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Concise International Chemical Assessment Document 30

1,3-BUTADIENE: HUMAN HEALTH ASPECTS

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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.

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TABLE OF CONTENTS

FOREWORD .................................................................................. 1

1. EXECUTIVE SUMMARY .............................................................. 4

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES ......................... 5

3. ANALYTICAL METHODS ................................................................ 5

4. SOURCES OF HUMAN EXPOSURE ................................................ 6
   4.1 Natural sources ........................................................................ 6
   4.2 Anthropogenic sources .............................................................. 6
   4.3 Production and uses ................................................................. 7

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION ...................................................................... 7
   5.1 Air ................................................................................ 7
   5.2 Water ............................................................................. 8
   5.3 Sediment and soil ................................................................... 8
   5.4 Biota .............................................................................. 8
   5.5 Environmental modelling ...................................................... 8

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE ............................................ 9
   6.1 Environmental levels ............................................................... 9
       6.1.1 Ambient air ....................................................................... 9
       6.1.2 Surface water .................................................................. 9
       6.1.3 Groundwater ................................................................... 9
   6.2 Human exposure ...................................................................... 9
       6.2.1 Indoor air ........................................................................ 9
       6.2.2 Drinking-water ................................................................ 10
       6.2.3 Food ........................................................................ 10
       6.2.4 Consumer products ........................................................ 10
       6.2.5 Occupational exposure ................................................... 10

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS ..................................................... 11

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS ................................. 13
   8.1 Single exposure ....................................................................... 13
   8.2 Irritation and sensitization ......................................................... 13
   8.3 Repeated exposure .................................................................. 13
   8.4 Carcinogenicity ...................................................................... 13
   8.5 Genotoxicity and related end-points ............................................ 18
   8.6 Reproductive toxicity ............................................................... 23
       8.6.1 Effects on fertility ........................................................... 23
       8.6.2 Developmental toxicity .................................................... 24
   8.7 Immunotoxicity ...................................................................... 24
9. EFFECTS ON HUMANS ........................................................................ 24

9.1 Clinical studies ........................................................................... 24
9.2 Epidemiological studies ............................................................. 25
  9.2.1 Cancer ........................................................................... 25
  9.2.2 Non-neoplastic effects ...................................................... 28
  9.2.3 Genotoxicity .................................................................... 28

10. EVALUATION OF HEALTH EFFECTS ................................................. 29

10.1 Hazard identification ................................................................. 29
  10.1.1 Carcinogenicity and genotoxicity ........................................ 29
  10.1.2 Non-neoplastic effects ...................................................... 32
10.2 Exposure–response assessment and criteria for setting tolerable concentrations or
guidance values .............................................................................. 33
  10.2.1 Carcinogenicity ................................................................. 33
    10.2.1.1 Epidemiological data .................................................. 33
    10.2.1.2 Data from studies in experimental animals .................. 34
  10.2.2 Non-neoplastic effects ...................................................... 35
10.3 Sample exposure and risk characterization .................................... 36
  10.3.1 Sample exposure characterization ....................................... 36
  10.3.2 Sample risk characterization ............................................. 36
10.4 Uncertainties and degree of confidence in human health hazard characterization and
sample risk characterization ............................................................. 37

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES .................. 40

REFERENCES ................................................................................ 41

APPENDIX 1 — SOURCE DOCUMENT .............................................. 49

APPENDIX 2 — CICAD PEER REVIEW ............................................ 50

APPENDIX 3 — CICAD FINAL REVIEW BOARD .............................. 51

APPENDIX 4 — QUANTITATION OF EXPOSURE–RESPONSE FOR CRITICAL EFFECTS ASSOCIATED
WITH EXPOSURE TO 1,3-BUTADIENE ........................................... 52

INTERNATIONAL CHEMICAL SAFETY CARD ...................................... 68

RÉSUMÉ D’ORIENTATION ............................................................... 70

RESUMEN DE ORIENTACIÓN .......................................................... 72
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 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

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 fulfills 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 ($\text{H}_2\text{C}=$CH@CH=CH$_2$) is also known as butadiene, $^-$, ( -butadiene, buta-1,3-diene, divinyl, divinyl, erythrene, vinylene, 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 EH9275000.

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

* 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. 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. There were releases of 17.2 tonnes into air included air fugitive releases (17.2 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).
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. 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).

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, hydroperoxy radical, hydroxyl radical, and 3,4-epoxy-1-butene (Atkinson et al., 1990; Howard et al., 1991; Mackay 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; Klöpfer 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

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1 Hazardous Substances Databank, National Library of Medicine’s TOXNET system, searched 10 December 1999.
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 m³/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-butaadiene 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 circum-

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\(^1\) 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.


\(^4\) 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).
stances, including the use of consumer products (e.g., 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/m³ (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/m³ (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/m³, while mean levels in “smoking” locations ranged from 1.3 to 18.9 µg/m³. 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, Cooper¹ 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/m³ (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. Brunnenmann 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/m³ 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/m³), with most below 1 ppm (2.2 mg/m³). In polymer manufacture in the United Kingdom, most time-weighted average exposures are below 2–3 ppm (4.4–6.6 mg/m³). 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/m³, while those in polymer production industries ranged from 0.04 to 32 mg/m³ (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).
1,3-Butadiene: Human health aspects

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
monooxepine 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 monooxepine in human liver microsomes [Duescher & Elfarra, 1994] or microsomes of kidney, lung, or liver of B6C3F1 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 13C-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 B6C3F1 mice oxidize butadiene to the monooxepine 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 diolepoxide formed from oxidation of the monooxepine. Levels of DEB were 40- to 160-fold higher in blood and other tissues of B6C3F1 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/m³) 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) (Csándy 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 (Csándy 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 monooxepine and monooxepine 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). 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.
In addition to quantitative interspecies differences in the metabolism of butadiene, there is also evidence that there is significant variation within the human population. Indeed, although available data are inadequate to assess interindividual variation in metabolism, which has been observed in in vitro investigations in microsomes from a small number of subjects (Boogaard & Bond, 1996; Krause et al., 1997), there has been significant interindividual variability in the extent of formation of haemoglobin adducts with butadiene metabolites in human populations (Neumann et al., 1995; Osterman-Golkar et al., 1996). Such variability is not unexpected, in view of the complexity of the metabolic pathways involved in the biotransformation of butadiene: i.e., the three principal enzymatic processes that determine the extent of exposure to the putatively toxic epoxide metabolites, namely formation via cytochrome P-450 2E1 and removal via epoxide hydrolase and glutathione conjugation. For example, the inductibility of cytochrome P-450 2E1 by low molecular weight compounds such as ethanol is likely to contribute to interindividual variability in sensitivity. Moreover, genetic polymorphisms for glutathione-S-transferases and epoxide hydrolase might also contribute to considerable variation in sensitivity. While the influence of genotype for epoxide hydrolase has not been well investigated (although data indicate that hydrolysis of EB predominates over oxidation and glutathione conjugation in humans), interindividual sensitivity to the genetic effects of the epoxide metabolites in in vitro studies has been clearly related to genotype for the glutathione-S-transferases (see section 9.2.3).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

Although few data are available, butadiene appears to be of low acute toxicity in experimental animals, with reported LC$_{50}$ values for rats and mice of >100 000 ppm (>221 000 mg/m$^3$). Lowest LC$_{50}$ values for butadiene are reported for mice, at 117 000 ppm (256 000 mg/m$^3$) (duration not specified) (Batinka, 1966) and 121 000 ppm (268 000 mg/m$^3$) (2 h) (Shugaev, 1969). The nervous system and the blood appear to be the principal targets; however, in only one study were data sufficient to determine a lowest-observed-effect level (LOEL) of 200 ppm (442 mg/m$^3$) for haematological effects (Leavens et al., 1997). Exposure to butadiene for 7 h caused a concentration-dependent depletion (by as much as 80%) of cellular non-protein sulphydryl content of liver, lung, or heart in mice, with a LOEL of 100 ppm (221 mg/m$^3$) (Deutschmann & Laib, 1989). Depletion of non-protein sulphydryl content may inhibit detoxification of epoxide metabolites via glutathione conjugation.

8.2 Irritation and sensitization

No investigations in experimental animals on the potential for irritation or sensitization of butadiene have been identified.

8.3 Repeated exposure

The majority of short-term and subchronic studies were designed as either range-finding studies preliminary to chronic bioassays or investigations of potential mechanisms of action for butadiene-induced cancer and are not adequate for determination of critical effect levels. Effects on body weight were observed in B6C3F$_1$ mice exposed to 625 ppm (1383 mg/m$^3$) butadiene or more for 2 weeks; no histopathological changes were noted at any concentration at or below 8000 ppm (17 696 mg/m$^3$) (NTP, 1984).

Haematological effects consistent with megaloblastic anaemia and effects on bone marrow, including alterations in stem cell development, have been observed in two strains of mice (B6C3F$_1$ and NIH Swiss) exposed to 1000 or 1250 ppm (2212 or 2765 mg/m$^3$) butadiene for up to 31 weeks (Irons et al., 1986a, 1986b; Leiderman et al., 1986; Bevan et al., 1996). Other effects, including decreased survival and body weight gain (with males being more sensitive than females), altered organ weights, and ovarian or testicular atrophy, have also been observed in B6C3F$_1$ mice exposed subchronically to similar or higher levels of butadiene (NTP, 1984; Bevan et al., 1996). In addition, an increased incidence of a variety of tumours has been observed in B6C3F$_1$ mice exposed to 625 ppm (1383 mg/m$^3$) butadiene for as little as 13 weeks (NTP, 1993) (see section 8.4). Although histopathological changes and haematological effects were reported in early studies in rats exposed to low concentrations (3 or 10 mg/m$^3$) (Batinka, 1966; Ripp, 1967; Nikiforova et al., 1969), these results were not confirmed in more recent investigations of rats exposed for up to 13 weeks to much higher concentrations (e.g., 17 600 mg/m$^3$) (e.g., Crouch et al., 1979; Bevan et al., 1996). In view of the limitations of the studies in rats, it is not possible to draw any conclusions regarding species differences in response to subchronic exposure to butadiene.

8.4 Carcinogenicity

The carcinogenic potential of inhaled butadiene has been studied in two strains of mice and one strain of rats. Butadiene was a multi-site carcinogen in all
The sensitivity to butadiene-induced thymic lymphoma/leukaemia appears to be enhanced by the presence of an endogenous ecotropic retrovirus in B6C3F1 mice, as the incidence of this tumour was greater in male B6C3F1 mice exposed to 1250 ppm (2765 mg/m³) butadiene for 52 weeks than in male Swiss mice, which do not express an endogenous retrovirus (57% versus 14%). Exposed mice of both strains had elevated incidences of thymic lymphoma/leukaemia compared with controls, as did B6C3F1 mice exposed to 1250 ppm (2765 mg/m³) for 12 weeks and then observed for an additional 40 weeks, although the MuLV env sequence for the retrovirus was detected only in tumours of the B6C3F1 mice. Other tumours reported in the mice exposed for 52 weeks included haemangiosarcomas of the heart (mainly in B6C3F1 mice) and lung tumours. Neoplasms of the glandular and non-glandular stomach were observed in
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<th>Protocol</th>
<th>Results</th>
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<td>Mice (70 males and 70 females per group; 50 males and 90 females per group at the highest concentration) were exposed to 0, 6.25, 20, 62.5, 200, or 625 ppm (0, 13.8, 44.2, 138, or 1383 mg/m3) butadiene for 6 h/day, 5 days/week, for 103 weeks. Up to 10 mice of each sex from each group were killed after 9 and 15 months of exposure.</td>
<td>Numbers of animals surviving until study termination were 35, 39, 24, 22, 4, and 0 (males) at 6.25, 20, 62.5, 200, and 625 ppm, respectively.</td>
<td>Haemangiosarcomas had not previously been observed in 573 male and 558 female NTP 2-year historical controls.</td>
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<td>Histopathological examination of a comprehensive range of tissues was carried out on mice in the control and 200 and 625 ppm exposure groups killed after 9 months, on all mice killed at 15 months except females exposed to 6.25 or 20 ppm, and on all mice exposed for 2 years.</td>
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<td>Renal tubule adenomas are rare in this strain, with a range of 0–1% occurrence in NTP 2-year historical controls. Carcinomas of the preputial gland are rare in B6C3F1 mice, with none having been observed in NTP historical controls; similarly, sarcomas of the subcutaneous tissue are uncommon, with the incidence in NTP historical control females being 2/561. Zymbal gland neoplasms have not been observed in NTP historical controls, nor have carcinomas of the small intestine been observed in recent NTP controls. Exposure to butadiene tended to be associated with malignant neoplasms in several organs, whereas tumours at the same sites in controls were generally benign.</td>
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<td><strong>Lymphohaematopoietic system</strong></td>
<td>Exposure was associated with the development of malignant lymphomas (particularly lymphocytic lymphomas, which occurred as early as week 23). The incidences were significantly increased in males at 625 ppm ($p &lt; 0.001$) and females at 200 and 625 ppm ($p &lt; 0.001$) (although all incidences in the females were within the range of historical control values [8–44%]). Incidences for the 0, 6.25, 20, 62.5, 200, and 625 ppm groups were: males: 4/50, 2/50, 4/50, 6/50, 2/50, and 51/73, or 8, 4, 8, 12, 4, and 70%; females: 6/50, 12/50, 11/50, 7/50, 9/50, and 32/80, or 12, 24, 22, 14, 18, and 40%. After poly-3 adjustment for survival, the incidences were: males: 9.0, 4.4, 10.0, 15.3, 7.4, and 97.3%; females: 13.1, 27.2, 27.5, 20.2, 40.1, and 85.5%.</td>
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<td>Histiocytic sarcomas were significantly increased in both males ($p &lt; 0.001$) and females ($p = 0.002$) at 200 ppm, and the incidence of these tumours was marginally higher than that in controls in males at 20, 62.5 and 625 ppm ($p = 0.021–0.051$) and females at 625 ppm ($p = 0.038$). Incidences: males: 0/50, 0/50, 4/50, 5/50, 7/50, and 4/73, or 0, 0, 8, 10, 14, and 5%; females: 3/50, 2/50, 7/50, 4/50, 7/50, and 4/80, or 6, 4, 14, 8, 14, and 5%. Adjusted incidences: males: 0, 0, 10.0, 12.9, 24.3, and 50.7%; females: 6.5, 4.4, 17.2, 11.8, 34.0, and 35.5%.</td>
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<td>The incidences of cardiac haemangiosarcomas were significantly increased compared with controls in males at 62.5 ppm and above and in females at 200 ppm and above. Incidences: males: 0/50, 0/49, 1/50, 5/48, 20/48, and 4/73, or 0, 0, 2, 10, 42, and 5%; females: 0/50, 0/50, 0/50, 1/49, 21/50, and 23/80, or 0, 0, 2, 10, and 29%. Adjusted incidences: males: 0, 0, 10.0, 12.9, 24.3, and 52.9%; females: 0, 0, 3.1, 71.9, and 83.4%.</td>
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<td>There was evidence of increased incidences of alveolar/bronchiolar adenomas or carcinomas compared with controls in males at 62.5 ppm and above ($p &lt; 0.001$) and in females at all concentrations ($p &lt; 0.001–0.004$). Incidences: males: 21/50, 23/50, 19/50, 31/49, 35/50, and 3/73, or 42, 46, 38, 63, 70, and 4%; females: 4/50, 15/50, 19/50, 24/50, 25/50, and 22/78, or 8, 30, 38, 48, 50, and 28%. Adjusted incidences: males: 47.5, 49.0, 44.9, 74.2, 87.8, and 45.1%; females: 8.8, 33.0, 46.5, 61.1, 81.5, and 82.4%.</td>
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<td><strong>Forestomach</strong></td>
<td>An increased incidence of forestomach tumours (squamous cell papillomas or carcinomas) was observed in males at 200 and 625 ppm ($p &lt; 0.001$) and females at 62.5 ppm and above ($p &lt; 0.001–0.044$). Incidences: males: 1/50, 0/50, 0/50, 1/50, 8/50, and 4/73, or 2, 0, 0, 2, 16, and 5%; females: 0/50, 0/50, 3/50, 2/50, 4/50, and 22/80, or 0, 0, 6, 4, 8, and 28%. Adjusted incidences: males: 2.3, 0, 0, 2.7, 28.7, and 53.5%; females: 0, 0, 7.8, 6.1, 22.5, and 82.6%</td>
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</table>
| **Ovary**    | Increased incidences of malignant and benign granulosa cell tumours were reported in females exposed to 62.5 ppm and above \( (p < 0.001) \).  
Incidences (benign and malignant): 1/49, 0/49, 1/48, 9/50, 8/50, and 6/79, or 2, 0, 2, 18, 16, and 8%  
Adjusted incidences: 2.3, 0, 2.6, 26.3, 41.1, and 46.5% |                                                                                               |
| **Harderian gland** | The incidence of Harderian gland adenomas and carcinomas was increased in both sexes at 62.5 and 200 ppm \( (p < 0.001–0.016) \).  
Incidences:  
males: 6/50, 7/50, 9/50, 20/50, 31/50 and 6/73, or 12, 14, 18, 40, 62 and 8%  
females: 8/50, 10/50, 7/50, 15/50, 20/50, and 9/80, or 16, 20, 14, 30, 40, and 11%  
Adjusted incidences:  
males: 13.5, 15.2, 22.4, 50.8, 80.6, and 64.2%  
females: 17.5, 22.7, 17.4, 41.2, 70.9, and 58.0% |                                                                                               |
| **Mammary gland** | The incidence of mammary gland tumours (adenoacanthomas, carcinomas, and malignant mixed tumours) was increased in females at 62.5 ppm and above \( (p < 0.001–0.004) \). Most of the neoplasms were carcinomas.  
Incidences: 0/50, 2/50, 4/50, 12/50, 15/50, and 16/80, or 0, 4, 8, 24, 30, and 20%  
Adjusted incidences: 0, 4.5, 10.2, 32.6, 56.4, and 66.8% |                                                                                               |
| **Liver**    | In males, the incidence of hepatocellular neoplasms (adenomas and carcinomas) at 200 ppm was significantly greater than that in the controls \( (p = 0.03) \). The authors also reported increases in hepatocellular neoplasms at 62.5 ppm in females \( (p = 0.027) \).  
Incidences (adenomas and carcinomas):  
males: 21/50, 23/50, 30/50, 25/48, 33/48, and 5/72, or 42, 46, 60, 52, 69, and 7%  
females: 15/49, 14/49, 15/50, 19/50, 16/50, and 2/80, or 31, 29, 30, 38, 32, and 3%  
Adjusted incidences (adenomas and carcinomas):  
males: 44.6, 48.2, 65.2, 61.6, 85.9, and 61.2%  
females: 33.3, 30.3, 36.4, 51.4, 64.9, and 21.7% |                                                                                               |
| **Other tumours** | Low incidences of certain uncommon neoplasms also occurred in exposed mice and were considered to be probably related to treatment. These included preputial gland carcinomas (in 5/50 males at 200 ppm, \( p < 0.001 \)) and renal tubule adenomas in both sexes (in 1/50 males at 6.25, 0/48 at 62.5 ppm, and 1/49 at 200 ppm, and in 2/50 females at 200 ppm, compared with none in controls).  
Tumours at other sites that “may be related to exposure” included neurofibrosarcomas or sarcomas of the subcutaneous tissue in females (1/50, 2/50, 3/50, 5/50, 3/50, and 3/80) and Zymbal gland neoplasia (one adenoma in control males, one adenoma and one carcinoma in females at 625 ppm). The investigators were uncertain whether the low incidence of carcinomas of the small intestine in the treated animals (females: 2 at 6.25 ppm, 1 at 625 ppm, males: 1 each at 6.25, 20, and 62.5 ppm, 2 at 200 ppm, compared with none in controls) was exposure related. |                                                                                               |
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Results</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Mice (males; 50 per group) were exposed to butadiene for 6 h/day, 5 days/week, at concentrations of 200 ppm (442 mg/m³) for 40 weeks (equivalent to a total exposure of 8000 ppm-weeks), 312 ppm (690 mg/m³) for 52 weeks (16 000 ppm-weeks), or 625 ppm (1383 mg/m³) for 13 or 26 weeks (8000 and 16 000 ppm-weeks, respectively). After exposure ceased, mice were kept in control chambers until 103 weeks and evaluated. Histopathological examination of a comprehensive range of tissues was conducted on all mice.</td>
<td></td>
<td>Renal tubule adenomas have only rarely been observed in NTP historical controls (1/571). Malignant gliomas and neuroblastomas of the brain rarely develop spontaneously in this strain of mice, with none having been observed in 574 NTP historical controls.</td>
</tr>
</tbody>
</table>

