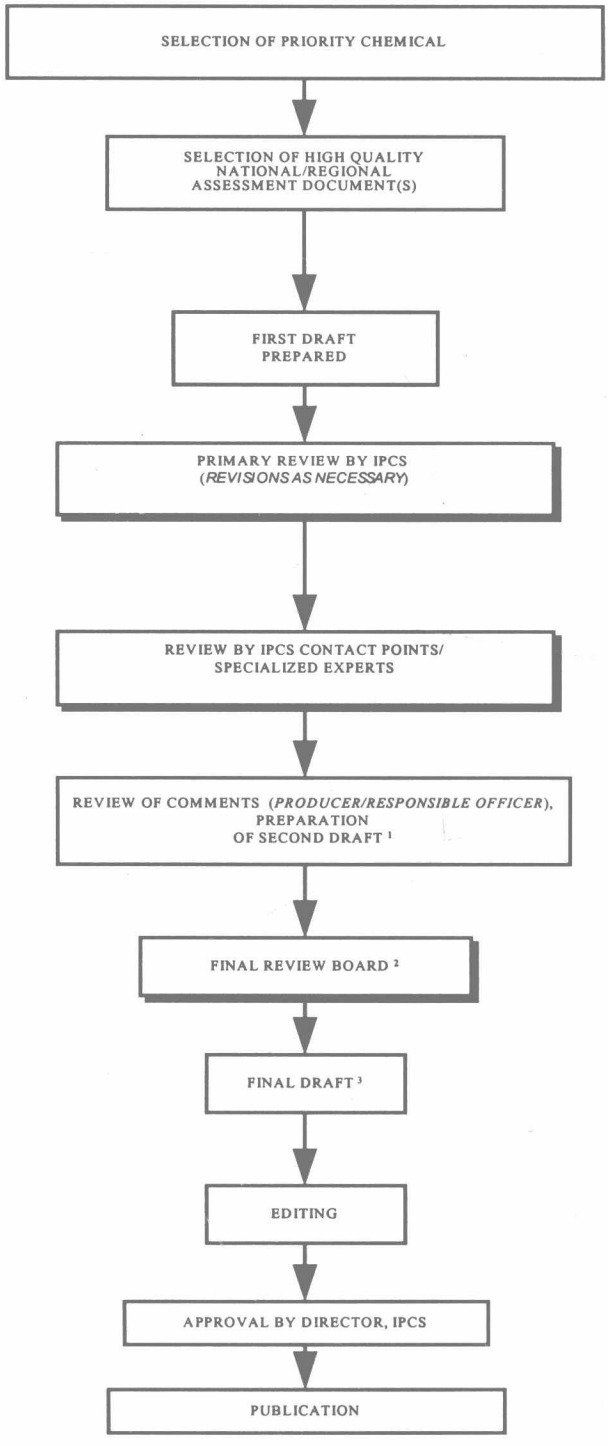
The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, whether a CICAD or an EHC is produced, and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents in order to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

is submitted to a Final Review Board together with the reviewers' comments.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on 1,3-butadiene was prepared by the Environmental Health Directorate of Health Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of health assessments on Priority Substances under CEPA is to assess the potential effects of indirect exposure in the general environment on human health. Data identified as of the end of April 1998 were considered in this review. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Helsinki, Finland, on 26–29 June 2000. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0017) for 1,3-butadiene, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

1,3-Butadiene (CAS No. 106-99-0) is a product of incomplete combustion resulting from natural processes and human activity. It is also an industrial chemical used primarily in the production of polymers, including polybutadiene, styrene-butadiene rubbers and lattices, and nitrile-butadiene rubbers. 1,3-Butadiene enters the environment from exhaust emissions from gasoline- and diesel-powered vehicles, from non-transportation fuel combustion, from biomass combustion, and from industrial on-site uses.

While 1,3-butadiene is not persistent, it is ubiquitous in the urban environment because of its widespread combustion sources. The highest atmospheric concentrations have been measured in air in cities and close to industrial sources.

The general population is exposed to 1,3-butadiene primarily through ambient and indoor air. In comparison, other media, including food and drinking-water, contribute negligibly to exposure to 1,3-butadiene. Tobacco smoke may contribute significant amounts of 1,3-butadiene.

Metabolism of 1,3-butadiene appears to be qualitatively similar across species, although there are quantitative differences in the amounts of putatively toxic metabolites formed; mice appear to oxidize 1,3-butadiene to the monoepoxide, and subsequently the diepoxide, metabolite to a greater extent than do rats or humans. However, there may also be interindividual variation in metabolic capability for 1,3-butadiene in humans, related to genetic polymorphism for relevant enzymes.

1,3-Butadiene is of low acute toxicity in experimental animals. However, long-term exposure to 1,3-butadiene was associated with the development of ovarian atrophy at all concentrations tested in mice. Other effects in the ovaries have also been observed in shorter-term studies. Atrophy of the testes was also observed in male mice at concentrations greater than those associated with effects in females. Based on limited available data, there is no conclusive evidence that 1,3-butadiene is teratogenic in experimental animals following maternal or paternal exposure or that it induces significant fetal toxicity at concentrations below those that are maternally toxic.

1,3-Butadiene also induced a variety of effects on the blood and bone marrow of mice; although data are limited, similar effects have not been observed in rats.

Inhaled 1,3-butadiene is a potent carcinogen in mice, inducing tumours at multiple sites at all concentrations tested in all identified studies. 1,3-Butadiene was also carcinogenic in rats at all exposure levels in the only relevant study available; although only much higher concentrations were tested in rats than in mice, rats appear to be the less sensitive species, based on comparison of tumour incidence data. The greater sensitivity in mice than in rats to induction of these effects by 1,3-butadiene is likely related to species differences in metabolism to the active epoxide metabolites.

1,3-Butadiene is mutagenic in somatic cells of both mice and rats, although the mutagenic potency was greater in mice than in rats. Similarly, 1,3-butadiene induced other genetic damage in somatic cells of mice, but not in those of rats. 1,3-Butadiene was also consistently genotoxic in germ cells of mice, but not in the single assay in rats identified. However, there were no apparent differences in species sensitivity to genetic effects induced by epoxide metabolites of 1,3-butadiene. There is also limited evidence from occupationally exposed populations that 1,3-butadiene is genotoxic in humans, inducing mutagenic and clastogenic damage in somatic cells.

An association between exposure to 1,3-butadiene in the occupational environment and leukaemia fulfils several of the traditional criteria for causality. In the largest and most comprehensive study conducted to date, involving a cohort of workers from multiple plants, mortality due to leukaemia increased with estimated cumulative exposure to 1,3-butadiene in the styrene-butadiene rubber industry; this association remained after controlling for exposure to styrene and benzene and

was strongest in those subgroups with highest potential exposure. Similarly, an association between exposure to 1,3-butadiene and leukaemia was observed in an independently conducted case–control study of largely the same population of workers. However, there was no increase in mortality due to leukaemia in butadiene monomer production workers who were not concomitantly exposed to some of the other substances present in the styrene-butadiene rubber industry, although there was some limited evidence of an association with mortality due to lymphosarcoma and reticulosarcoma in some subgroups.

The available epidemiological and toxicological data provide evidence that 1,3-butadiene is carcinogenic in humans and may also be genotoxic in humans. The carcinogenic potency (the concentration associated with a 1% increase in mortality due to leukaemia) was determined to be 1.7 mg/m^3, based on the results of the largest well conducted epidemiological investigation in exposed workers. This value is similar to the lower end of the range of tumorigenic concentrations determined on the basis of studies in rodents. 1,3-Butadiene also induced reproductive toxicity in experimental animals. As a measure of its potency to induce reproductive effects, a benchmark concentration of 0.57 mg/m^3 was derived for ovarian toxicity in mice.

Although the health effects associated with exposure to 1,3-butadiene and the mode of action for induction of these effects have been extensively investigated, there continues to be considerable research on this substance in an effort to address some of the uncertainties associated with the database.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

1,3-Butadiene ($H_2C{=}CH{\cdot}CH{=}CH_2$) is also known as butadiene, α,γ-butadiene, buta-1,3-diene, bivinyl, divinyl, erythrene, vinylethylene, biethylene, and pyrrolylene. Its Chemical Abstracts Service (CAS) registry number is 106-99-0, and its Registry of Toxic Effects of Chemical Substances (RTECS) number is EI9275000.

At room temperature, butadiene is a colourless, flammable gas with a mild aromatic odour. The molecular weight of butadiene is 54.09 g/mol. It has a high vapour pressure (281 kPa at 25 °C), a vapour density of 1.9, a moderately low water solubility (735 mg/litre at 25 °C), a low boiling point (−4.4 °C), a low octanol/water partition coefficient (K_{ow} 1.99) (Mackay et al., 1993), and a Henry's law constant of 7460 Pa·m^3/mol (equivalent to an air/water partition coefficient, or dimensionless Henry's law constant, of 165.9).

Further chemical and physical characteristics of butadiene are given in the International Chemical Safety Card reproduced in this document.

The conversion factor for butadiene in air is as follows: 1 ppm = 2.21 mg/m^3.

3. ANALYTICAL METHODS

Selected methods for the analysis of butadiene in various matrices are listed in Table 1 (IARC, 1999). Gas detection tubes can also be used to detect butadiene.

Table 1: Methods for analysis of butadiene (modified from IARC, 1999).

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Adsorb (charcoal); extract (carbon disulfide)	GC/FID	200 µg/m^3	US OSHA, 1990
	Adsorb (coconut, charcoal); extract (dichloromethane)	GC/FID	0.2 mg/sample (5–25 litres)	NIOSH, 1994
	Adsorb on Perkin-Elmer ATD 400 packed with polymeric or synthetic adsorbent material; thermal desorption	GC/FID	200 µg/m^3	UK HSE, 1992
Foods and plastic food-packing material	Dissolve (dimethylacetamide) or melt; inject headspace sample	GC/MS-SIM	~1 µg/kg	Startin & Gilbert, 1984
Plastics, liquid foods	Dissolve in *o*-dichlorobenzene; inject headspace sample	GC/FID	2–20 µg/kg	US FDA, 1987
Solid foods	Cut or mash sample; inject headspace sample	GC/FID	2–20 µg/kg	US FDA, 1987

[a] Abbreviations: GC/FID: gas chromatography/flame ionization detection; GC/MS-SIM: gas chromatography/mass spectrometry with single-ion monitoring.

4. SOURCES OF HUMAN EXPOSURE

Data on sources and emissions from Canada, the source country of the national assessment on which this CICAD is based, are presented here as an example. Sources and patterns of emissions in other countries are expected to be similar, although quantitative values may vary.