**Lymphohematopoietic system**

The incidence of malignant lymphomas (the majority of which were lymphocytic lymphomas) was markedly increased in both groups exposed to 625 ppm ($p < 0.001$) and occurred as early as 23 weeks in the 625 ppm (26 weeks) group. Incidences: 4/50, 8/50, 22/50, 8/50, and 33/50, or 8, 16, 44, 16, and 66%, in the control, 200 ppm (40 weeks), 625 ppm (13 weeks), 312 ppm (52 weeks), and 625 ppm (26 weeks) groups, respectively. Poly-3 adjusted incidences (adjusted for survival): 9.0, 24.1, 56.1, 35.0, and 87.2%.

The incidence of histiocytic sarcomas was increased in exposed groups ($p < 0.001–0.036$). Incidences: 0/50, 5/50, 2/50, 7/50, and 2/50, or 0, 10, 4, 14, and 4%.

Adjusted incidences: 0, 16.3, 9.4, 30.6, and 20.4%.

**Heart**

The incidence of cardiac haemangiosarcomas was significantly ($p < 0.001$) increased in all groups, but particularly in mice exposed to 200 or 312 ppm.

Incidences: 0/50, 15/50, 7/50, 33/50, and 13/50, or 0, 30, 14, 66, and 26%.

Adjusted incidences: 0, 47.1, 30.9, 85.2, and 74.5%.

**Lungs**

There was a significant ($p < 0.001$) increase in the incidence of pulmonary neoplasms (alveolar/bronchiolar adenoma or carcinoma) in all exposed groups, particularly when the figures were adjusted to take account of mortality.

Incidences: 21/50, 36/50, 28/50, 32/50, and 17/50, or 42, 72, 56, 64, and 34%.

Adjusted incidences: 47.5, 88.6, 89.5, 88.0, and 87.2%.

**Liver**

The incidence of adenomas or carcinomas in the liver was significantly greater in the 200 ppm group ($p = 0.004$) than in the controls and in all exposed groups when adjusted for survival ($p < 0.01–0.05$).

Incidences: 21/50, 33/49, 24/49, 24/50, and 13/50, or 42, 67, 48, and 26%.

Adjusted incidences: 44.6, 82.4, 80.3, 75.9, and 77.3%.

**Forestomach**

There was a significant ($p < 0.001$) increase in the incidence of squamous cell papillomas or carcinomas of the forestomach in mice exposed to 312 or 625 ppm (both 13 and 26 weeks).

Incidences: 21/50, 33/50, 7/50, 9/50, and 10/50, or 2, 6, 14, 18, and 20%.

Adjusted incidences: 2.3, 10.2, 28.7, 39.2, and 60.7%.

**Harderian gland**

The incidence of Harderian gland adenomas or carcinomas was significantly ($p < 0.001$) increased compared with controls in all exposed groups.

Incidences: 6/50, 27/50, 23/50, 30/50, and 13/50, or 12, 54, 46, 60, and 26%.

Adjusted incidences: 13.5, 72.1, 82.0, 88.6, and 76.5%.

**Other tumours**

The incidences of kidney adenomas were 0/50, 4/48, 1/50, 3/49, and 1/50 in the control, 200 ppm (40 weeks), 625 ppm (13 weeks), 312 ppm (52 weeks), and 625 ppm (26 weeks) groups, respectively. The incidence of adenomas or carcinomas of the preputial gland was significantly ($p < 0.001–0.003$) increased in the 312 ppm and 625 ppm (13 or 26 weeks) groups, with incidences of 0/50, 1/50, 5/50, 4/50, and 3/50. Malignant gliomas, which were considered to be exposure related, occurred in two mice exposed to 625 ppm for 13 weeks and one exposed to 625 ppm for 28 weeks. Malignant neuroblastomas were observed in two mice exposed to 625 ppm for 13 weeks. The incidence of adenomas or carcinomas of the Zymbal gland was significantly ($p = 0.009$) increased in mice exposed to 625 ppm for 26 weeks (1/50, 1/50, 0/50, 2/50, and 2/50).
the B6C3F₁ mice, whereas adenocarcinomas of the Harderian gland and the thyroglossal duct were observed in the Swiss mice (Irons et al., 1989).

In the only identified long-term bioassay in rats (Hazleton Laboratories Europe Ltd., 1981a; Owen et al., 1987; Owen & Gaiaister, 1990), male and female Sprague-Dawley rats were exposed to 0, 1000, or 8000 ppm (0, 2212, or 17 696 mg/m³) butadiene for up to 111 weeks. At 8000 ppm (17 696 mg/m³), survival was reduced in both sexes; there were also changes in the relative weights of a number of organs in males at this concentration, along with an increase in the severity of nephropathy of the kidney relative to controls. Relative liver weights were increased in all exposed groups, although there were no exposure-related histopathological effects on the liver. At 8000 ppm (17 696 mg/m³), there were increased incidences of follicular cell adenomas and carcinomas of the thyroid gland in females and exocrine adenomas of the pancreas in males (with a carcinoma occurring in a rat of either sex) (incidence data presented in Table 3). In females, the incidence of benign or malignant mammary gland tumours, along with the incidence of animals with multiple mammary gland tumours, was increased at both 1000 and 8000 ppm (2212 and 17 696 mg/m³). The incidence of sarcomas of the uterus and carcinomas of the Zymbal gland increased significantly with level of exposure in females; in addition, a Zymbal gland carcinoma occurred in one male rat at each exposure level. The incidence of Leydig cell tumours of the testes was increased in both groups of exposed males. The investigators suggested that the occurrence of tumours of the testes and Zymbal gland may have been unrelated to exposure, as the incidences observed were reportedly similar to those in other control rats of the same strain in the study laboratory, although it is noted that Zymbal gland tumours were noted in the chronic bioassays in mice discussed above.

Both the mono- and diepoxide metabolites (EB and DEB) have induced local tumours at the site of application in Swiss mice or Sprague-Dawley rats (Van Duuren et al., 1963, 1965, 1966), although available studies are inadequate to evaluate species differences in sensitivity.

It has been hypothesized that the observed greater sensitivity of B6C3F₁ mice compared with Sprague-Dawley rats to the induction of thymic lymphoma by butadiene may be related to differences in the potential of EB to affect haematopoietic stem cell differentiation observed in in vitro investigations, as suppression of clonogenic response was greater in bone marrow cells from C56BL/6 mice than in those from Sprague-Dawley rats or humans; it was also hypothesized that the sub-population of progenitor cells affected in mice is not present in humans (Irons et al., 1995).

8.5 Genotoxicity and related end-points

The genotoxicity of butadiene has been investigated in a limited range of in vitro assays and a more extensive range of in vivo tests. Butadiene was mutagenic in Salmonella typhimurium strains TA1530 and TA1535 in the presence of metabolic activation with rodent or human S9 preparations (de Meester et al., 1978, 1980; Arce et al., 1990; NTP, 1993; Araki et al., 1994), although it was generally inactive in strains TA97, TA98, and TA100 with or without exogenous activation under similar experimental conditions (Victorin & Ståhlberg, 1988; Arce et al., 1990; NTP, 1993). Results of mouse lymphoma assays have been conflicting, with an increased frequency of mutations at the tk locus in one study at very high concentrations (i.e., 200 000–800 000 ppm [442 400–1 796 600 mg/m³]) in the presence of metabolic activation (Sernau et al., 1986), while there was no convincing activity at concentrations of up to 300 000 ppm (663 600 mg/m³) in another study (although the authors noted that the lack of a positive response may have been due to the low solubility of butadiene in the culture medium; NTP, 1993). Butadiene dissolved in ethanol induced sister chromatid exchanges in cultured mammalian cells (hamsters and humans) (Sasiadek et al., 1991a, 1991b), while in vitro exposure to gaseous butadiene did not induce this effect in preparations from rats, mice, and humans (Arce et al., 1990; Walles et al., 1995).

An overview of the results of available in vivo assays for genotoxicity in germ and somatic cells in mice and rats is presented in Table 4; in general, the data are consistent with species-specific differences in sensitivity to butadiene-induced genetic damage, likely related to the quantitative differences in the formation of active metabolites, although fewer studies have been conducted in rats. Butadiene induced dominant lethal mutations in two strains of mice (CD-1 and (102/E1 × C3H/E1)F₁) following short-term or subchronic exposure of males to concentrations as low as 500 ppm (1106 mg/m³) for 5 days or 65 ppm (144 mg/m³) for 4 weeks; however, exposure to 6250 ppm (13 825 mg/m³) for 6 h did not induce dominant lethal mutations in CD-1 mice. The results of these studies, which depended upon the timing of mating relative to exposure, suggested that the induction of dominant lethal mutations in mice was likely caused by effects on mature germ cells. In the only similar study in rats identified, there was no evidence of dominant lethal mutations in Sprague-Dawley rats exposed to up to 1250 ppm (2765 mg/m³) butadiene for 10 weeks.

Short-term exposure to 500 or 1300 ppm (1106 or 2876 mg/m³) butadiene also induced an exposure-related increase in the incidence of heritable chromosomal
Table 3: Incidence of neoplastic lesions in critical carcinogenicity bioassays for butadiene in Sprague-Dawley CD rats
(Hazleton Laboratories Europe Ltd., 1981a; Owen et al., 1987; Owen & Glaister, 1990).

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Results</th>
<th>Comments</th>
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<tr>
<td>Rats (110 males and 110 females per group) were exposed to concentrations of 0, 1000, or 8000 ppm (0, 2212, or 17 696 mg/m³) butadiene for 6 h/day, 5 days/week. Ten rats per sex per group were killed at 52 weeks. The study was terminated at 105 weeks in females and 111 weeks in males. A comprehensive range of tissues from rats at the high concentration and control rats and a more limited range from rats at the lower concentration were examined microscopically in animals killed after 52 weeks and at the end of the study.</td>
<td>Survival at study termination was 45, 51, and 32% (males) and 48, 34, and 25% (females) at 0, 1000, and 8000 ppm, respectively (based on interpretation of survival curves in published accounts).</td>
<td>The authors indicated that the incidence of pancreatic adenomas may be overestimated, due to difficulties in distinguishing between adenomas and hyperplastic foci or nodules in this organ. The authors noted that the incidence of testicular tumours was similar to that observed in historical controls at Hazleton Laboratories (i.e., 0–6%). It was stated that the incidences of both uterine sarcomas and Zymbal gland carcinomas were similar to those reported in untreated Sprague-Dawley rats at the study laboratory and may not have been treatment related. The authors also indicated that additional support for the observed increases in tumour incidences not being associated with exposure was provided by the fact that the majority of the Zymbal gland tumours were present in animals killed within 76–90 weeks, while none was observed at the end of the study.</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>The incidence of total mammary gland tumours (adenomas or carcinomas) was significantly increased in treated females in both groups (p &lt; 0.01; incidences 50/100, 79/100, and 81/100 in the control, 1000, and 8000 ppm groups, respectively). The positive trend was significant (p &lt; 0.001). The incidence of multiple mammary gland tumours was also increased in exposed females (8/100, 42/100, and 38/100, or 1.38, 3.70, and 3.33 adenomas per adenoma-bearing rat; latter values from Melnick &amp; Huff, 1992).</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Testes</td>
<td>There was a significant (p &lt; 0.01) exposure-related increase in the incidence of Leydig cell tumours in the testis (incidences 0/100, 3/100, and 8/100).</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>Other tumours</td>
<td>The incidence of Zymbal gland carcinomas was significantly increased (p &lt; 0.01) at the highest concentration in females (0/100, 0/100, and 4/100); in males, the incidences were 0/100, 1/100, and 1/100.</td>
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Table 4: Overview of genotoxicity of butadiene and its metabolites in rodents.