Estimates of emissions of butadiene are highly variable, depending on the method of estimation and the quality of the data upon which they are based. Total Canadian emissions for 1994 were estimated to range between 12 917 and 41 622 tonnes (Environment Canada, 1998). Major uncertainties are associated with estimates for combustion sources, notably forest fires.

4.1 Natural sources

Butadiene is released from biomass combustion, especially forest fires. Total global emissions of butadiene from biomass combustion were estimated to be 770 000 tonnes per year (Ward & Hao, 1992). Releases from forest fires in Canada were estimated to range between 3607 and 26 966 tonnes, which constituted 49.3% (range of estimates is 28–65%) of the total annual emissions of butadiene in Canada (CPPI, 1997). Although Altshuller et al. (1971) suggested that butadiene can be released from natural gas losses and diffusion through soil from petroleum deposits, no data were identified on this possible source.

4.2 Anthropogenic sources

All internal combustion engines may produce butadiene as a result of incomplete combustion. The amount generated and released depends primarily on the composition of fuel, the type of engine, the emission control used (i.e., presence and efficiency of catalytic converter), the operating temperature, and the age and state of repair of the vehicle.[1] Cyclohexane, 1-hexene, 1-pentene, and cyclohexene have been identified as primary fuel precursors for butadiene (Schuetzle et al., 1994). As well, very low levels of butadiene itself may be present in gasoline and in liquefied petroleum gas.

Butadiene can also enter the environment from any stage in the production, storage, use, transport, or disposal of products with residual, free, or unreacted butadiene. Data on Canadian industrial emissions have been collected for industrial processes, plastic products industries, refined petroleum and coal products industries, and chemical and chemical products industries as part of the National Pollutant Release Inventory (NPRI) (Environment Canada, 1996a, 1997). Emissions other than those reported to the NPRI may occur, including from combustion of other fuels (e.g., natural gas, oil, and wood space heating), prescribed forest burning, cigarettes, waste incineration, releases from polymer products, releases from the use and disposal of products containing butadiene, and spillage (Ligocki et al., 1994; Environment Canada, 1996b; OECD, 1996).

The following amounts of butadiene were estimated to have been released into the Canadian environment in 1994 from key transportation and related sources (Environment Canada, 1996a; CPPI, 1997): 3376–7401 tonnes from on-road gasoline- and diesel-powered motor vehicles (with about 45–89% of those releases from gasoline engines and 11–55% from diesel engines); 150–258 tonnes from aircraft; 84–1689 tonnes from off-road motor vehicles; 84 tonnes from lawnmowers; 40 tonnes from the marine sector; and 17 tonnes from the rail sector.

In addition, data from NPRI for 1994 (Environment Canada, 1996a) listed a total of 270.4 tonnes released from the chemical and chemical products industries. Of this, 270.3 tonnes were released into air, 0.058 tonnes into water (St. Clair River, Ontario), and 0.002 tonnes onto land. There were releases of 17.5 tonnes into air from the plastic products industries. A total of 22.3 tonnes was released from the refined petroleum and coal products industries, of which 22.2 tonnes were released into air. Off-site transfer of wastes (material sent for final disposal or treatment prior to final disposal) from industrial sites in Canada in 1994 was estimated to include a total of 131.3 tonnes of butadiene, with 128.7 tonnes being sent to incineration, 2.1 tonnes to landfill, and 0.5 tonnes to municipal sewage treatment plants (Environment Canada, 1996a). Based on 1995 NPRI data (Environment Canada, 1997), the amount of butadiene estimated to have been released into the Canadian environment was 225.8 tonnes from industrial on-site uses, with 0.058 tonnes released into water, 0.002 tonnes into land, and 225.4 tonnes into air. Releases into air included air fugitive releases (172.8 tonnes), air stack releases (36.3 tonnes), air storage releases (4.8 tonnes), air spill releases (1.1 tonnes), and other air releases (10.4 tonnes).

Based on data in NPRI, it was estimated that the total release of butadiene from fuel distribution in 1994 was 24 tonnes (Environment Canada, 1996a), although gasoline and diesel fuel contain little or no butadiene (US EPA, 1989).

[1] Personal communication from L.A. Graham, River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, 1996.

CPPI (1997) estimated that releases into the Canadian environment in 1994 were 1191 tonnes from prescribed forest burning, 3706 tonnes from wood space heating, 11 tonnes from natural gas/oil space heating, and 1–9 tonnes from cigarettes.

4.3 Production and uses

Butadiene is produced during the combustion of organic matter in both natural processes and human activities. In addition, it is produced commercially for use in the chemical polymer industry.

Butadiene is purified by extraction from a crude petroleum butadiene stream. In 1994, there was one Canadian commercial producer of butadiene (located in Sarnia, Ontario), with a domestic production of 103.7 kilotonnes. Importation into Canada from the USA was 1.7 kilotonnes in 1994. The Canadian domestic use of butadiene in 1994 amounted to 105.4 kilotonnes (98.3 kilotonnes for total domestic demand and 7.1 for export sales) (Camford Information Services, 1995). In the USA, total production in 1993 was 1.4 billion kilograms.[1] According to data summarized in IARC (1999), in 1996, production of butadiene in China (Taiwan), France, Germany, Japan, the Republic of Korea, and the USA was 129, 344, 673, 1025, 601, and 1744 kilotonnes, respectively.

The largest end use of butadiene in Canada is the production of polybutadiene rubber (51.4 kilotonnes; 52.3% of total Canadian consumption for 1994) (Camford Information Services, 1995). Other derivatives produced include styrene-butadiene lattices (31.0 kilotonnes; 31.5% of total Canadian consumption for 1994), nitrile-butadiene rubbers (10.0 kilotonnes; 10.2% for 1994), acrylonitrile-butadiene-styrene terpolymer (3.4 kilotonnes; 3.5% for 1994), and specialty styrene-butadiene rubbers (2.5 kilotonnes; 2.5% of total Canadian consumption for 1994).

Butadiene has a long history of use, notably related to production of polymers. Several industrial and commercial products are manufactured with it or may contain it as a component. Examples include tires, car sealants, plastic bottles and food wrap, epoxy resins, lubricating oils, hoses, drive belts, moulded rubber goods, adhesives, paint, latex foams for carpet backing or underpad, shoe soles, moulded toys/household goods, medical devices, and chewing gum (CEH-SRI International, 1994; OECD, 1996).

[1] Hazardous Substances Databank, National Library of Medicine's TOXNET system, searched 10 December 1999.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 Air

Since butadiene is released primarily to air, its fate in that medium is of primary importance. Butadiene is not expected to persist in air, since it oxidizes rapidly with several oxidant species. Destruction of atmospheric butadiene by the gas-phase reaction with photochemically produced hydroxyl radicals is expected to be the dominant photo-initiated pathway. Products that can be formed include formaldehyde, acrolein, and furan. Destruction by nitrate radicals is expected to be a significant nighttime process in urban areas. Acrolein, *trans*-4-nitroxy-2-butenal, and 1-nitroxy-3-buten-2-one have been identified as products of this reaction. Reaction with ozone is also rapid but less important than reaction with hydroxyl radicals. The products of the reaction of butadiene with ozone are acrolein, formaldehyde, acetylene, ethylene, formic acid, formic anhydride, carbon monoxide, carbon dioxide, hydrogen gas, hydroperoxyl radical, hydroxyl radical, and 3,4-epoxy-1-butene (Atkinson et al., 1990; Howard et al., 1991; McKone et al., 1993; US EPA, 1993).

Average atmospheric half-lives for photo-oxidation of butadiene, based on measured as well as calculated data, range from 0.24 to 1.9 days (Darnell et al., 1976; Lyman et al., 1982; Atkinson et al., 1984; Becker et al., 1984; Klöpffer et al., 1988; Howard et al., 1991; Mackay et al., 1993). However, half-lives for butadiene in air can vary considerably under different conditions. Estimations for atmospheric residence time in several US cities ranged from 0.4 h under clear skies at night in the summer to 2000 h (83 days) under cloudy skies at night in the winter. Daytime residence times for different cities within a given season varied by factors of 2–3. Nighttime residence times varied by larger factors. The differences between summer and winter conditions were large at all sites, with winter residence times 10–30 times greater than summer residence times (US EPA, 1993). Because of the long residence times under some conditions, especially in winter under cloudy conditions, there is a possibility of day-to-day carryover. Nonetheless, given the generally short daytime residence times, the net atmospheric lifetime of butadiene is short, and there is generally limited potential for long-range transport of this compound.

It is predicted from its physical/chemical properties that when butadiene is released into air, almost all of it will exist in the vapour phase in the atmosphere (Eisenreich et al., 1981; Environment Canada, 1998). Wet and dry deposition are not expected to be important

as transfer processes. Evaporation from rain may be rapid, and the compound is returned to the atmosphere relatively quickly unless it is leached into the soil.

5.2 Water

Volatilization, biodegradation, and oxidation by singlet oxygen are the most prominent processes involved in determining the fate of butadiene in water. The estimated half-lives of butadiene by reaction in water range from 4.2 to 28 days (Howard et al., 1991; Mackay et al., 1993).

5.3 Sediment and soil

The processes that are most prominent in determining the environmental fate of butadiene in sediment are biotic and abiotic degradation. The modelled half-lives of butadiene by reaction in sediment range from 41.7 to 125 days (Mackay et al., 1993).

Based on its vapour pressure and its solubility, volatilization of butadiene from soil and other surfaces is expected to be significant. Butadiene's organic carbon/water partition coefficient indicates that it should not adsorb to soil particles to a great degree and would be considered moderately mobile (Kenaga, 1980; Swann et al., 1983). However, the rapid rate of volatilization and the potential for degradation in soil suggest that it is unlikely that butadiene will leach into groundwater. Based on modelling predictions, the half-life of butadiene by reaction, given by Howard et al. (1991) and Mackay et al. (1993), ranges from 7 to 41.7 days.

5.4 Biota

There are no measured bioconcentration factors. Butadiene is metabolized by the mixed-function oxidase system in higher organisms, which contributes to the expected lack of accumulation by many organisms. Estimated bioconcentration factors for butadiene in fish have been reported to range from 4.6 to 19 (Lyman et al., 1982; OECD, 1996). Even though estimation methods likely overestimate the true bioconcentration potential for a readily metabolized substance, they indicate that butadiene is not expected to bioconcentrate in aquatic organisms or to biomagnify in the aquatic food chain.