<table>
<thead>
<tr>
<th>End-point</th>
<th>Mice (strain)</th>
<th>Rats (strain)</th>
<th>Comments</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><strong>BUTADIENE</strong></td>
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<tr>
<td>Germ cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant lethal mutations</td>
<td>+ (CD-1)</td>
<td>! (Sprague-Dawley)</td>
<td>results in mice depended upon duration of exposure and timing of exposure relative to mating; rats were exposed to concentrations similar to those that induced effects in mice</td>
<td>Morrissey et al., 1990; Anderson et al., 1993; Adler et al., 1994, 1998; BIBRA International, 1996a, 1996b; Brinkworth et al., 1998</td>
</tr>
<tr>
<td>Heritable translocations</td>
<td>+ (C3H/E1)</td>
<td>NT</td>
<td></td>
<td>Adler et al., 1995a, 1998</td>
</tr>
<tr>
<td>Other genetic effects on male germ cells (chromosomal aberrations in embryos, DNA damage, sperm head morphology, micronuclei)</td>
<td>+ ((102/E1 × C3H/E1)F₁)</td>
<td>NT</td>
<td></td>
<td>Morrissey et al., 1990; Xiao &amp; Tates, 1995; Brinkworth et al., 1998; Pacchierotti et al., 1998a; Tommasi et al., 1998</td>
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<tr>
<td>Somatic cells</td>
<td></td>
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<tr>
<td>Chromosomal aberrations (bone marrow)</td>
<td>+ (B6C3F₁)</td>
<td>NT</td>
<td></td>
<td>Irons et al., 1987; Tice et al., 1987; Shelby, 1990; NTP, 1993</td>
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<tr>
<td>+ (Swiss)</td>
<td></td>
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<td></td>
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<tr>
<td>Sister chromatid exchanges (bone marrow)</td>
<td>+ (B6C3F₁)</td>
<td>! (Sprague-Dawley)</td>
<td>rats were exposed to much higher concentrations than those that induced effects in mice</td>
<td>Choy et al., 1986; Cunningham et al., 1986; Irons et al., 1986a, 1986b; Tice et al., 1987; Jauhar et al., 1988; Arce et al., 1990; Shelby, 1990; Victorin et al., 1990; NTP, 1993; Przygoda et al., 1993; Adler et al., 1994; Autio et al., 1994; Leavens et al., 1997; Stephanou et al., 1998</td>
</tr>
<tr>
<td>Micronuclei (bone marrow, blood, spleen)</td>
<td>+ (NMRI)</td>
<td>! (Sprague-Dawley)</td>
<td>effects in mice were observed at the lowest concentration tested (i.e., 6.25 ppm); male mice appeared to be more sensitive than female mice; rats were exposed to concentrations similar to those that induced effects in mice</td>
<td>Choy et al., 1986; Cunningham et al., 1986; Irons et al., 1986a, 1986b; Tice et al., 1987; Jauhar et al., 1988; Arce et al., 1990; Shelby, 1990; Victorin et al., 1990; NTP, 1993; Przygoda et al., 1993; Adler et al., 1994; Autio et al., 1994; Leavens et al., 1997; Stephanou et al., 1998</td>
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<tr>
<td>+ (B6C3F₁)</td>
<td>! (Wistar)</td>
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<tr>
<td>+ (CB6F₁)</td>
<td>! (Wistar)</td>
<td></td>
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<tr>
<td>+((102/E1 × C3H/E1)F₁)</td>
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<tr>
<td>+ (NIH Swiss)</td>
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<tr>
<td>hprt&lt;sup&gt;+&lt;/sup&gt; mutations (spleen, thymus)</td>
<td>+ ((102/E1 × C3H/E1)F₁) + (F344)</td>
<td></td>
<td>mice appeared to be more sensitive than rats</td>
<td>Cochrane &amp; Skopek, 1993, 1994b; Tates et al., 1994, 1998; Meng et al., 1998, 2000</td>
</tr>
<tr>
<td>+ (B6C3F₁)</td>
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<tr>
<td>+ (CD-1)</td>
<td></td>
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<tr>
<td>Specific locus mutations (mouse spot test)</td>
<td>+ ((102/E1 × C3H/E1)F₁)</td>
<td>NT</td>
<td></td>
<td>Adler et al., 1994</td>
</tr>
<tr>
<td>Transgenic systems (&lt;i&gt;lacZ&lt;/i&gt;, &lt;i&gt;lacI&lt;/i&gt;)</td>
<td>+ (CD2F₁, derived)</td>
<td>NT</td>
<td></td>
<td>Recio et al., 1992, 1993, 1996; Sisk et al., 1994; Recio &amp; Meyer, 1995</td>
</tr>
<tr>
<td>+ (B6C3F₁, derived)</td>
<td></td>
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<tr>
<td>Unscheduled DNA synthesis (liver)</td>
<td>! (B6C3F₁)</td>
<td>! (Sprague-Dawley)</td>
<td></td>
<td>Vincent et al., 1986; Arce et al., 1990</td>
</tr>
<tr>
<td>DNA–DNA or DNA–protein cross-links (liver)</td>
<td>+/! (B6C3F₁)</td>
<td>! (Sprague-Dawley)</td>
<td></td>
<td>Jelitto et al., 1989; Ristau et al., 1990; Vangala et al., 1993</td>
</tr>
<tr>
<td>DNA binding (liver, lung)</td>
<td>+ (B6C3F₁)</td>
<td>+ (Wistar)</td>
<td>levels of adducts were slightly higher in mice than in rats</td>
<td>Kreiling et al., 1986; Sorsa et al., 1996b; Kolvisto et al., 1997, 1998; Tretyakova et al., 1999a, 1999b</td>
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<tr>
<td>+ (CB6F₁)</td>
<td>+ (Sprague-Dawley)</td>
<td>+ (F344)</td>
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</table>
### 1,3-Butadiene: Human health aspects

Table 4 (contd).

<table>
<thead>
<tr>
<th>End-point</th>
<th>Mice (strain)</th>
<th>Rats (strain)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA strand breaks and other damage (liver, lung, testes)</td>
<td>+ (B6C3F1)</td>
<td>+ (Sprague-Dawley)</td>
<td>results were dependent on analytical method used; there was little quantitative species difference in the degree of strand breakage</td>
<td>Vangala et al., 1993; Walles et al., 1995; Anderson et al., 1997</td>
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<tr>
<td></td>
<td>+ (NMRI)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>! (CD-1)</td>
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</tbody>
</table>

**1,2-EPOXY-3-BUTENE (EB)**

**Germ cells**

- Dominant lethal mutations
  - (! ((102/E1 × C3H/E1)F1)) NT
  - Adler et al., 1997

- Other genetic effects on male germ cells (micronuclei)
  - + (F1(102 × C3H)) + (Lewis) Lewis rats appeared to be slightly more sensitive than mice
  - Xiao & Tates, 1995; Lähdetie et al., 1997; Russo et al., 1997
  - + (BALB/c) + (Sprague-Dawley)

**Somatic cells**

- Chromosomal aberrations (bone marrow)
  - + (C57Bl/6) NT
  - Sharief et al., 1986

- Sister chromatid exchanges (spleen)
  - + (BALB/c) NT
  - Stephanou et al., 1997

- Micronuclei (spleen, blood, bone marrow)
  - + (F1(102 × C3H)) + (Lewis) (F1(102 × C3H) mice appeared to be more sensitive than Lewis rats; CD-1 mice appeared to be more sensitive than Sprague-Dawley rats
  - Xiao & Tates, 1995; Adler et al., 1997; Anderson et al., 1997; Lähdetie & Grävé, 1997; Russo et al., 1997
  - + (BALB/c) + (Sprague-Dawley)

- hprt- mutations (spleen)
  - + (B6C3F1) ! (Lewis) + (F344)
  - Cochrane & Skopek, 1994b; Tates et al., 1998; Meng et al., 1999

- Transgenic systems (lacI)
  - ! (B6C3F1 derived) + (F344 derived) rats appeared to be more sensitive than mice
  - Saranko et al., 1998

- DNA strand breaks and other damage (bone marrow, testes)
  - + (CD-1) !/+ (Sprague-Dawley) damage was observed only in bone marrow cells of rats
  - Anderson et al., 1997

- Unscheduled DNA synthesis (testes)
  - ! (CD-1) NT
  - Anderson et al., 1997

**1,2,3,4-DIEPOXYBUTANE (DEB)**

**Germ cells**

- Dominant lethal mutations
  - + ((102/E1 × C3H/E1)F1) NT
  - Adler et al., 1995b

- Other genetic effects on male germ cells (chromosomal aberrations in zygotes, micronuclei)
  - + ((C57Bl/Cne × C3H/Cne)F1) + (Lewis) Lewis rats appeared to be more sensitive to induction of micronuclei than F1(102 × C3H) mice
  - Adler et al., 1995b; Xiao & Tates, 1995; Lähdetie et al., 1997; Russo et al., 1997
  - + (F1(102 × C3H)) + (Sprague-Dawley)

- Effects on female germ cells (chromosomal aberrations in embryos)
  - + (B6C3F1) NT
  - Tiveron et al., 1997

**Somatic cells**

- Chromosomal aberrations (bone marrow)
  - + (NMRI) NT
  - positive results were also obtained in Chinese hamsters, with NMRI mice being more sensitive than hamsters
  - Walk et al., 1987

- Sister chromatid exchanges (bone marrow, lung, liver)
  - + (NMRI) NT
  - positive results were also obtained in Chinese hamsters, with NMRI mice being more sensitive than hamsters
  - Conner et al., 1983; Walk et al., 1987

- Chromosomal aberrations (bone marrow)
  - + (NMRI) NT
  - positive results were also obtained in Chinese hamsters, with NMRI mice being more sensitive than hamsters
  - Walk et al., 1987

- Sister chromatid exchanges (bone marrow, lung, liver)
  - + (NMRI) NT
  - positive results were also obtained in Chinese hamsters, with NMRI mice being more sensitive than hamsters
  - Conner et al., 1983; Walk et al., 1987
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<th>Mice (strain)</th>
<th>Rats (strain)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronuclei (spleen, blood, bone marrow)</td>
<td>+ (F1(102 × C3H))</td>
<td>+ (Lewis)</td>
<td>there was little difference in sensitivity between F1(102 × C3H) mice and Lewis rats or between CD-1 mice and Sprague-Dawley rats</td>
<td>Adler et al., 1995b; Xiao &amp; Tates, 1995; Anderson et al., 1997; Lähdetie &amp; Grawé, 1997; Russo et al., 1997; Stephanou et al., 1997</td>
</tr>
<tr>
<td></td>
<td>+ (BALB/c)</td>
<td>+ (Sprague-Dawley)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ ((102/E1 × C3H/E1)F1)</td>
<td>+ (CD-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hprt mutations (spleen)</td>
<td>+ (B6C3F1)</td>
<td>! (Lewis)</td>
<td>F344 rats appeared to be more sensitive than B6C3F, mice</td>
<td>Cochrane &amp; Skopek, 1994b; Tates et al., 1998; Meng et al., 1999</td>
</tr>
<tr>
<td></td>
<td>! ((102/E1 × C3H/E1)F1)</td>
<td>+ (F344)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transgenic systems (lacI)</td>
<td>! (B6C3F, derived)</td>
<td>! (F344 derived)</td>
<td></td>
<td>Recio et al., 1998</td>
</tr>
<tr>
<td>DNA binding</td>
<td>+ (ICR)</td>
<td>NT</td>
<td></td>
<td>Mabon et al., 1996</td>
</tr>
<tr>
<td>DNA strand breaks and other damage (bone marrow, testes)</td>
<td>+/- (CD-1)</td>
<td>+/- (Sprague-Dawley)</td>
<td>damage was noted in bone marrow cells only</td>
<td>Anderson et al., 1997</td>
</tr>
<tr>
<td>Unscheduled DNA synthesis (testes)</td>
<td>+ (CD-1)</td>
<td>NT</td>
<td></td>
<td>Anderson et al., 1997</td>
</tr>
</tbody>
</table>

1,2-DIHYDROXY-3,4-EPOXYBUTANE (EBdiol)

**Germ cells**

| Dominant lethal mutations | ! ((102/E1 × C3H/E1)F1) | NT | | Adler et al., 1997 |
| Other genetic effects on male germ cells (micronuclei) | NT | + (Sprague-Dawley) | | Lähdetie et al., 1997 |

**Somatic cells**

| Micronuclei (bone marrow) | + ((102/E1 × C3H/E1)F1) | + (Sprague-Dawley) | | Adler et al., 1997; Lähdetie & Grawé, 1997 |

Translocations in mice; an increased incidence of chromosomal aberrations was also noted in zygotes of male mice exposed to $500$ ppm ($1106$ mg/m$^3$) for 5 days. Other butadiene-induced effects observed in male germ cells of mice include sperm head abnormalities, micronuclei in spermatids, and DNA damage (strand breaks and alkaline-labile sites). Investigations of these end-points in rats have not been identified.

Butadiene was consistently genotoxic in somatic cells of several strains of mice, inducing chromosomal aberrations, sister chromatid exchanges, and micronuclei in numerous assays; micronuclei have been observed following exposure to concentrations as low as 6.25 ppm (13.8 mg/m$^3$) butadiene for 13 weeks or 62.5 ppm (138 mg/m$^3$) for 8 h. Although only few studies were identified, these effects were not observed in rats exposed to much higher concentrations. However, gene mutations at the hprt locus have been induced in both mice and rats, with a four- to sevenfold greater mutagenic potency being determined for mice than for rats. Mutagenic activity was also observed in two transgenic mouse systems and in the mouse spot test. Binding to DNA has been observed in all strains of mice and rats tested; following exposure to butadiene, adducts of both guanine and adenine with the monoepoxide as well as the monoepoxide diol metabolites (EB and EBdiol, respectively) have been observed. The degree of adduct formation was generally similar in the two species or, in some studies, up to twofold greater in mice than in rats. Similarly, there was little quantitative difference in the amount of butadiene-induced single strand breaks in DNA of mice and rats. DNA–DNA and DNA–protein cross-links were noted in one of two studies in mice, but not in rats exposed to higher concentrations of butadiene.

Metabolites of butadiene have also been mutagenic and clastogenic in numerous in vitro and in vivo assays (see Table 4 for overview of results of in vivo assays). EB, DEB, and EBdiol all induced mutations in bacteria and yeast in the absence of exogenous metabolic activation (IARC, 1992; NTP, 1993; Thier et al., 1994; Adler et al., 1997); mutagenic activity was also observed for all three metabolites at two foci in human TK6 lymphoblastoid cells, with DEB being much more potent (Cochrane & Skopek, 1993, 1994a). Conversely, the monoepoxide was much more potent than the diepoxide in the induction of mutations at the lacI transgene of fibroblasts obtained from a transgenic rat strain (Saranko & Recio, 1998; Saranko et al., 1998). Both EB and DEB also induced sister chromatid exchanges,
employed to measure cross-links (Anderson et al., 1997). In vitro exposure to DEB, but not EB or EBdiol, induced micronuclei in spermatids isolated from rats (Sjöblom & Lättem, 1996).

The monoepoxide, diepoxide, and monoepoxide diol metabolites all induced micronuclei in germ cells of male mice and rats; in one of these studies, the magnitude of the effect was greater in Lewis rats than in F1 (102 x C3H) mice. There were no consistent patterns in the relative potency of the three metabolites. Chromosomal aberrations in zygotes produced by exposed males and dominant lethal mutations were induced by DEB in mice (strains (C57B1/6C3He × C3H/He)F1 and (102/E1 × C3H/ E1)F1, respectively), whereas EB and EBdiol did not induce dominant lethal mutations. In the only identified investigation of the potential effects on female germ cells, pre-mating exposure of female B6C3F1 mice to DEB resulted in an increased frequency of chromosomal aberrations in embryos in the absence of ovarian toxicity.

EB, DEB, and EBdiol were also genotoxic in somatic cells (bone marrow, peripheral blood, lung, and spleen), inducing sister chromatid exchanges, chromosomal aberrations, or micronuclei in several strains of mice, rats, and hamsters, with little consistent evidence of interspecies differences in sensitivity; in general, the diepoxide was more potent than the monoepoxide or the monoepoxide diol. Although negative results were obtained in Lewis rats, both EB and DEB induced an increased frequency of hprt mutations in B6C3F1 mice and F344 rats, with rats being more sensitive than mice, which may be related to slower clearance in rats. EB induced mutations in the bone marrow of lacI transgenic rats, but not in lacI transgenic mice; DEB did not induce lacI mutations in either species. Meng et al. (1999) suggested that the hprt assay is more sensitive to the detection of large deletions induced by DEB than the lacI transgene assay. DNA damage (strand breaks or alkali-labile sites) was caused by EB and DEB in the bone marrow of rats and mice, with DEB being less potent than EB; the only damage observed in haploid testicular cells was in mice exposed to EB. It was suggested that the apparent greater potency of EB compared with DEB may be due to the bifunctional alkylation ability of DEB, subsequent induction of DNA repair, and the inability of the alkaline Comet assay employed to measure cross-links (Anderson et al., 1997).

8.6 Reproductive toxicity
8.6.1 Effects on fertility

Few data on the effects of butadiene on reproductive ability were identified. Exposure to up to 1300 ppm (2876 mg/m3) for 5 days did not affect the reproductive abilities of male (102/E1 x C3H/E1)F1 mice, based on percentages of successful pairings with unexposed females and unfertilized metaphase I oocytes (Paccierotti et al., 1998a). Similarly, there were no decreases in mating frequency or pregnancy rate in the dominant lethal studies in mice and rats (Anderson et al., 1993, 1998; BIBRA International, 1996a, 1996b; Brinkworth et al., 1998). Documentation of an earlier study in rats, guinea-pigs, and rabbits (Carpenter et al., 1944) is too limited for evaluation.