There are no reported measurements of plant root bioconcentration in soils. However, McKone et al. (1993) estimated the uptake of butadiene by roots from soil solution to be 1.84 litres/kg, which is the ratio of butadiene concentration in root (mg/kg, fresh mass) to the concentration in soil solution (mg/litre). The partition coefficient of butadiene concentration in roots (mg/kg, fresh mass) to concentration in soil solids (mg/kg) was estimated to range from 0.32 to 15 (dimensionless).

The partition coefficient of butadiene concentration in whole plants (mg/kg, fresh mass) to its concentration in soil solids (mg/kg) was estimated to range from 0.1 to 2.9 (dimensionless). The steady-state plant/air partition coefficient for foliar uptake of butadiene in plant leaves was estimated to be 0.63 m^3/kg. There are no reported bioaccumulation data for any terrestrial invertebrates.

5.5 Environmental modelling

Fugacity modelling was conducted to provide an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for butadiene and of its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity modelling) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Assumptions, input parameters, and results are presented in Environment Canada (1998). Based on butadiene's physical/chemical properties, Level III fugacity modelling predicts that:

- when butadiene is released into air, the distribution of mass is almost 100% in air, with very small amounts in soil and water;
- when butadiene is released into water, the distribution of mass is 99.0% in water, with small amounts in air;
- when butadiene is released into soil, the distribution of mass is 38.6% in soil, 59.3% in air, and 2.1% in water.

Modelling predictions do not purport to reflect actual expected measurements in the environment but rather indicate the broad characteristics of the fate of the substance in the environment and its general distribution between media. Thus, when butadiene is discharged into air or water, most of it is expected to be found in the medium receiving the discharge directly. For example, if butadiene is discharged into air, almost all of it will exist in the atmosphere, where it will react rapidly and will also be transported away. If butadiene is discharged to water, it will react in water, and some will also evaporate into air. If butadiene is discharged to soil, most will be present in air or soil, where it will react (Mackay et al., 1993; Environment Canada, 1998).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data on environmental levels and human exposure from Canada, the source country of the national assessment on which this CICAD is based, are presented here as a basis for the sample risk characterization. Patterns of exposure in other countries are expected to be similar, although quantitative values may vary.

6.1 Environmental levels

6.1.1 Ambient air

Butadiene was detected (detection limit 0.05 μg/m^3) in 7314 (or 80%) of 9168 24-h samples collected between 1989 and 1996 from 47 sites across Canada.[1] The mean concentration in all samples was 0.3 μg/m^3 (in the calculation of the mean, a value of one-half the detection limit was assumed for samples in which levels were below the detection limit), and the maximum concentration measured was 14.1 μg/m^3. Concentrations of butadiene in ambient air corresponding to the 50th and 95th percentiles were 0.21 and 1.0 μg/m^3, respectively. Concentrations were generally higher in urban areas, with a mean exposure to 0.4 mg/m^3 (95th percentile 1.3 mg/m^3) estimated as a "reasonable worst-case scenario," based on data from four sites. Similar levels were measured in smaller surveys in Canada (Bell et al., 1991, 1993; Hamilton-Wentworth, 1997; Conor Pacific Environmental, 1998).[2] In areas influenced by industrial point sources of butadiene, concentrations in air were greater, with maximum and mean levels of 28 and 0.62 mg/m^3, respectively (95th percentile 6.4 mg/m^3) being measured between 1 and 3 km from the source (MOEE, 1995).

Butadiene has also been detected in air in enclosed structures. Concentrations of butadiene between 4 and 49 μg/m^3 were measured during the winter months of 1994–1995 in Canadian underground parking garages (Environment Canada, 1994) because of its presence in vehicle exhaust. Similarly, butadiene was frequently detected in samples from 10 parking structures in California, with the maximum concentration being 28 μg/m^3 (Wilson et al., 1991). Butadiene has also been detected in urban road tunnels during rush hours in Australia (mean concentration 28 μg/m^3; Duffy & Nelson, 1996) and Sweden (mean concentrations 17 μg/m^3 and 25 μg/m^3 in two tunnels; Barrefors, 1996). Butadiene was measured at concentrations ranging from 0.2 to 28 μg/m^3 in 96 of 97 5-min air samples collected from a pumping island at randomly identified self-service filling stations in California (Wilson et al., 1991).

6.1.2 Surface water

No data on concentrations of butadiene in Canadian lake, river, estuarine, or marine waters were identified in the literature. Butadiene is being monitored in effluents discharged into the St. Clair River from the butadiene production plant in Sarnia, Ontario. It was detected only twice, at 2 and 5 μg/litre, in 2103 composite samples of aqueous effluent taken every 4 h in 1996 (detection limit 1 μg/litre). In daily sampling of effluents from the four individual outfalls (detection limit 1 μg/litre in 736 samples and 50 μg/litre in 789 samples), butadiene was detected in only three samples, at concentrations of 21, 80, and 130 μg/litre.[3]

6.1.3 Groundwater

Butadiene was detected but not quantified in a groundwater plume near a waste site in Quebec where refinery oil residues and a variety of organic chemicals had been dumped (Pakdel et al., 1992).

6.2 Human exposure

6.2.1 Indoor air

In available surveys in Canada, 1,3-butadiene was detected up to 6 times more frequently in indoor air in homes than in corresponding samples of outdoor air, with concentrations being up to 10-fold higher indoors than outdoors (Bell et al., 1993; Hamilton-Wentworth, 1997; Conor Pacific Environmental, 1998).[4] Concentrations in air of indoor environments are highly variable and depend largely on individual activities and circumstances, including the use of consumer products (e.g.,

[1] Unpublished data on butadiene levels in Canada from National Air Pollution Surveillance program, provided by T. Dann, River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, April 1997.