The reproductive organs have consistently been targets of non-neoplastic effects induced by butadiene in subchronic and long-term bioassays in B6C3F1 mice but not in Sprague-Dawley rats, although butadiene-induced tumours of the reproductive organs have been observed in both species. Ovarian atrophy and decreased weight were observed in mice exposed to 1000 ppm (2212 mg/m3, the only concentration tested) for 13 weeks (Bevan et al., 1996). In the 2-year bioassay conducted by the NTP, there was a significant increase in the incidence of ovarian atrophy in females exposed for up to 2 years to all concentrations tested (i.e., $6.25$ ppm [$13.8$ mg/m3]); both the incidence and the severity of this lesion increased with exposure. Ovarian atrophy was also observed at the interim sacrifices at 9 and 15 months at higher concentrations ($200$ and $62.5$ ppm ($442$ and $138$ mg/m3), respectively). Atrophied ovaries characteristically had no evidence of oocytes, follicles, or corpora lutea. Aniectasis and germinal epithelial hyperplasia of the ovaries were reported at $62.5$ and $200$ ppm ($138$ and $442$ mg/m3), respectively, after exposure for 2 years. Uterine atrophy was also noted at concentrations of 200 ppm (442 mg/m3) or greater. Survival was decreased at $20$ ppm ($44.2$ mg/m3), principally due to neoplastic lesions at several sites, including the ovaries (Melnick et al., 1990; NTP, 1993).

Effects on the testes, including reduced weight, degeneration, or atrophy, were observed in B6C3F1 mice exposed to concentrations at or above 200 ppm (442 mg/m3) for 2 years or to higher levels for shorter durations (NTP, 1993; Bevan et al., 1996). Cytotoxic effects on differentiating spermatogonia were noted in (102/E1 x C3H/E1)F1 mice 21 days after exposure to $130$ ppm ($288$ mg/m3) for 5 days; a decrease in elongated spermatids was noted in mice exposed to 1300 ppm (2876 mg/m3) (Paccierotti et al., 1998a).
No non-neoplastic effects were noted in the reproductive organs of male or female Sprague-Dawley rats exposed to up to 8000 ppm (17 696 mg/m²) butadiene for 2 years (Hazleton Laboratories Europe Ltd., 1981a; Owen et al., 1987).

Both the mono- and diepoxide metabolites of butadiene induced ovarian toxicity (depletion of small and growing follicles) and alkylation with macromolecules in the ovary in B6C3F₁ mice repeatedly exposed via intraperitoneal injection. In contrast, effects in the ovary in Sprague-Dawley rats were observed only in rats exposed to the diepoxide at doses higher than those that were active in the mice (Doerr et al., 1996). Since the results of structure–activity studies with 4-vinylcyclohexene and several of its analogues, butadiene monoepoxide and diepoxide, epoxybutane, and isoprene indicated that compounds that form only monooxepoxides do not induce ovarian toxicity (Doerr et al., 1995), it appears that conversion to the bifunctional diepoxide may be required for the induction of these effects. A single intraperitoneal injection of DEB reduced various testicular cell populations and induced morphological changes in the epithelium of the seminiferous tubules in male B6C3F₁ mice (Spano et al., 1996).

### 8.6.2 Developmental toxicity

Few studies on the potential for butadiene to induce developmental effects have been identified. There was no evidence of teratogenicity following exposure of pregnant CD-1 mice to up to 1000 ppm (2212 mg/m³) butadiene on days 6 through 15 of gestation, although maternal toxicity (decreased body weight gain) and fetal toxicity (reduced fetal body weight and skeletal abnormalities) occurred at 200 ppm (442 mg/m³) and above, and there was a slight reduction in male fetal body weight at 40 ppm (88 mg/m³) of questionable biological significance (Hackett et al., 1987b; Morrissey et al., 1990). In Sprague-Dawley rats exposed to 8000 ppm (17 696 mg/m³) butadiene on days 6 through 15 of gestation, there was an increased incidence of “major” abnormalities of the skull, spine, sternum, long bones, and ribs. Abnormalities believed to be associated with retarded embryonic growth were observed at 200 and 1000 ppm (442 and 2212 mg/m³). Maternal toxicity (decreased body weight gain or loss of body weight) was observed in all exposed groups (Hazleton Laboratories Europe Ltd., 1981b, 1982). However, there was no evidence of developmental toxicity in Sprague-Dawley rats exposed to up to 1000 ppm (2212 mg/m³) butadiene, also on days 6 through 15 of gestation, although maternal toxicity (decreased body weight gain) was noted at the highest concentration (Hackett et al., 1987a; Morrissey et al., 1990).

Although evidence of male-mediated teratogenicity was observed when male CD-1 mice exposed to 12.5 ppm (27.7 mg/m³) butadiene for 10 weeks were mated with unexposed females (Anderson et al., 1993), there was no increase in malformations when the study was repeated at 12.5 and 125 ppm (27.7 and 277 mg/m³) (Brinkworth et al., 1998). The authors suggested that the discrepant results may be a function of the statistical significance in the first study being due to the lack of abnormalities in controls (compared with 2.5% in exposed), whereas a low incidence was noted in exposed and control mice in the follow-up study. Similarly, there were no significant increases in fetal abnormalities in CD-1 mice following paternal exposure to up to 6250 ppm (13 825 mg/m³) butadiene for 6 h (Anderson et al., 1993) or concentrations up to 130 ppm (288 mg/m³) for 4 weeks (BIBRA International, 1996a), although it was noted in the latter study that some females may have been sacrificed too early for detection of abnormalities. There was no evidence of male-mediated teratogenicity in offspring of male Sprague-Dawley rats exposed for 10 weeks to concentrations as high as 1250 ppm (2765 mg/m³) butadiene and then mated with unexposed females (BIBRA International, 1996b).

### 8.7 Immunotoxicity

Although the haematopoietic system is a target of butadiene-induced toxicity, no effects on immune system function of biological significance were observed in the only relevant study identified in which B6C3F₁ mice were exposed to 1250 ppm (2765 mg/m³) butadiene for up to 24 weeks, although there were depressions in cellularity and plaque-forming cells as well as histopathological changes in the spleen (Thurmond et al., 1986).

### 9. EFFECTS ON HUMANS

#### 9.1 Clinical studies

Slight irritation of the eyes or respiratory tract was observed in volunteers exposed to very high concentrations of butadiene (i.e., >2000 ppm [>4400 mg/m³]) in the few early clinical investigations identified (Larionov et al., 1934; Carpenter et al., 1944); however, these studies are inadequate for evaluation of the potential effects of butadiene in humans, as only subjective symptoms appear to have been evaluated.
### Table 5: Summary of measures of risk for cancers of the lymphohaematopoietic system in populations occupationally exposed to butadiene.

<table>
<thead>
<tr>
<th>Cohort description</th>
<th>Cohort size</th>
<th>Number of cases</th>
<th>Exposure</th>
<th>Risk measure&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Styrene-butadiene rubber workers</td>
<td>15,649</td>
<td>48</td>
<td>0 ppm-years</td>
<td>SMR = 131 (97–174)</td>
<td>SMR was significant in some subgroups; increasing trend in RRs remained when adjusted for styrene</td>
<td>Delzell et al., 1995</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7</td>
<td>&gt;0–19 ppm-years</td>
<td>RR = 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>14</td>
<td>20–99 ppm-years</td>
<td>RR = 1.4 (0.4–4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>18</td>
<td>100–199 ppm-years</td>
<td>RR = 2.3 (0.7–7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7</td>
<td>$200 ppm-years</td>
<td>RR = 2.6 (0.7–10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td></td>
<td>RR = 4.2 (1.0–17.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butadiene production workers</td>
<td>2,795</td>
<td>13</td>
<td>low</td>
<td>SMR = 113 (60–193)</td>
<td>no association between qualitative measure of cumulative exposure and leukaemia risk</td>
<td>Divine &amp; Hartman, 1996</td>
</tr>
<tr>
<td></td>
<td>996</td>
<td>3</td>
<td>low</td>
<td>SMR = 67 (13–195)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1,874</td>
<td>11</td>
<td>varied</td>
<td>SMR = 154 (77–275)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butadiene production workers</td>
<td>364</td>
<td>2</td>
<td></td>
<td>SMR = 123 (15–444)</td>
<td></td>
<td>E.M. Ward et al., 1995</td>
</tr>
<tr>
<td><strong>Lymphosarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Styrene-butadiene rubber workers</td>
<td>15,649</td>
<td>11</td>
<td></td>
<td>SMR = 80 (40–144)</td>
<td>SMRs were increased for maintenance workers (O = 8; SMR = 192; 95% CI = 83–379) and labourers (O = 3; SMR = 123; 95% CI = 25–359), but not in production or laboratory workers</td>
<td>Delzell et al., 1995</td>
</tr>
<tr>
<td>Butadiene production workers</td>
<td>2,795</td>
<td>9</td>
<td>background</td>
<td>SMR = 191 (87–364)</td>
<td>no association with duration of employment, based on only two and one cases in the two higher categories</td>
<td>Divine &amp; Hartman, 1996</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>background</td>
<td>SMR = 0 (0–591)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>low</td>
<td>SMR = 109 (12–395)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7</td>
<td>varied</td>
<td>SMR = 249 (100–513)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butadiene production workers</td>
<td>364</td>
<td>4</td>
<td>&lt;2 years</td>
<td>SMR = 577 (157–1480)</td>
<td>Trend with duration of employment when dichotomized at 2 years</td>
<td>E.M. Ward et al., 1995</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>$2 years</td>
<td>SMR = 303</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td></td>
<td>SMR = 827 ($p &lt; 0.05$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> SMR = standardized mortality ratio; CI = confidence interval; RR = relative risk; O = observed cases.

<sup>b</sup> SMR = observed/expected × 100.

### 9.2 Epidemiological studies

#### 9.2.1 Cancer

The carcinogenicity of butadiene has been investigated in several populations of workers occupationally exposed during its manufacture or use. Although most of these studies are limited by the paucity of historical monitoring data, there is evidence that occupational exposure to butadiene in the styrene-butadiene rubber industry is associated with excess mortality due to leukaemia and weaker evidence of an association with lymphosarcoma<sup>1</sup> in butadiene monomer production workers. A summary of the measures of risk for lymphohaematopoietic cancers is presented in Table 5.

In the most recent update of the largest of the cohorts of male monomer workers (n = 2,795) at the Port Neches butadiene production facility in Texas, USA (Divine & Hartman, 1996), mortality due to lymphohaematopoietic cancer was significantly elevated (standardized mortality ratio [SMR]<sup>2</sup> = 147; 95% confidence interval [CI] = 106–198), due largely to a non-significant increase in the number of deaths due to lymphosarcoma and reticulosarcoma (SMR = 191, 95% CI = 87–364), based on nine cases. However, there was no association with duration of employment (SMRs of 261,
employed at eight styrene-butadiene rubber manufacturing facilities in North America (Delzell et al., 1995). The results of this study are emphasized here and considered to supplant those of earlier investigations, as there is considerable overlap in the cohort population with the earlier studies (i.e., 14,869 of these subjects had been employed at one of the two plants studied previously by Meinhardt et al. [1982] or at seven of the eight plants investigated by Matanoski et al. [1990, 1993] and Santos-Burgoa et al. [1992], although they had been employed for different time periods [Delzell et al. (1995) included several more years of follow-up] and selected using different inclusion criteria). Estimates of cumulative exposure and peak exposure frequency were derived for workers from six of the eight plants based on complete work histories for 97% of these employees, information on processes and plant conditions based on available records, walk-through surveys, and interviews with long-term employees, plant engineers, and managers and were compared with monitoring data from surveys conducted from the late 1970s onward. There was an increase in mortality due to leukaemia, which was of borderline statistical significance, in the overall cohort, based on 48 cases (SMR = 131; 95% CI = 97–174); this excess was concentrated in workers who had had 10 or more years of employment and 20 or more years since date of hire (O = 29; SMR = 201; 95% CI = 134–288). Similarly, there was a significant increase in mortality due to leukaemia in “ever hourly” workers (i.e., workers who had ever been paid on an hourly basis) whose jobs were most likely to have involved exposure to butadiene (O = 45; SMR = 143; 95% CI = 104–191), which was again concentrated in workers with longer duration of employment and time since hire and was greater in black workers than in white workers in this subgroup. The SMRs for leukaemia also increased with duration of employment for ever hourly workers. When examined by type of employment, the number of deaths due to leukaemia was significantly increased in production workers (O = 22; SMR = 159; 95% CI = 100–241), labourers (O = 16; SMR = 195; 95% CI = 112–317; concentrated among black workers), laboratory workers (O = 12; SMR = 462; 95% CI = 238–806), and black workers in other operations (O = 3; SMR = 680; 95% CI = 137–1986); no significant increases were observed in maintenance workers (O = 13; SMR = 107; 95% CI = 57–184). (Although analyses were not presented and no further information is given, Delzell et al. [1995], in the Discussion section of their report, reported that there was no increase in mortality due to leukaemia in 851 workers in butadiene production areas

1 It is not possible to determine, with any certainty, the size of the population in these earlier studies that was not subsumed in the later investigation by Delzell et al. (1995). One of the small plants of approximately 600 workers included in the Matanoski et al. (1990, 1993) cohort was not examined by Delzell et al. (1995).
[which would not involve exposure to styrene], with very low numbers of observed and expected deaths (1 versus 2.1, respectively.). As well, the SMRs for lymphosarcoma were non-significantly increased for maintenance workers (O = 8; SMR = 192; 95% CI = 83–379) and labourers (O = 3; SMR = 123; 95% CI = 25–359), while there was no increase in mortality due to lymphosarcoma in production workers or laboratory workers. When individual plants were considered separately, there were non-statistically significant increases in mortality due to leukaemia at most (but not all) plants (SMRs ranged from 72 to 780, excluding groups in which zero cases were observed and less than one case was expected); numbers of observed cases of lymphosarcoma were too low to permit meaningful conclusions with respect to mortality at individual plants.

In regression analyses, mortality due to leukaemia was observed to increase with cumulative exposure to butadiene, as relative risk (RR) values for exposure categories of 0, >0–19, 20–99, 100–199, and >200 ppm-years were 1.0, 1.4, 2.3, 2.6, and 4.2, respectively (for cases in which leukaemia was considered the underlying cause of death). There was only limited evidence of an association with cumulative exposure to peak levels of butadiene. The authors also investigated the potential influence of exposure to styrene or benzene on mortality and determined that the trend for increased risk with increased cumulative exposure to styrene was less pronounced, while exposure to benzene was considered to be too infrequent (few subjects were exposed) and too low to be a confounding factor. There was no association between cumulative exposure to butadiene and non-Hodgkin’s lymphoma in regression analyses.

Based on the results of this study, Delzell et al. (1995) concluded that there was a relationship between employment in the styrene-butadiene industry and leukaemia, with the increased risk of leukaemia being most strongly associated with exposure to butadiene or to butadiene and styrene in combination (although the association with butadiene remained after controlling for exposure to styrene). Data were insufficient to draw any firm conclusions with respect to an association with any specific form of leukaemia.

In a subsequent study in which Delzell et al. (1996) attempted to better define exposure of this cohort to peak levels of butadiene, the RR for leukaemia increased with increasing average annual number of peaks to which workers were exposed (RRs of 1.0, 2.3, and 3.1 for 0, >0–3288, and >3288 peaks), as well as again with cumulative exposure to butadiene (RRs of 1.0, 1.1, 2.0, 2.4, and 4.6 for 0, >0–19, 20–99, 100–199, and >200 ppm-years). Although the analyses were not presented, adjusting for cumulative exposure to styrene apparently had little influence on the exposure–response relationship. Risk of leukaemia also increased with duration of employment in areas in which there was “definite” exposure to peaks (RRs of 1.0, 2.3, and 2.7 for 0, >0–4, and >5 years) and in areas for which elevated SMRs had been noted in the previous analyses (RRs of 1.0, 1.9, and 3.1 for 0, >0–4, and >5 “high SMR-years”). The authors noted that it was not possible to distinguish between the roles of estimated peak or cumulative exposure.

The estimates of exposure were further refined for workers at one of the plants included in the investigation by Delzell et al. (1995) through more extensive research of historical conditions (Macaluso et al., 1997). Although there was little change in classification of various workers as exposed or non-exposed, the revised estimates of cumulative exposure to butadiene for many job groups were generally greater (two- to threefold) than the original; the most substantial increase (by an order of magnitude) was determined for tasks among unskilled labourers during the 1950s and 1960s. It was not indicated in the report if the rank order of the cumulative exposure estimates differed (although it is likely that it did not; Gerin & Siemiatycki, 1998). There was little change in estimated exposure to peak levels of butadiene or in cumulative exposure to styrene. These revised exposure estimates have not yet been incorporated into cancer mortality analyses.

Sathiakumar et al. (1998) re-examined the mortality of this cohort based on currently accepted terminology for lymphoepitheliocytic cancers (other than leukaemia). There were no significant increases in deaths in the overall cohort due to non-Hodgkin’s lymphoma, Hodgkin’s disease, multiple myeloma, or cancers of other lymphatic tissue, nor were there any associations between mortality due to these causes and duration of exposure and year of hire. Similarly, mortality due to these causes was not associated with any process group; however, the authors noted that an association for non-Hodgkin’s lymphoma may be obscured by the possibility that some cases of non-Hodgkin’s lymphoma had transformed to leukaemia, with the latter form of cancer being recorded on the death certificate.

An association between exposure to butadiene and leukaemia, as well as Hodgkin’s disease, was also observed in a recent independently conducted nested case–control study of 58 cases of lymphoepitheliocytic cancers from a cohort of styrene-butadiene rubber workers (from many of the same plants investigated by Delzell et al. [1995]), in which exposure was estimated based on analyses of monitoring data obtained in the last 15–20 years of operation (Matanoski et al., 1997).
compared with values for 145 workers exposed to much butadiene (up to about 53 ppm [117 mg/m$^3$]) and 8 workers exposed to high concentrations of butadiene (up to 143 ppm [316 mg/m$^3$]) when analyzed on the basis of mean concentrations of butadiene ranging up to 10 ppm (22 mg/m$^3$) (with a maximum time-weighted average concentration of 143 ppm [316 mg/m$^3$]) and 2600 unexposed workers at a butadiene production facility in Texas, USA (Cowles et al., 1994). However, Checkoway & Williams (1982) observed changes in haematological parameters consistent with bone marrow depression in eight workers exposed to high concentrations of butadiene (up to about 53 ppm [117 mg/m$^3$]) when compared with values for 145 workers exposed to much lower levels (i.e., <1 ppm [<2.2 mg/m$^3$]).

9.2.3 Genotoxicity

The potential genotoxicity of butadiene has recently been investigated in several studies of groups of workers exposed in the production of butadiene, styrene-butadiene rubber, or polybutadiene rubber. Although the data available to date are not completely consistent, they indicate that there is some evidence that exposure to butadiene induces genetic effects in occupationally exposed populations and that sensitivity to the induction of these effects is related to genetic polymorphism for enzymes involved in the metabolism of butadiene, most notably those within the glutathione-S-transferase class. The results of several in vitro studies in human lymphocytes have demonstrated that sensitivity to DEB-induced sister chromatid exchanges and micronuclei is associated with the presence or absence of homozygous deletion of the GSTT1 gene, which codes for GSTZ (Kelsey et al., 1995; Norppa et al., 1995; Wiencke et al., 1995; Land et al., 1996; Pelin et al., 1996; Vlachodimitropoulos et al., 1997), for which the prevalence of the null genotype is reported to be between 15 and 30% (Nelson et al., 1995; Abdel-Rahman et al., 1996; Bailey et al., 1998). Similarly, sensitivity to sister chromatid exchanges induced by EB appears to be related to genotype for GSTM1, which codes for GSTm (Wiencke & Kelsey, 1993; Usukula et al., 1995), and possibly also GSTT1 genotype in GSTM1-null individuals (Bernardini et al., 1998). However, there were no differences in sensitivity to sister chromatid exchanges induced by EBdiol in individuals with and without deletions for GSTT1 or GSTM1 (Bernardini et al., 1996).

Although no increased frequencies of sister chromatid exchanges, chromosomal aberrations, or micronuclei were observed in earlier studies in butadiene production workers in Portugal and the Czech Republic compared with controls (Sorsa et al., 1994, 1996b), positive results for chromosomal aberrations and sister chromatid exchanges were obtained in the most recent study of the Czech workers (Tates et al., 1996; Šrám et al., 1998). When genotype was considered, there was a significant increase in the frequency of chromosomal aberrations in both exposed and control subjects from both plants who were deficient for the GSTT1 gene (Sorsa et al., 1996a).

An increased frequency of hprt$^-$ mutants in peripheral blood lymphocytes has been observed in two studies of exposed workers at a butadiene production facility in Texas, USA (Legator et al., 1993; Ward et al., 1994; Au et al., 1995) and in preliminary results of a study of styrene-butadiene rubber workers from the...
same region (J.B. Ward et al., 1996). Although analyses by genotype are not yet available, it was noted that the highest frequency of \textit{hprt} variants occurred in an individual who was \textit{GSTT1} null. In contrast to the observations in the Texan plants, however, no increase in \textit{hprt} mutant frequency was observed in workers exposed to similar levels of butadiene at the monomer plant in the Czech Republic (Tates et al., 1996) or in a population of polybutadiene rubber workers in China (Hayes et al., 1996) (no information on genotype was presented). These investigations involved different analytical methodologies (autoradiographic versus clonal assays), which may account for the discordance in the results; in addition, differences in occupational scenarios, exposure levels, age, smoking habits, or other lifestyle factors may have contributed to the discrepancy. Current ongoing research (including genotyping) may explain the differences in the results.

Decreased DNA repair ability was also observed in peripheral blood lymphocytes of exposed workers at the monomer production and styrene-butadiene rubber facilities in Texas in both a \textit{-radiation} challenge assay and a CAT-Host Cell Reactivation assay (Hallberg et al., 1997). However, the difference between exposed and “unexposed” monomer workers in the response to the challenge assay was no longer significant after ambient levels in the plant were reduced. Similarly, the effect on DNA repair ability in styrene-butadiene rubber workers was less when only non-smokers were considered. The detection of alkylated DNA (the same adduct as detected in the liver of mice and rats exposed to butadiene; Jelitto et al., 1984, 1993; Koivisto et al., 1997) in the urine of an exposed worker (Peltonen et al., 1993) also provides some evidence of the interaction of butadiene or its metabolites with genetic material in humans.

10. EVALUATION OF HEALTH EFFECTS

10.1 Hazard identification

Although the metabolism of butadiene appears to be qualitatively similar across species, there are extensive data that indicate that the putatively active epoxide metabolites are formed to a greater degree in mice than in rats. Similarly, although \textit{in vivo} data are limited, humans appear to metabolize butadiene to the mono- and diepoxide metabolites to a much lesser extent than mice. However, based on the observed variability in the formation of adducts of haemoglobin with butadiene metabolites in occupationally exposed human populations, there appears to be interindividual variation in humans, which is likely related to polymorphism for genes that code for enzymes involved in the metabolism of butadiene. The weight of evidence for the carcinogenicity, genotoxicity, and non-neoplastic effects of butadiene needs to be considered, therefore, in the context of these interspecies and interindividual variations.

10.1.1 Carcinogenicity and genotoxicity

Data supporting the interspecies differences in production of active epoxide metabolites are in concordance with the observed difference in sensitivity between mice and rats (at least for the few strains investigated) to butadiene-induced carcinogenicity, in that the substance appears to be much more potent in mice than in rats. Although butadiene was a multi-site carcinogen in both mice and rats at all exposure levels tested (Hazleton Laboratories Europe Ltd., 1981a; NTP, 1984, 1993; Irons et al., 1989), the concentrations that induced tumours in the only study available in rats were much greater than those that were tumorigenic in mice (i.e., $1000$ ppm ($2212$ mg/m$^3$) versus $6.25$ ppm ($13.8$ mg/m$^3$)).

Species differences in sensitivity to genetic effects induced by butadiene have also been observed. Although butadiene was mutagenic in somatic cells of both mice and rats, its mutagenic potency was greater in mice. Other genotoxic endpoints (chromosomal aberrations, sister chromatid exchanges, and micronuclei) were noted in somatic cells of mice but not in those of rats exposed to much higher concentrations. Butadiene was genotoxic in germ cells of male mice in multiple assays, while negative results were obtained in the single dominant lethal study in rats. Unlike the observations with the parent compound, however, there is little evidence that there are species differences in the sensitivity to genotoxic effects induced by the epoxide metabolites of butadiene (EB, DEB, and EBDiol), although there was some indication of interstrain variability. These data suggest that interspecies differences in sensitivity to butadiene-induced
genotoxicity are related to quantitative differences in the formation of active metabolites.

There is also limited evidence of the genotoxicity of butadiene in exposed workers; although data are not completely consistent, increased frequencies of chromosomal aberrations, sister chromatid exchanges, and hprt mutations and decreased DNA repair capability have been reported in some studies of workers in the monomer and/or styrene-butadiene rubber manufacturing industries (Legator et al., 1993; J.B. Ward et al., 1994, 1996; Au et al., 1995; Tates et al., 1996; Hallberg et al., 1997; Šrám et al., 1998). The discrepancy in the results may be due to the use of different methods for the detection of mutations or differences in exposure levels. In addition, since sensitivity to induction of genetic effects by butadiene and its metabolites has been linked to genotype for glutathione-S-transferase enzymes in several in vitro and a few in vivo studies, interpretation of the inconsistent observations in the available database is complicated by the lack of information on genotype for most of the small populations examined.

There have been several epidemiological investigations of the carcinogenicity of butadiene that serve as a basis for assessment of the weight of evidence for causality based on traditional criteria. In the most recent cohort study (Delzell et al., 1995), which is also the largest and most comprehensive investigation conducted to date and that in which exposure was most extensively characterized, an association between exposure to butadiene in the styrene-butadiene rubber industry and leukaemia was observed (i.e., there was a quantifiable exposure–response relationship). SMRs for leukaemia were elevated for the overall cohort of workers from eight plants; the strength of this association was generally greater when specific subgroups with greater potential for exposure were considered. In addition, there was an increase in the RR for leukaemia with increased cumulative exposure to butadiene in workers from the six plants for which exposure was best characterized. The association between leukaemia and exposure to butadiene remained when the potential role of two other substances present in the work environment (i.e., styrene and benzene) was considered. Although further refinement of the estimates of exposure at one of these plants resulted in increases for several job categories (Macaluso et al., 1997), it is unlikely that these changes would affect the relative ranking of the categories and analyses in which exposed workers were compared with “non-exposed” workers (Gerin & Siemiatycki, 1998);

Therefore, these results are not inconsistent with the association observed by Delzell et al. (1995).

However, no increase in mortality due to leukaemia was observed in studies of workers involved in the production of butadiene monomer who were not concomitantly exposed to the other substances present in the styrene-butadiene rubber industry (E.M. Ward et al., 1995, 1996; Divine & Hartman, 1996). Although there was some evidence of increased mortality due to lymphosarcoma and reticulosarcoma in the subgroup of workers potentially exposed to the highest concentrations of butadiene in the largest of these investigations, there was no association with duration of employment or estimated cumulative exposure (based on qualitative ranking of potential for exposure). Although mortality due to lymphosarcoma was non-significantly elevated in some process groups in the styrene-butadiene rubber cohort (Delzell et al., 1995), there were no consistent patterns (other than for leukaemia), even when currently accepted terminology for lympho-haematopoietic cancers was used (Sathiakumar et al., 1998).

The traditional criterion of consistency for the observed association between exposure to butadiene and leukaemia is fulfilled, at least in part, in that similar excesses were observed among plants in the large cohort study of styrene-butadiene rubber workers (Delzell et al., 1995); i.e., there is internal consistency. A similar exposure–response was also noted in an independent nested case–control study of mostly the same population in which different exposure assessment methodology was employed (Matanoski et al., 1997).

Observation of external consistency with results of other cohort studies of styrene-butadiene rubber workers is largely precluded, in view of the scope of the large epidemiological cohort study that included a large proportion of all of the styrene-butadiene rubber workers in North America. Indeed, it is difficult to envisage additional studies in this occupational group that would contribute meaningfully to weight of evidence for consistency of the observed association.

One criterion for causality of observed associations in epidemiological studies, namely coherence, may not have been adequately fulfilled, in view of the difference in the specific form of lympho-haematopoietic cancer in excess in available investigations for the two principal types of populations of workers studied. Indeed, increases in lymphosarcoma and reticulosarcoma have been observed in monomer production workers, whereas increases in leukaemia have been observed in styrene-butadiene rubber workers. Although it is plausible that this difference may be related to variation in the extent of information available for characterization of exposure or to the nature of exposures in the two industries, this has not been systematically investigated. There is also the possibility

1 Also personal communications (letter dated 17 October 1997 and electronic correspondence dated 15 November 1997) from J.B. Ward, Jr., Division of Environmental Toxicology, Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, to Health Canada.
of misclassification of cause of death on death certificates (although Sathiakumar et al. [1998] did not observe an association with forms of lymphohaematopoietic cancer other than leukaemia in the large cohort of styrene-butadiene rubber workers when causes of death were examined using current terminology). The potential for transformation of one form of lymphohaematopoietic cancer to another (e.g., non-Hodgkin’s lymphoma to leukaemia) has also been noted (Sathiakumar et al., 1998). In addition, available data for the large study of styrene-butadiene rubber workers were insufficient to determine if butadiene was causally associated with a specific form of leukaemia. Moreover, it is noteworthy that these different tumours observed in styrene-butadiene rubber workers and monomer production workers are of the same organ system, and perhaps even share the same pluripotential stem cell.

An association between exposure to butadiene and the induction of leukaemia is also biologically plausible. The haematopoietic system is a target for butadiene-induced effects in rodents (i.e., lymphocytic lymphomas [NTP, 1993], cytogenetic effects in bone marrow [Cunningham et al., 1986; Irons et al., 1986a, 1987; Tice et al., 1987; NTP, 1993; Leavens et al., 1997], and suppression of stem cell differentiation [Irons et al., 1996]). Aneuploidy, which is believed to be associated with leukaemia in humans, has been induced in human lymphocytes exposed in vitro to the mono- and diepoxide metabolites of butadiene (Vlachodimitropoulos et al., 1997; Xi et al., 1997). Moreover, the presence of relevant metabolizing enzymes in progenitor cells believed to be important targets for the induction of leukaemia in humans (i.e., CD34+ cells) has been demonstrated in studies of the metabolism of benzene (a documented human leukemogen) (Schattenberg et al., 1994; Ross et al., 1996) (although exposure of human CD34+ cells to EB at “physiologically relevant concentrations” did not alter cytokine-induced clonogenic response, an early change frequently observed in the development of leukaemia; Irons et al., 1996). Therefore, available data also support the biological plausibility of an association between exposure to butadiene and leukaemia observed in humans, although the active metabolite has not been identified.

Therefore, although not completely convincing in their own right, the available epidemiological studies of the association between leukaemia and exposure to butadiene in occupationally exposed human populations fulfill several of the traditional criteria for causality, including strength of association (RR of 4.2 in the highest exposure group [based on five cases], which would be considered moderately strong), quantifiable exposure–response relationship, temporal relationship (the critical investigation [i.e., Delzell et al., 1995] is a historical cohort study), biological plausibility, and, to some degree, consistency, although the criterion for coherence is not fully satisfied.

Assessment of the weight of evidence for carcinogenicity in human populations should not, however, be considered in isolation from the extensive supporting data on carcinogenicity, genotoxicity, and inter- and intraspecies variations in metabolism and response. The association between exposure to butadiene and development of cancer is supported by limited evidence of genetic damage in exposed workers, as well as the wealth of evidence that butadiene is carcinogenic and/or genotoxic in all species of experimental animals tested (mice, rats, and hamsters), inducing a wide range of tumours and genetic damage at relatively low concentrations in mice (i.e., within the same order of magnitude as current occupational health limits). Moreover, while there are quantitative differences in the potency of the substance to induce tumours in various species, likely related to observed quantitative differences in metabolism, there are indications of considerable interindividual variations in the metabolism of butadiene in the human population, consistent with expectations for a complex metabolic pathway.

The observation of an association between exposure in the occupational environment and leukaemia that fulfills several of the traditional criteria for causality of associations observed in epidemiological studies, as well as supporting limited data on genotoxicity in human populations and the well documented carcinogenicity and genotoxicity at relatively low concentrations in some species of experimental animals, provides weight of evidence that butadiene is carcinogenic in humans.

Although relevant data in humans are limited, the results of in vivo studies in experimental animals indicate that butadiene induces mutations in somatic cells and male germ cells as well as male-mediated heritable clastogenic damage. While most of the studies have been conducted in mice, rats appear to be less sensitive to these effects, which is consistent with species differences in metabolism. However, in view of the likely considerable heterogeneity in the metabolism of butadiene in human populations, butadiene may be a human somatic and germ cell genotoxicant.