[2] Also letter dated 28 August 1996 from P. Steer, Science and Technology Branch, Ontario Ministry of Environment and Energy, to J. Sealy, Health Canada, re. 1,3-butadiene and chloroform data (File No. 1E080149.MEM).

[3] Personal communication from H. Michelin, Bayer Inc., Sarnia, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, 1997.

[4] Also personal communication dated 24 December 1997 from X.-L. Cao to Health Canada, re. method detection limits for 24-h air samples from multimedia exposure pilot study (File No. MDL.XLS).

cigarettes), the infiltration of vehicle exhaust from nearby traffic and possibly from attached garages, and cooking activities involving heated fats and oils (see section 6.2.3). While data are inadequate to determine the relative contributions of each of these potential indoor sources, the highest concentrations of butadiene in indoor air in Canada have generally been detected in indoor environments contaminated with environmental tobacco smoke (ETS). In a survey of 94 homes across Canada, the mean level in "non-smoking" homes was <1 μg/m^3 (data censored by considering levels to be one-half the detection limit in samples in which butadiene was not detected), compared with a mean of 2.5 μg/m^3 (data censored) in homes where smoking was present (Conor Pacific Environmental, 1998). Similarly, mean concentrations in indoor air from "non-smoking" locations in Windsor, Ontario, ranged from 0.3 to 1.6 μg/m^3, while mean levels in "smoking" locations ranged from 1.3 to 18.9 μg/m^3. At non-residential indoor sampling sites in Windsor, the frequency of detection of butadiene was 75–100% where ETS was present (Bell et al., 1993).

6.2.2 Drinking-water

There are no data available concerning the presence of butadiene in drinking-water. In an investigation on whether the use of polybutylene pipe in water distribution systems is likely to result in the contamination of drinking-water with butadiene, Cooper[1] did not detect the substance in water from these types of pipes (no further information was presented in the secondary account [CARB, 1992] of this study).

6.2.3 Food

There are no data available concerning the presence or concentrations of butadiene in food in Canada. In the USA, the migration of butadiene from rubber-modified plastic containers to food was investigated by McNeal & Breder (1987). Butadiene was detected in some of the containers, but was generally not detected in the foods (detection limits 1–5 ng/g). Similarly, in the United Kingdom, butadiene was not detected (detection limit 0.2 ng/g) in five brands of soft margarine, although its presence was demonstrated (at concentrations ranging from <5 to 310 ng/g) in the plastic containers (Startin & Gilbert, 1984). Butadiene has been detected in the emissions from heated cooking oils, including Chinese rapeseed, peanut, soybean, and canola oils, at levels ranging from 23 to 504 μg/m^3 (Pellizzari et al., 1995; Shields et al., 1995).

6.2.4 Consumer products

Data on emissions of butadiene from potential indoor sources such as styrene-butadiene rubber were not identified.

Butadiene has been detected in both mainstream smoke and sidestream smoke from cigarettes in Canada and the USA. For 18 brands of Canadian cigarettes, the mean butadiene content ranged from 14.3 to 59.5 μg/cigarette (overall mean concentration 30.0 μg/cigarette) in the mainstream smoke and from 281 to 656 μg/cigarette (overall mean concentration 375 μg/cigarette) in the sidestream smoke, according to "preliminary" data (Labstat, Inc., 1995). The US DHHS (1989) reported that the vapour phase of mainstream smoke of non-filter cigarettes contained butadiene at levels of 25–40 μg/cigarette. Brunnemann et al. (1989) measured butadiene levels ranging from 16 to 75 μg/cigarette in mainstream smoke from seven brands of cigarettes and levels ranging from 205 to 361 μg/cigarette in the sidestream smoke from six types of cigarettes. As discussed in section 6.2.1, the presence of ETS contributes to elevated levels of butadiene in indoor air.

6.2.5 Occupational exposure

Potential occupational exposure to butadiene can occur in petroleum refining and related operations, production of butadiene monomer, production of butadiene-based polymers, or the manufacture of rubber and plastics products (IARC, 1999). Arithmetic mean concentrations in petroleum and petrochemical operations in several European countries ranged from 0.1 to 6.4 mg/m^3 during 1984–1987 (IARC, 1999; European Chemicals Bureau, 2001). Based on occupational hygiene surveys of butadiene production facilities in the United Kingdom, personal airborne exposures are generally below a mean concentration of 5 ppm (11 mg/m^3), with most below 1 ppm (2.2 mg/m^3). In polymer manufacture in the United Kingdom, most time-weighted average exposures are below 2–3 ppm (4.4–6.6 mg/m^3). Similar concentrations were reported in other facilities in the European Union (IARC, 1999). In monomer production facilities in the USA surveyed in 1985, arithmetic mean concentrations ranged from 1 to 277 mg/m^3, while those in polymer production industries ranged from 0.04 to 32 mg/m^3 (IARC, 1999).

[1] Personal communication from R. Cooper, Department of Biomedical and Environmental Health, School of Public Health, University of California, Berkeley, California, 1989 (cited in CARB, 1992).

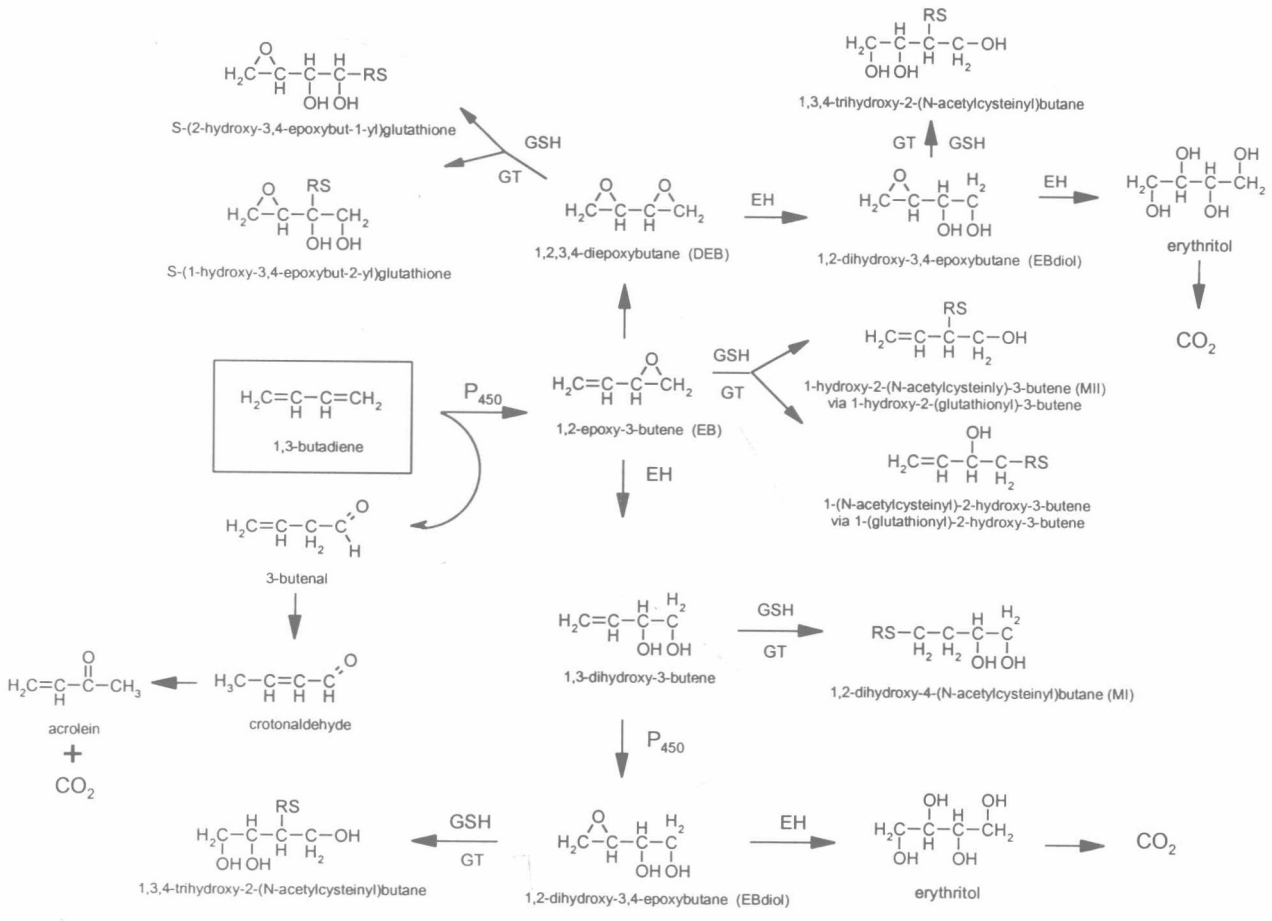


Figure 1: Proposed metabolism of 1,3-butadiene.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The database on the toxicokinetics and metabolism of butadiene is relatively extensive. The proposed metabolism is outlined in Figure 1, based on the pathways described by Henderson et al. (1993, 1996) and Himmelstein et al. (1997). Available data for the pathways most extensively investigated indicate that metabolism is qualitatively similar among the various species studied, although there may be quantitative differences in the amount of butadiene absorbed as well as in metabolic rates and the proportion of metabolites generated. These differences appear to be in concordance with the observed variation in sensitivity to butadiene-induced toxic effects of the few strains of rodent species tested to date, in that mice appear to metabolize a greater proportion of butadiene to active epoxide metabolites than do rats. While less of these metabolites are also formed in samples of human tissues *in vitro* than in those of mice, available data are insufficient to characterize interindividual variability in humans. Although there are known genetic polymorphisms for a number of the enzymes involved in the metabolism of butadiene, information on genotype was not included in most investigations in humans.