1 Also personal communication (correspondence dated 30 March 1998) from R.D. Irons, University of Colorado Health Sciences Center, Denver, CO, to Health Canada.
10.1.2 Non-neoplastic effects

The available data on effects of butadiene other than carcinogenicity or genotoxicity are limited. Based on the limited data available, species differences in the ability of butadiene to induce other non-neoplastic effects again appear to be consistent with variations in metabolism of butadiene to active metabolites. However, butadiene is of low acute toxicity in both rats and mice, in contrast to its ability to induce cancer and genetic damage at relatively low concentrations in mice.

Haematological effects suggestive of macrocytic anaemia have been consistently observed in mice (two strains) following short-term, subchronic, or chronic exposure to butadiene at concentrations similar to or lower than those that induced general toxicity (as indicated by decreased body weight gain and increased organ weights) (Irons et al., 1986a, 1986b; NTP, 1993; Bevan et al., 1996). For example, changes in haematological parameters were noted in mice exposed to $62.5 \text{ ppm} \left(138 \text{ mg/m}^3\right)$ butadiene for 9 months or longer in the NTP bioassay. Butadiene also induced effects on bone marrow (including atrophy, decreased cellularity, regeneration, and alterations in stem cell development) in mice (Irons et al., 1986a, 1986b; Leiderman et al., 1986; NTP, 1993), although available data are inadequate to assess the potential effects on immune system function. While effects on the blood and bone marrow have not been reported in rats in recent investigations (including the only identified chronic bioassay; Hazleton Laboratories Europe Ltd., 1981a), the database is considerably more limited. In addition, the lack of observation of haematotoxicity in rats may again reflect the species differences in metabolism. Although the available epidemiological studies are too limited to assess the haematotoxicity in humans, available data support the haematopoietic system being a critical target for butadiene-induced toxicity, since the lymphohaematopoietic system is a target for butadiene-induced leukaemia in humans. However, it has not been established if the non-neoplastic effects observed in animals may be preliminary to, or associated with, the development of lymphohaematopoietic cancers.

The reproductive organs are also critical targets of butadiene-induced non-neoplastic effects in mice. Ovarian atrophy, the severity and incidence of which increased with concentration or duration of exposure, was observed at all concentrations (i.e., $6.25 \text{ ppm} \left(13.8 \text{ mg/m}^3\right)$) in the chronic bioassay conducted by the NTP (1993); in all exposure groups, the level of degeneration at 2 years, characterized by lack of oocytes, follicles, or corpora lutea, was incompatible with reproductive capacity. Although recent re-examination of some of the tissue samples indicated that the atrophy observed in the ovaries may be related to senile changes, it may be that butadiene is exacerbating these changes. It should be noted, though, that the incidence of these lesions was increased as early as 9 months (although the slides from these interim sacrifices have not been re-examined). That butadiene is causally associated with these lesions is also difficult to dismiss on the basis of currently available data, in view of the consistency with the results of other studies, including the earlier NTP (1984) bioassay and a subchronic study at higher concentrations (Bevan et al., 1996) in which such lesions were also observed, the presence of a clear dose–response relationship, and biological plausibility. Based on the observation of depletion of ovarian follicles and alkylation with ovarian macromolecules in mice following intraperitoneal administration of the monoepoxide or diepoxide metabolite and in rats administered the diepoxide (Doerr et al., 1995), it is possible that the ovarian toxicity is mediated through generation of the active epoxide metabolites.

Testicular atrophy was noted only in male mice exposed to concentrations greater than those that induced effects in females (NTP, 1993). Consistent with metabolic differences, butadiene did not induce ovarian or testicular toxicity in the limited number of available studies in rats, although, as noted above, the diepoxide metabolite was ovotoxic in both species (Doerr et al., 1995, 1996).

Although available data are limited, there is no conclusive evidence that butadiene is teratogenic in mice or rats following maternal or paternal exposure or that it induces significant fetal toxicity at concentrations below those that are maternally toxic.

Available epidemiological data are inadequate for evaluation of potential reproductive or developmental toxicity; in fact, none of the identified analytical studies was conducted in women. However, in view of the qualitative similarities in the metabolism of butadiene in mice, rats, and humans and the likely variation across the general population associated with genetic polymorphism for the relevant enzymes, and on the basis of the observed ovarian toxicity in butadiene-exposed mice, butadiene may be a reproductive toxicant in humans, although additional work to clarify the relevance of these observed effects is clearly desirable.

Available data on other systemic or organ-specific effects are inadequate to determine if such effects might be considered critical.

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1 Personal communication (electronic correspondence dated 26 June 1998) from B. Davis, National Institute for Environmental Health and Safety, National Toxicology Program, Research Triangle Park, NC, to Health Canada.
10.2 Exposure–response assessment and criteria for setting tolerable concentrations or guidance values

As per the approach adopted for several genotoxic carcinogens, measures of the potency of a substance to induce effects for which there is believed to be no threshold may be used to establish guideline values for environmental media. Since air is the principal route of exposure to butadiene in the general environment (available data indicate that other routes contribute negligibly), quantitation of exposure–response for cancer as well as non-cancer effects is limited to exposure by inhalation.

In order to eliminate the uncertainty associated with extrapolation from animal species, quantitative measures of carcinogenic potency (i.e., tumorigenic concentrations, or TCs)\(^1\) have been developed on the basis of available epidemiological data. This is based on the conclusion that the weight of evidence for an association between butadiene and leukaemia satisfies several of the traditional criteria for causality in epidemiological studies. However, uncertainties in the exposure estimates for the critical cohort of workers as well as confounding or effect-modifying aspects that could impact on quantitative estimates of risk are recognized. In view of these factors and to serve as a basis for comparison, quantitative measures of cancer potency have also been developed on the basis of results of long-term bioassays in rats and mice, with those in mice being considered justifiably conservative, considering the likely heterogeneity in metabolic transformation of butadiene in humans. (See discussion considering the likely heterogeneity in metabolicism, butadiene achieves a steady state during prolonged inhalation exposure. Exposures of the same concentration in animals presented here.

In addition to inducing tumours at multiple sites in experimental animals, butadiene is also genotoxic in somatic and germ cells and induces reproductive and haematological effects in animals. As a measure of exposure–response for non-cancer effects, where considered appropriate, benchmark concentrations\(^2\) have been calculated on the basis of data from long-term studies in mice.

Several physiologically based pharmacokinetic (PBPK) models have been developed as a basis for reducing uncertainty in interspecies extrapolations for butadiene by various groups of investigators. However, none of the models currently available has adequately accounted for the distribution of metabolites in the compartments included; the principal researchers in this field have concluded that there are likely more factors involved in butadiene metabolism than have been included in the models developed to date (Csanády et al., 1996; Sweeney et al., 1997). In addition, none of the models has included the formation of EBdiol, a putatively active metabolite that is believed to be important in humans, since it has been observed to bind to haemoglobin to a greater degree than EB in workers exposed to butadiene. Nor has bone marrow been incorporated as a compartment, although it appears to be a target site of butadiene-induced toxic effects. Moreover, none of the PBPK models has been validated in humans. For these reasons, therefore, such models have not been used to quantitatively account for interspecies variations in metabolism in the quantitation of exposure–response for critical end-points based on studies in experimental animals presented here.

In addition, owing to its relatively slow metabolism, butadiene achieves a steady state during prolonged inhalation exposure. Exposures of the same concentration and duration would be expected to result in equivalent toxicity across species, and interspecies scaling to account for variations in inhalation rate to body weight ratios or body surface areas between humans and animals is not considered necessary.

10.2.1 Carcinogenicity

10.2.1.1 Epidemiological data

In only one epidemiological investigation of the association between butadiene and leukaemia have data on exposure of the study population been sufficiently characterized to permit quantitation of exposure–response (Delzell et al., 1995). The Delzell et al. (1995) study also presents results for the largest cohort studied

\(^1\) The potency estimate for carcinogenicity is determined by calculating the dose or concentration associated with an increase in cancer incidence or mortality of an appropriate percentage. When based on toxicological data from studies in experimental animals, a 5% increase is generally chosen, as these values usually lie within or close to the observable range (i.e., a TC\(_0\) is calculated). When epidemiological data form the basis for derivation of a tumorigenic concentration, the percent increase selected is that which falls within the area of the exposure–response curve that represents the majority of the observable data; this is often less than 5%. In the case of butadiene, the carcinogenic potency calculated on the basis of modelling of epidemiological data (as described herein) was considered to be best defined as a 1% increase in mortality due to leukaemia (i.e., a TC\(_{1\%}\)).

\(^2\) Similar to tumorigenic concentrations (TC\(_c\)), benchmark concentrations for non-cancer effects (or BMC\(_c\)), when based on data in experimental animals, represent the dose or concentration associated with a 5% increase in the incidence of an effect compared with controls.
to date (including subjects from eight plants, six of which were included in the exposure–response analyses); it is also considered to subsume the observations of mortality in workers at these plants reported previously by other researchers (i.e., Meinhardt et al., 1982; Matanoski et al., 1990, 1993; Santos-Burgos et al., 1992), because of the considerable overlap in the cohort definition. The exposure assessment of study subjects was of extremely high quality, being very thorough and based on research of plant records concerning work histories, processes and local emissions, and consultation with staff from each plant, and is, therefore, considered appropriate for quantification of exposure–response (limited industrial hygiene monitoring data were also available, although used primarily for comparison with estimated concentrations). For comparison with estimates based on the data from the cohort study, carcinogenic potency was also calculated on the basis of the results of the case–control study nested within essentially the same population of workers (Matanoski et al., 1997), although data available in the published report were too limited to permit detailed analysis here.

A detailed description of the methods employed and the assumptions made in the derivation of tumorigenic potency estimates (i.e., TC$_{0.1}$, or the concentration associated with a 1% increase in mortality due to leukaemia based on the observations in Delzell et al. [1995]) is presented in Appendix 4. Although several mathematical models were applied, the choice of model had little impact on the resulting TC$_{0.1}$, as there was only a threefold variation in the range of values. However, the estimated TC$_{0.1}$ in which confidence is highest (i.e., that for which the model provided the best fit) is 1.7 mg/m$^3$. The TC$_{0.1}$ calculated on the basis of the data of Matanoski et al. (1997) was only slightly lower than this value.

10.2.1.2 Data from studies in experimental animals

As described in section 10.1.1, butadiene induced an increase in the incidence of tumours at multiple sites in both B6C3F$_1$ mice (liver, lung, Harderian gland, mammary gland, ovaries, forestomach, Zymbal gland, and kidney, along with malignant lymphomas, histiocytic sarcomas, and cardiac haemangiosarcomas) and Sprague-Dawley rats (mammary gland, thyroid gland, uterus, Zymbal gland, pancreas, and testes). As discussed above, consistent with the species differences in metabolism, mice were much more sensitive to butadiene-induced cancer than were rats for the strains investigated. Based on data available (i.e., evidence from genotoxicity studies that butadiene and its metabolites are active in both species), this difference in sensitivity is quantitative rather than qualitative and is related to the greater amounts of putatively active metabolites formed in mice compared with rats. In addition, the different profiles of tumours observed in the two species may be related to differential roles of the epoxide metabolites in the induction of the various tumours; i.e., the diepoxide may be more critical to tumour induction in mice than in rats (since it was reported recently that formation of DEB increased with level of exposure to butadiene in mice but not in rats; Thornton-Manning et al., 1998), while the monoepoxide or monoepoxide diol may be more important in rats.

The relevance for extrapolation to humans of exposure–response for some of the types of tumours observed in rodents has been questioned. For example, Irons et al. (1989) hypothesized that the thymic lymphoma/leukaemia induced in B6C3F$_1$ mice may be related to the presence of an endogenous ecotropic retrovirus, as a much lower incidence was observed in Swiss mice that do not possess this retrovirus (although the incidence was significantly elevated compared with controls). Therefore, although the haematopoietic system is a target for the induction of cancer by butadiene in humans, the observed exposure–response relationship for this end-point is not considered appropriate for quantitative extrapolation to humans — on the basis that this retrovirus is not present in humans and its presence in B6C3F$_1$ mice renders this strain quite susceptible to induction of lymphoma — although the relevant information is included for comparative purposes.

It has also been suggested that the tumours observed in the study in rats (i.e., mammary gland, thyroid gland, pancreas, uterus, and testes) and some of the tumours induced in mice (i.e., ovaries and mammary gland) may be mediated through effects on the endocrine system. Indeed, tumours at these sites are often associated with disruption of hormonally mediated functions. In addition, non-neoplastic or pre-neoplastic effects, including atrophy, degeneration, and hyperplasia, have also been observed in mice exposed subchronically to butadiene. However, the mechanism by which butadiene induces tumours at these sites has not yet been adequately investigated; i.e., it has not been established whether these tumours are induced via a mechanism for which there may be a threshold of exposure (e.g., through induction of hormonally mediated effects), although the possibility is recognized. In addition, the results of in vivo genotoxicity assays indicate that butadiene or its metabolites induce genetic effects in the reproductive organs of multiple strains of mice.

Based on these considerations, estimates of carcinogenic potency were calculated on the basis of the malignant lymphomas, histiocytic sarcomas, cardiac haemangiosarcomas, alveolar/bronchiolar adenomas or
carcinomas, hepatocellular adenomas or carcinomas, squamous cell papillomas or carcinomas of the forestomach, adenomas or carcinomas of the Harderian gland, granulosa cell tumours of the ovaries, and adenoanchnomas, carcinomas, or malignant mixed tumours of the mammary gland observed in B6C3F₁ mice in the chronic bioassay conducted by the NTP (1993) and the mammary gland tumours, pancreatic exocrine adenomas, Leydig cell tumours, Zymbal gland carcinomas, thyroid follicular cell adenomas or carcinomas, and uterine sarcomas in Sprague-Dawley rats reported by Hazleton Laboratories Europe Ltd. (1981a). It is noted that the characterization of exposure–response is much better in the study in mice (which involved five closely spaced exposure levels) than in the bioassay in rats (in which only two more widely spaced exposure levels were used, the higher of which was likely above the level of metabolic saturation). (Although there were also increased incidences of tumours at several sites in B6C3F₁ mice in the “stop-exposure” study conducted by the NTP [1993], only TC₁₀₀ determined on the basis of the 2-year study were included, as the latter study provides better information for characterization of exposure–response in mice following long-term exposure [i.e., more exposure levels for up to 2 years].)

The methods employed for development of estimates of tumorigenic potency (i.e., the concentrations associated with a 5% increased incidence of tumours, or TC₁₀₀) based on these data are described in Appendix 4. TC₁₀₀ based on observations in mice ranged from 2.3 mg/m³ (95% lower confidence limit [LCL] = 1.7 mg/m³) for Harderian gland tumours in males to 99 mg/m³ (95% LCL = 23 mg/m³) for malignant lymphomas in males. For rats, calculated TC₁₀₀ ranged from 6.7 mg/m³ (95% LCL = 4.7 mg/m³) to 4872 mg/m³ (95% LCL = 766 mg/m³) for tumours of the mammary gland and Zymbal gland in females, respectively.

Although not presented here, modelling of the incidence of micronucleated polychromatic erythrocytes in B6C3F₁ mice exposed to butadiene for up to 15 months in the NTP bioassay resulted in a benchmark concentration (BMC₁₀₀) that was very similar to the lower end of the range of estimates of tumorigenic potency.

10.2.2 Non-neoplastic effects

There have been recent attempts to quantitatively estimate risk of heritable genetic damage in humans based on a parallelogram approach and data on male-mediated heritable translocations and bone marrow micronuclei in mice and chromosomal aberrations in lymphocytes of exposed workers (Pacchierotti et al., 1998b). In view, however, of the reported ovarian atrophy due to reduction of primordial follicles (to a degree that would preclude reproduction) following chronic exposure of mice to concentrations of butadiene considerably lower than those associated with adverse effects on the testes, investigation of the response of female germ cells in mice to butadiene is desirable, since this may well be the most sensitive end-point for development of quantitative estimates of heritable damage. (Determination of putatively toxic metabolites in the ovaries of butadiene-exposed female mice would also be informative.) For this reason, quantitation of exposure–response for heritable genetic damage is not presented here. However, in view of the apparent greater sensitivity of the reproductive organs in female mice, a benchmark concentration was derived for non-neoplastic effects in the ovary, which is considerably more protective than that for male-mediated heritable damage developed by Pacchierotti et al. (1998b). (Although the relative role of butadiene in the induction of the observed atrophy in mice in the NTP study is unclear, as discussed in section 10.1.2, information currently available is not considered a sufficient basis upon which to dismiss this end-point as being inappropriate for quantification of exposure–response. However, this uncertainty should be kept in mind in the interpretation or application of the BMC₁₀₀’s derived below.)