Based on the metabolic pathways described in Figure 1, butadiene is first oxidized via cytochrome P-450 enzymes (primarily P-450 2E1 in humans, although other isoforms may also be involved, the relative contributions of which vary between tissues and species) to the monoepoxide 1,2-epoxy-3-butene, or EB, which is subsequently further oxidized via P-450 enzymes to the diepoxide 1,2,3,4-diepoxybutane, or DEB, or hydrolysed via epoxide hydrolase (EH) to butenediol (1,2-dihydroxy-3-butene). The monoepoxide, the diepoxide, and the butenediol may all be conjugated with glutathione (GSH) to form mercapturic acids, which are eventually eliminated in the urine. Hydrolysis of the diepoxide via epoxide hydrolase or oxidation of the butenediol via cytochrome P-450 will result in the formation of the

monoepoxide diol (EBdiol). A small amount of butadiene may be converted to 3-butenal, which is subsequently transformed to crotonaldehyde (about 2–5% of the amount that is oxidized to the monoepoxide in human liver microsomes [Duescher & Elfarra, 1994] or microsomes of kidney, lung, or liver of B6C3F$_1$ mice [Sharer et al., 1992]). However, this pathway has not been extensively investigated, nor was crotonaldehyde detected in a sensitive analysis (using nuclear magnetic resonance spectroscopy) of urinary metabolites of rats and mice exposed to ^{13}C-butadiene (Nauhaus et al., 1996).

Metabolism of butadiene and subsequent conversion of EB to DEB may also take place to a more limited degree in the bone marrow (e.g., Maniglier-Poulet et al., 1995) by means other than P-450 oxidation (possibly via myeloperoxidase; Elfarra et al., 1996), based on *in vitro* observations and the detection of the epoxides in the bone marrow of rodents (Thornton-Manning et al., 1995a, 1995b), although this potential pathway has not yet been extensively investigated. EB may also react with both myeloperoxidase and chloride to form a chlorohydrin (1-chloro-2-hydroxy-3-butene) (Duescher & Elfarra, 1992). Metabolites arising from other possible pathways have been identified in the urine of mice exposed to butadiene (including metabolites known to be derived from metabolism of acrolein or acrylic acid) (Nauhaus et al., 1996), but no further research has yet been generated.

There is a substantial amount of evidence from *in vitro* and *in vivo* investigations that B6C3F$_1$ mice oxidize butadiene to the monoepoxide via P-450 in the liver to a greater extent than do Sprague-Dawley rats and humans. Levels of EB in the blood and other tissues of mice were two- to eightfold higher than those in rats exposed to similar levels of butadiene (Bond et al., 1986; Himmelstein et al., 1994, 1995; Bechtold et al., 1995; Thornton-Manning et al., 1997).

Available data also suggest that there are similar species differences in the amount of the diepoxide formed from oxidation of the monoepoxide. Levels of DEB were 40- to 160-fold higher in blood and other tissues of B6C3F$_1$ mice than in Sprague-Dawley rats exposed to the same concentration of butadiene (Thornton-Manning et al., 1995a, 1995b). While concentrations of EB at various sites were similar in male and female rats, levels of DEB were at least fivefold higher in females than in males, which correlates with the greater incidence of tumours in female rats. Although the mammary gland is a target tissue in rats, extended exposure to butadiene at 8000 ppm (17 696 mg/m^3) for 10 days did not result in any accumulation of DEB at this site (Thornton-Manning et al., 1998), which suggests that DEB may not play a significant role in the induction of mammary tumours in rats. Available *in vitro* data in human liver and lung samples suggest that humans also form less of the active metabolites of butadiene than do mice (although somewhat varying results have been reported with respect to the magnitude of the differences between species) (Csanády et al., 1992; Duescher & Elfarra, 1994; Krause & Elfarra, 1997).

Although epoxide metabolites of butadiene are formed to a greater extent in mice than in rats or humans, they are also cleared via glutathione conjugation more rapidly in mice (Kreuzer et al., 1991; Sharer et al., 1992; Boogaard et al., 1996a, 1996b). Conversely, hydrolysis of EB and DEB is greater in humans than in rats (based on *in vitro* data, as DEB has not been detected in tissues of exposed humans), and hydrolysis of EB and DEB in rats is in turn greater than that in mice (Csanády et al., 1992; Krause et al., 1997). In both humans and monkeys, removal of EB via hydrolysis appears to predominate over conjugation with glutathione, based on analysis of urinary metabolites (Sabourin et al., 1992; Bechtold et al., 1994). Although hydrolysis of the epoxide metabolites is generally considered to be a detoxifying mechanism, it may also lead to the formation of the diolepoxide, EBdiol, which is biologically reactive. However, no data were identified on species differences in the formation of EBdiol via metabolism of both epoxide metabolites.

The formation of stable adducts of both the monoepoxide and monoepoxide diol metabolites of butadiene with the *N*-terminal valine of haemoglobin has been observed in experimental animals and humans exposed to butadiene (Albrecht et al., 1993; Osterman-Golkar et al., 1993, 1996; Neumann et al., 1995; Sorsa et al., 1996b; Tretyakova et al., 1996; Pérez et al., 1997).[1] Consistent with the greater formation of epoxide metabolites, greater concentrations of haemoglobin–EB adducts were measured in mice than in rats exposed to the same concentration of butadiene. However, levels of haemoglobin–EB adducts in butadiene-exposed workers, although significantly elevated compared with levels in non-exposed workers, were considerably less than would be expected on the basis of results of studies in mice and rats (Osterman-Golkar et al., 1993). Based on observations in rats and humans exposed to butadiene, levels of haemoglobin–EBdiol adducts are substantially greater than levels of haemoglobin–EB adducts (although it is noted that the same adduct can result from binding with DEB). Metabolites of butadiene may also form adducts with DNA (see sections 8.5 and 9.2.3).

[1] Also personal communication (correspondence dated 25 March 1998) from J.A. Swenberg, University of North Carolina, Chapel Hill, NC, to Health Canada.