Ovarian atrophy was observed in both long-term NTP (1984, 1993) bioassays in mice and a subchronic study (Bevan et al., 1996). Although limited, available data indicate that rats are less sensitive to induction of this effect, which may, again, be a consequence of interspecies variations in metabolism. Therefore, although additional research into the etiology of the observed ovarian atrophy in mice would be desirable, the data from the later NTP study are considered most appropriate for characterization of exposure–response (i.e., development of a BMC₁₀₀). In this investigation, the incidence of atrophy of the ovaries was significantly increased in an exposure-related manner at all concentrations tested (i.e., $6.25 \text{ ppm (}$13.8 \text{ mg/m}^3$)$). The severity of this effect also increased with exposure.

The derivation of the BMC₁₀₀ for ovarian atrophy is presented in detail in Appendix 4. Because the exposure–response curve plateaus at the higher exposure levels, the two highest exposure groups were omitted from the calculations. The resulting BMC₁₀₀ for ovarian atrophy in mice was determined to be 0.57 mg/m³ (95% LCL = 0.44 mg/m³), when all degrees of severity were considered. If only lesions of moderate or marked severity were considered, the resulting BMC₁₀₀ would be about fivefold higher.

Haematotoxicity is considered to be a critical effect associated with exposure to butadiene. Although the haematopoietic system appears to be a target for butadiene-induced cancer in humans, available data on the potential non-neoplastic effects on this system are
inadequate for quantitation of exposure–response. However, since statistically significant changes were observed in mice only at concentrations greater than those that induced other toxic effects, and since benchmark concentrations derived for effects on the blood are greater than those for these other effects, quantitation of the exposure–response for haematological effects has not been presented here.

10.3 Sample exposure and risk characterization

10.3.1 Sample exposure characterization

The principal source of environmental exposure to butadiene is air. Although few data were identified regarding levels in drinking-water and food, due to its physical/chemical properties (e.g., vapour pressure and partition coefficients) and environmental release patterns (i.e., principally atmospheric emissions), intake of butadiene in these media is expected to be negligible in comparison with that in air.

As an example of population exposure characterization, estimates are presented on the basis of data available for Canada. Based on concentrations measured in outdoor air in several rural, suburban, and urban locations across Canada\(^1\) (see section 6.1.1), 95% of the general population can be expected to be exposed to average concentrations of up to 1.0 µg/m\(^3\). However, since levels are generally greater in highly urbanized areas, estimated “reasonable worst-case exposure” is expected to be up to 1.3 µg/m\(^3\) (95th percentile). In areas influenced by industrial point sources, exposure could be as high as 6.4 µg/m\(^3\), based on the 95th percentile of concentrations measured near a source in Ontario (MOEE, 1995).

Individuals may also be exposed to butadiene for short durations while at self-service gasoline filling stations or in parking garages; however, these intakes are still much less than average daily intakes for the general population from inhalation of background concentrations in outdoor and indoor air.

Although available Canadian data indicate that butadiene is detected with greater frequency in indoor air than in outdoor air, there are insufficient data to characterize the distributions of concentrations of butadiene in various indoor environments. In general, butadiene is detected more frequently and at higher concentrations in indoor environments contaminated by ETS than in areas where smoking does not occur. Non-smokers who spend a considerable proportion of their time in indoor environments where ETS is present can be exposed to concentrations of butadiene that are an order of magnitude higher than the average levels in the outdoor air. Tobacco use (e.g., 20 cigarettes per day) can increase the daily intake of butadiene by smokers by five times over the daily intake by non-smokers in ETS-contaminated indoor locations. The daily intake of butadiene by smokers can be 100 times greater than the daily intake of non-smokers who are not exposed to ETS.

10.3.2 Sample risk characterization

Butadiene is released to air from both industrial point sources and more dispersive, non-point sources, the latter due to its production primarily during incomplete combustion. Based on estimates derived using monitoring data from Canada, intake for the general population is primarily from air, with intake from other media likely being negligible in comparison. The focus of the human health risk characterization is, therefore, the general population exposed in outdoor and indoor air in the general environment and those exposed through air in the vicinity of industrial point sources.

For compounds such as butadiene, where data are sufficient to support a plausible mode of action for induction of tumours by direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of cancer potency to characterize risk.

Tumorigenic concentrations were calculated on the basis of data from both epidemiological studies and investigations in experimental animals. For the critical epidemiological investigation (Delzell et al., 1995), a TC\(_0\) (i.e., the concentration associated with a 1% increase in mortality due to leukaemia) was considered the appropriate measure of carcinogenic potency, since the majority of the observable data fell within this range. Although four different mathematical models were considered, the TC\(_{0.1}\) generated by the model with the best fit was 1.7 mg/m\(^3\).

Quantitative estimates of carcinogenic potency derived on the basis of data in experimental animals were calculated as TC\(_{0.05}\) (i.e., the concentration associated with a 5% increase in tumour incidence). Based on the 2-year bioassay in mice (NTP, 1993), TC\(_{0.05}\) ranged from 2.3 mg/m\(^3\) (95% LCL = 1.7 mg/m\(^3\)) to 99 mg/m\(^3\) (95% LCL = 23 mg/m\(^3\)). The TC\(_{0.05}\) derived on the basis of the more limited study in rats (Hazleton Laboratories Europe Ltd.,

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\(^1\) 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.
The values derived on the basis of studies in humans are preferred as the basis for comparison with estimates of exposure to characterize risk. While there are a number of uncertainties in the use of the epidemiological data for both hazard evaluation and exposure–response analyses (section 10.4), these are likely far less than uncertainties associated with interspecies extrapolation. Moreover, estimated potency for humans is similar to that developed on the basis of the cancer bioassays in experimental animals. (Indeed, although in an area of the exposure–response curve where data were more sparse, it is noteworthy that \( TC_{95} \) calculated on the basis of epidemiological data [as opposed to the \( TC_{95} \) presented above] are within the range of values derived from the studies in rodents.)

Based on the sample exposure scenarios presented above (section 10.3.1), 95% of the population in Canada is exposed to concentrations of butadiene in outdoor air of 1.0 \( \mu \text{g/m}^3 \) or less. For the proportion of the general population that is regularly exposed to higher concentrations of butadiene in urban areas (i.e., the “reasonable worst-case scenario”), the 95th percentile of the distribution of concentrations is 1.3 \( \mu \text{g/m}^3 \). In the only area of Canada identified as having an industrial point source, the 95th percentile of the distribution of concentrations is 6.4 \( \mu \text{g/m}^3 \).

The margins between carcinogenic potency and estimated exposure for the general population (including ambient and reasonable worst case) and those in the vicinity of a point source are presented in Table 6. Equivalent low-dose risk estimates are also presented in this table.

In view of the relative potency of butadiene to induce some non-cancer effects, these end-points are also important in risk characterization. As presented above, a benchmark concentration (BMC\(_{95}\)) of 0.57 \( \text{mg/m}^3 \) (95% LCL = 0.44 \( \text{mg/m}^3 \)) was derived on the basis of data for the incidence of ovarian atrophy of all severities (i.e., female reproductive toxicity) in mice exposed to butadiene for up to 2 years (NTP, 1993). And while there is uncertainty about the relevance of the ovarian atrophy observed in mice for humans (section 10.4), the BMC\(_{95}\) is slightly less than the lower end of the range of estimates of cancer potency based on the incidence of tumours in the same study in mice, as well as the \( TC_{95} \) for cancer based on the epidemiological data. The mode of induction of ovarian atrophy is unknown. However, if it is (reasonably) assumed that the mode of action is related to that by which tumours are induced (i.e., direct interaction with genetic material), risk to human health for reproductive effects may be characterized in the same manner as presented for cancer. Therefore, estimates of the margin between the BMC\(_{95}\) for ovarian toxicity and a sample exposure characterization are presented in Table 7. It should be noted, though, that even if the mode of induction of ovarian atrophy does not involve direct interaction with genetic material, the margin between exposure and effect level (i.e., for which a tolerable concentration is normally developed) is still small — i.e., exposure levels in Canada are 90–570 times lower than the benchmark concentration, as presented in Table 7.

10.4 Uncertainties and degree of confidence in human health hazard characterization and sample risk characterization

There is a high degree of certainty that butadiene is being released to ambient air in Canada in significant amounts in vehicular exhaust. There is a moderate degree of certainty that exhaust emissions of butadiene are lower in well maintained vehicles equipped with catalytic converters than in older non-equipped vehicles, and that evaporative emissions during refuelling and vehicle operation contribute less to concentrations of butadiene in ambient air than do emissions in vehicular exhaust.

There is a moderate degree of certainty that butadiene is not being released to the Canadian environment in significant amounts from industrial activities in Canada, as only a single major point source (i.e., in Sarnia, Ontario) of discharge to the atmosphere has been identified. Although there is some uncertainty that the available measurements of butadiene in samples taken over a few days in the vicinity of this source are representative of population exposure over the long term, since the samples were taken at distances of up to a few kilometres from the source, there is a moderate degree of certainty that a segment of the population would be exposed to the measured concentrations. There is a high degree of certainty that populations in rural areas are exposed to lower concentrations of butadiene in ambient air than are communities in more densely populated areas.

Available data on concentrations of butadiene in ambient air in Canada are quite extensive. A large proportion of the numerous samples from several sampling sites across the country contained concentrations of butadiene above the level of detection. Therefore, there is a high degree of certainty in the estimations of exposure to butadiene via ambient air.
Table 6: Comparison of estimates of carcinogenic potency with exposure levels.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Potency (TC_{01} or TC_{05})</th>
<th>Margin between potency and exposure</th>
<th>Equivalent low-dose risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 µg/m^{3} (95th percentile for all sites in Canada)</td>
<td>1.7 mg/m^{3} (TC_{01} for leukaemia in humans)</td>
<td>1700</td>
<td>5.9 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>2.3 mg/m^{3} (TC_{05} for most sensitive tumour site in mice [Harderian gland])</td>
<td>2300</td>
<td>22 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>1.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in mice)</td>
<td>1700</td>
<td>29 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>6.7 mg/m^{3} (TC_{05} for most sensitive tumour site in rats [mammary gland])</td>
<td>6700</td>
<td>7.5 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>4.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in rats)</td>
<td>4700</td>
<td>11 × 10^{-4}</td>
</tr>
<tr>
<td>1.3 µg/m^{3} (95th percentile for reasonable worst-case scenario)</td>
<td>1.7 mg/m^{3} (TC_{01} for leukaemia in humans)</td>
<td>1300</td>
<td>7.7 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>2.3 mg/m^{3} (TC_{05} for most sensitive tumour site in mice [Harderian gland])</td>
<td>1800</td>
<td>28 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>1.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in mice)</td>
<td>1300</td>
<td>38 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>6.7 mg/m^{3} (TC_{05} for most sensitive tumour site in rats [mammary gland])</td>
<td>5200</td>
<td>9.6 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>4.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in rats)</td>
<td>3600</td>
<td>14 × 10^{-4}</td>
</tr>
<tr>
<td>6.4 µg/m^{3} (95th percentile for area affected by industrial point source)</td>
<td>1.7 mg/m^{3} (TC_{01} for leukaemia in humans)</td>
<td>270</td>
<td>3.7 × 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>2.3 mg/m^{3} (TC_{05} for most sensitive tumour site in mice [Harderian gland])</td>
<td>360</td>
<td>14 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>1.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in mice)</td>
<td>270</td>
<td>19 × 10^{-4}</td>
</tr>
<tr>
<td></td>
<td>6.7 mg/m^{3} (TC_{05} for most sensitive tumour site in rats [mammary gland])</td>
<td>1000</td>
<td>5.0 × 10^{-5}</td>
</tr>
<tr>
<td></td>
<td>4.7 mg/m^{3} (95% LCL of TC_{05} for most sensitive tumour site in rats)</td>
<td>730</td>
<td>6.8 × 10^{-5}</td>
</tr>
</tbody>
</table>

The most limiting aspect of the exposure assessment is the lack of sufficient data on the concentrations of butadiene in indoor air. This is an important shortcoming, since humans spend significantly more time in indoor environments than outdoors. In the absence of indoor sources, it is reasonably certain that concentrations of butadiene in indoor environments are similar to the concentrations in the local ambient air.

Higher concentrations of butadiene have been measured in indoor air where ETS was known to be present. However, the data on concentrations of butadiene in ETS-contaminated indoor air are highly variable and are not sufficient to reasonably define the range of mean concentrations. Nevertheless, there is a high degree of certainty that non-smokers spending a considerable proportion of their time in indoor environments where ETS is present are exposed to...
higher concentrations of butadiene than are non-smokers who are not exposed to ETS. There is a high degree of certainty that smokers are exposed to higher concentrations of butadiene and have significantly higher daily intakes than do non-smokers.

There is somewhat less certainty that butadiene monomer is not released in detectable amounts from consumer products (e.g., synthetic materials) incorporating this compound in their production. Although there may be contributions to indoor concentrations of butadiene from certain cooking activities, the data are not sufficient to identify specific sources or activities or to identify a range of emissions of butadiene during cooking.

Although data on levels of butadiene in foodstuffs are scarce, based on the physical and chemical properties of the substance and the fact that it is released primarily to ambient air (where it is likely to remain without partitioning to other media), there is a reasonable degree of certainty that food does not represent a major source of exposure. Similarly, although the database for concentrations of butadiene in drinking-water is limited, there is a reasonable degree of certainty that drinking-water is not an important source of exposure for the general public in Canada, based on the volatility and release patterns of the compound.

There is some degree of uncertainty that the weight of epidemiological evidence for the association between butadiene and leukaemia satisfies criteria for causality. In particular, the need for coherence is seemingly not addressed, since the observed increase in mortality due to leukaemia in styrene-butadiene rubber workers was not observed in the cohorts of monomer workers (although there was some evidence of an association with other forms of lympho-haematopoietic cancer, particularly in short-term workers). This may be related to the nature of exposure to both butadiene and other substances in these two industries. However, in view of the overwhelming evidence of carcinogenicity and genotoxicity in experimental animals, available information on species differences in sensitivity likely being related to differences in metabolism, and the potential for considerable interindividual variability in metabolism to putatively toxic metabolites in the human population, along with the limited evidence of genotoxicity in occupationally exposed populations, there is a high degree of confidence that butadiene is likely to be carcinogenic in humans. Based on the extensive database on the genotoxicity of butadiene and its principal metabolites both in vitro and in vivo in both somatic and germ cells, confidence that butadiene induces tumours (and possibly other effects) through direct interaction with genetic material is high.

Although the assessment of the exposure of the critical cohort of workers is likely one of the most comprehensive published to date, there is also uncertainty in the estimates of carcinogenic potency derived on the basis of this study, due primarily to the fact that the estimates of exposure are based on few actual historical monitoring data. For example, when the exposure of workers at one plant was re-examined, there were 2- to 3-fold changes in the estimates for several job groups (with a 10-fold increase for one job group). In addition, with the exception of incorporating exposure to styrene as a stratification variable in the analyses, potential interactions between various occupational exposures could not be taken into account in the derivation of the carcinogenic potency based on the observations in this cohort. It has also been demonstrated that genetic polymorphism for several of the enzymes involved in metabolism of butadiene affects sensitivity to toxic effects induced by the substance. Also, since information on genotype for the relevant enzymes was not available for this large cohort and only a small amount of information on the distribution in the general population has been identified, it is not possible to determine how representative the study cohort is of the genetic susceptibility to butadiene of the general public.

With respect to the quantitation of exposure–response and derivation of potency estimates based on the epidemiological data, the inability of any of the models to consistently predict leukaemia rates in the validation study contributes to additional uncertainty. In addition, the small number of leukaemia cases being modelled contributes to model instability. However, the fact that the range of potency estimates for the four models is narrow (i.e., 1.4–4.3 mg/m$^3$) increases the confidence in the calculated potencies. There is also some uncertainty associated with the fact that the potency estimates were based only on cases in which leukaemia was considered the underlying cause of death, rather than all cases, which could result in an underestimation of leukaemogenic potency.

In view of the likely variability in metabolism of butadiene across the human population related to genetic polymorphism for relevant enzymes, estimates of carcinogenic potency as well as benchmark concentrations for non-cancer effects based on studies in mice are considered justifiably conservative. However,
because of the high mortality in the study in mice in which exposure–response could best be characterized and the limitations in the study in rats (high mortality at the higher of only two widely spaced exposure levels), there is a moderate degree of uncertainty in estimates of carcinogenic potency derived on the basis of investigations in experimental animals. In addition, since the available PBPK models were considered inadequate, the potency estimates developed here are based on an inhaled concentrations exposure metric; i.e., none of the available information on species differences in metabolism is taken into account. It is noteworthy that if the calculated margins between exposure and carcinogenic potency presented above that serve to characterize risk were derived on the basis of the 95% LCLs of the TC\textsubscript{05}s for tumours in mice, the values would differ by only 1.4- to 3.3-fold (i.e., within the same order of magnitude) from those calculated on the basis of the point estimates; similarly, use of the 95% LCLs of the TC\textsubscript{05}s for tumours in rats would result in a 1.1- to 6.4-fold difference in the margins between exposure and potency. In addition, although confidence in the use of the potency estimate for lymphomas in mice is low, due to the inherent sensitivity associated with the presence of an endogenous retrovirus, it is noteworthy that the TC\textsubscript{05} for this tumour would not be limiting, as it falls within the range of values determined for cancers at other sites. Also, it should be noted that, although these margins and measures of risk presented above were based on comparison of the 95th percentile of the exposure data for each scenario, use of the median concentration (i.e., the 50th percentile) and either the point estimates of carcinogenicity or the associated 95% LCLs would result in a 5-fold difference in the resulting values for the general population and a 10-fold difference in values for those in an area influenced by a point source.

There is uncertainty about the relevance of the ovarian atrophy observed in mice to humans, based on lack of data on the relative role of butadiene in the etiology of these lesions. Although the observed effects in the 2-year bioassay may have been related to senile changes, possibly exacerbated by butadiene, atrophy of the ovaries was detected in these mice as early as 9 months, and there is consistent evidence in other chronic and subchronic studies that the ovaries are targets of toxic effects induced by butadiene or its epoxide metabolites. As a result of this uncertainty, quantitative measures of dose–response developed on the basis of ovarian atrophy must necessarily be interpreted with caution. In addition, the BMC\textsubscript{05} presented above was based on inclusion of atrophy of all severities, including “minimal” severity, the biological significance of which is unclear. If only lesions of moderate or marked severity are considered, the resulting BMC\textsubscript{05} and hence the calculated margin between exposure and effect level and risk estimates would differ by about fivefold. (Use of the 95% LCLs of the BMC\textsubscript{05}s for atrophy of all severities or of only moderate or marked severity would result in only a 1.5- or 3-fold difference in the measure of risk.) However, in view of the weight of evidence of causality for the association between butadiene and these effects in mice and the relatively low value for the measure of dose–response compared with that for other types of effects, additional investigation in this area is deemed to be of high priority.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

An IARC Working Group that convened in 1998 has classified 1,3-butadiene as probably carcinogenic to humans (Group 2A) based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity for 1,3-butadiene and 1,2:3,4-diepoxybutane in experimental animals (IARC, 1999).
cycloalkenes, and monoterpenes at 291 K.


REFERENCES

BBRA International (1996b) The detection of dominant lethal mutations and foetal malformations in the offspring of male rats treated subchronically with 1,3-butadiene by inhalation. Carshalton, Surrey (Report No. 1642/2).


Boogaard PJ, Bond JA (1996) The role of hydrolysis in the detoxification of 1,2,3,4-diepoxybutane by human, rat, and mouse liver and lung in vitro. Toxicology and applied pharmacology, 141:617–627.


Cochrane JE, Skeple TR (1994a) Mutagenicity of butadiene and its epoxide metabolites: I. Mutagenic potential of 1,2-epoxybutane, 1,2,3,4-diepoxybutane and 3,4-epoxy-1,2-butanediol in cultured human lymphoblasts. Carcinogenesis, 15:713–717.

Cochrane JE, Skeple TR (1994b) Mutagenicity of butadiene and its epoxide metabolites: II. Mutational spectra of butadiene, 1,2-

epoxybutane and diepoxybutane at the hprt locus in splenic T cells from exposed B6C3F1 mice. Carcinogenesis, 15:719–723.


Conor Pacific Environmental (1998) A report on multimedia exposures to selected PS2L substances. Prepared by Conor Pacific Environmental (formerly Bovar Environmental) and Maxxam Analytics Inc. for Health Canada, Ottawa, Ontario (Project No. 741-6705; Contract # DIS File No. 02555.H4078-6-C574).


Crouch CN, Pullinger DH, Gauft IF (1979) Inhalation toxicity studies with 1,3-butadiene — 2, 3 month toxicity study in rats. American Industrial Hygiene Association journal, 40:796-802.


1,3-Butadiene: Human health aspects


Duescher RJ, Ellarra AA (1994) Human liver microsomes are efficient catalysts of 1,3-butadiene oxidation: evidence for major roles by cytochromes P450 2A6 and 2E1. Archives of biochemistry and biophysics, 311(2):342-349.


Environment Canada (1996a) Summary report — 1994 Hull, Quebec, Environment Canada, Pollution Data Branch, National Pollutant Release Inventory (NPRI).


Lähdetie J, Gräwe J (1997) Flow cytometric analysis of micronucleus induction in rat bone marrow polychromatic erythrocytes by 1,2,3,4-depoxbutylene, 3,4-epoxy-1-butene, and 1,2-epoxybutane-3,4-diol. Cytometry, 28:228–235.


Mabon N, Moorthy B, Randarath E, Randarath K (1996) Monophosphate P-postlabeling assay of DNA adducts from 1,2:3,4-diepoxybutane, the most genotoxic metabolite of 1,3-butadiene: in vitro methodological studies and in vivo dosimetry. Mutation research, 371:87–104.


Saranko CJ, Recio L (1998) The butadiene metabolite, 1,2,3,4-diepoxybutane, induces micronuclei but is only weakly mutagenic at lacI in the Big Blue® Rat2 lact transgenic cell line. Environmental and molecular mutagenesis, 31:32–40.


Sjöblom T, Låhdetie J (1996) Micronuclei are induced in rat spermatids in vitro by 1,2,3,4-diepoxybutane but not 1,2-epoxy-3-butene and 1,2-dihydroxy-3,4-epoxybutane. Mutagenesis, 11(5):525–528.


Sweeney LM, Schlosser PM, Medinsky MA, Bond JA (1997) Physiologically based pharmacokinetic modeling of 1,3-butadiene, 1,2-epoxy-3-butene, and 1,2,3,4-diepoxybutane toxicokinetics in mice and rats. Carcinogenesis, 18(4):611–625.


Tates AD, van Dam FJ, van Teylingen CMM, de Zwart FA, Zwinderman AH (1998) Comparison of induction of hprt mutations by 1,3-butadiene and/or its metabolites 1,2-epoxybutene and 1,2,3,4-diepoxypentane in lymphocytes from spleen of adult male mice and rats in vivo. *Mutation research*, 397:21–36.


1,3-Butadiene: Human health aspects

APPENDIX 1 — SOURCE DOCUMENT

Government of Canada (2000)

Copies of the Canadian Environmental Protection Act Priority Substances List Assessment Report on 1,3-butadiene (Government of Canada, 2000) are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or on the Internet at:

www.ec.gc.ca/ceeb1/eng/public/index_e.html

Unpublished supporting documentation for the health effects assessment, which presents additional information, is available upon request from:

Environmental Health Centre
Room 104
Health Canada
Tunney’s Pasture
Ottawa, Ontario
Canada K1A 0L2

Sections of the Assessment Report and supporting documentation on genotoxicity and reproductive and developmental toxicity were reviewed by D. Blakey and W. Foster, respectively, of the Environmental and Occupational Toxicology Division of Health Canada. A review of the exposure assessment included in the critical epidemiological studies was prepared under contract by M. Gerin and J. Siemiatycki of the Institut Armand-Frappier, University of Quebec.

In the first stage of external review, sections of the supporting documentation pertaining to human health were considered by the following individuals, primarily to address adequacy of coverage: J. Aquavella, Monsanto Company; M. Bird, Exxon Biomedical Sciences, Inc.; J.A. Bond, Chemical Industry Institute of Toxicology; I. Brooke, United Kingdom Health and Safety Executive; G. Granville, Shell Canada Ltd.; R. Keefe, Imperial Oil Ltd.; A. Koppikar, US Environmental Protection Agency; R.J. Lewis, Exxon Biomedical Sciences, Inc.; K. Petlonen, Finnish Institute of Occupational Health; and F. Ratan, Nova Chemicals.

In the second stage of external review, accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered in written review by BIRRA International and the following individuals: R.J. Albertini, University of Vermont; J.A. Bond, Chemical Industry Institute of Toxicology; I. Brooke, United Kingdom Health and Safety Executive; J. Bucher, US National Toxicology Program; B. Davis, US National Toxicology Program; E. Delzell, University of Alabama at Birmingham; B.J. Divine, Texaco; A.A. Elfarra, University of Wisconsin-Madison; E. Frome, Oak Ridge National Laboratory; B.D. Goldstein, Environmental and Occupational Health Sciences Institute; R.F. Henderson, Lovelace Respiratory Research Institute; R.D. Irons, University of Colorado Health Sciences Center; A. Koppikar, US Environmental Protection Agency; J. Lubin, US National Cancer Institute; J. Lynch, Exxon Biomedical Sciences, Inc. (retired); R.L. Melnick, US National Toxicology Program; K. Petlonen, Finnish Institute of Occupational Health; A.G. Renwick, University of Southampton;
In the third and final stage of external expert review, adequacy of incorporation of the comments received during the second stage was considered at a final meeting of a panel of the following members convened by Toxicology Excellence in Risk Assessment (TERA) in November 1998: H. Clewell, K.S. Crump Division of ICF Kaiser; M.L. Dourson, TERA; and L. Erdreich, Bailey Research Associates, Inc.

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting. The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Concurrent with review of the draft CICAD, there was also a public comment period for the source national assessment, in which the Priority Substances List Assessment Report was made available for 60 days (2 October to 1 December 1999). A summary of the comments and responses is available on the Internet at www.ec.gc.cceb1/eng/public/index_e.html.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 1,3-butadiene was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

M. Baril, International Programme on Chemical Safety/Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, USA

T. Berzins, National Chemicals Inspectorate (KEMI), Sweden

R. Cary, Health and Safety Executive, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, USA

P. Edwards, Department of Health, United Kingdom

H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, USA

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

J. Heuer, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

J. Jinot, US Environmental Protection Agency, USA

C. Kimmel, US Environmental Protection Agency, USA

A.M. Koppikar, US Environmental Protection Agency, USA

S. Kristensen, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia

N. Moore, BP Amoco Chemicals (commented through Department of Health, United Kingdom)

H. Nagy, National Institute of Occupational Safety and Health, USA

S. Tarkowski, Nofer Institute of Occupational Medicine, Poland

L. Vodickova, National Institute of Public Health, Centre of Industrial Hygiene and Occupational Diseases, Czech Republic

P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, People’s Republic of China

K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit, Germany (transmitted comments from BUA and industry representatives)
APPENDIX 3 — CICAD FINAL REVIEW BOARD

Helsinki, Finland, 26–29 June 2000

Members

Mr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Dr R.M. Bruce, Office of Research and Development, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Mr R. Cary, Health and Safety Executive, Liverpool, United Kingdom (Rapporteur)

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Dr H. Choudhury, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Dr S. Dobson, Centre for Ecology and Hydrology, Monks Wood, Abbots Ripton, United Kingdom (Chairman)

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Ms K. Hughes, Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr G. Koennecker, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr A. Nishikawa, Division of Pathology, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan

Dr V. Riihimäki, Finnish Institute of Occupational Health, Helsinki, Finland

Dr J. Risher, Agency for Toxic Substances and Disease Registry, Division of Toxicology, US Department of Health and Human Services, Atlanta, GA, USA

Professor K. Savolainen, Finnish Institute of Occupational Health, Helsinki, Finland (Vice-Chairman)

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, Alexandria, Egypt

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, NSW, Australia

Observer

Dr R.J. Lewis (representative of European Centre for Ecotoxicology and Toxicology of Chemicals), Epidemiology and Health Surveillance, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Secretary)

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
APPENDIX 4 — QUANTITATION OF EXPOSURE–RESPONSE FOR CRITICAL EFFECTS ASSOCIATED WITH EXPOSURE TO 1,3-BUTADIENE

Tumorigenic concentrations based on epidemiological data

Methods

The raw study data\(^1\) for the six plants investigated by Delzell et al. (1995) were used to calculate the potency estimates. The data consisted of the cumulative occupational exposures to butadiene and styrene at each year of each subject’s life (person-year), beginning with his entry into the cohort and terminating with death or other exit from the cohort. The data also contained information on race, age, calendar year, and years since hire of each subject.

The response of interest was cases of death due to all forms of leukaemia, as information on the specific type of leukaemia was insufficient; only cases in which leukaemia was considered the underlying cause of death were considered in these analyses. Exposure estimates were cumulative occupational exposures in ppm-years assumed to be incurred for 8 h/day, 240 days/year over a 45-year working life.

The objective of this exposure–response analysis was to compute the carcinogenic potency, expressed as the TC\(_0\), or the concentration of butadiene associated with a 1% excess probability of dying from leukaemia. This analysis involved two stages. First, the relationship between exposure and the death rate due to leukaemia within the cohort was modelled. This was accomplished by collapsing (or stratifying) the data into discrete exposure categories and then modelling the mean exposure in each category versus the death rates due to leukaemia. In the second stage of analysis, the TC\(_0\) was calculated based on this exposure–response relationship and the background mortality rates in the Canadian population.

Exposure–response modelling

In addition to stratifying by exposure, the data were stratified by race, age, calendar year, years since hire, and styrene exposure in order to incorporate this information into the exposure–response relationship. Each of these variables was collapsed into a small number of discrete categories in order to reduce the number of strata, thereby improving model stability. These variables and their categories are presented in Table A-1. Exposure, defined as the mean cumulative exposure per person-year, was calculated for person-years falling into each possible combination of the stratification variables.

The data were imported to Epicure (1993)\(^2\) for exposure–response modelling. All fitted models were of the form:

\[
RR = \frac{O}{E} = g(D(t))
\]

where RR is the rate ratio, O and E are the observed and expected numbers of leukaemia deaths, D(t) is cumulative butadiene exposure up to time t, and g is the exposure–response model, which is constrained to pass through one at zero exposure. Four different models, discussed in more detail below, were fitted to the data. At the model-fitting stage, the expected number of deaths is calculated on the basis of the non-exposed person-years in the cohort, and not from population background rates.

Lifetime probability of death due to leukaemia

Once the fitted exposure–response model was obtained, the lifetime probability of death due to leukaemia was computed using lifetable methods taking into account the death rates in the Canadian population. The derivation of the formula used for the lifetime probability of death due to leukaemia proceeds as follows.

Let \(d(t)\) represent the exposure concentration of butadiene in ppm at age \(t\) years, and let \(D(t)\) denote the cumulative exposure in ppm-years, with:

\[
D(t) = \int_0^t d(x) \, dx
\]

This formulation of cumulative exposure allows for the possibility of non-constant exposure scenarios.

At a cumulative exposure of \(D(t)\) ppm-years, the probability of dying from leukaemia by age \(t\) is given by:

\[
P(D(t); t) = \int_0^t h_x(D(x); x) S(x) \, dx
\]

(1)

where \(h_x(D(t); t)\) is the mortality rate from leukaemia at age \(t\) given a cumulative exposure to butadiene of \(D(t)\), and \(S(t)\) is the probability of survival up to age \(t\). Equation (1) follows from the argument that the probability of death by age \(t\) is equal to the probability of death at age \(t\) multiplied by the probability of surviving up until age \(t\). In lifetable analysis, the mortality and survival rates are constant for each year, so the integral in (1) can be replaced by a summation over year.

Exposure to butadiene is assumed to augment the background rate of leukaemia in a multiplicative fashion. In other words, the mortality rate, given exposure to butadiene, is equal to the background exposure rate multiplied by the excess risk due to exposure to butadiene. This is known as the “proportional hazard” model and is expressed as:

\[
H_x(D(t); t) = h(t) \times [g(D(t))]
\]

(2)

where \(h(t)\) is the background mortality rate from leukaemia in the population, calculated from Canadian age-specific death rates\(^3\) due to leukaemia, and \(g(D(t))\) is the fitted exposure–response model, or excess risk at age \(t\).

The survival rate, \(S(t)\), appearing in equation (1) is computed from Canadian age-specific death rates due to all causes, where the reported Canadian leukaemia mortality rate is

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\(^1\) The cooperation of the sponsors and researchers for the Delzell et al. (1995) study in the provision of these data is gratefully acknowledged.

\(^2\) Epicure is a collection of interactive programs used to fit models to epidemiological data. The specific program used to model the data for this cohort of styrene-butadiene rubber workers is called AMFIT, which is specially designed to model hazard functions for censored cohort survival data. The strength of Epicure lies in its ability to easily allow the background rate to depend on user-specified strata, such as age, calendar period, and race.

\(^3\) Mortality data were provided to Health Canada by Statistics Canada. The cooperation of the registrars of vital statistics in the provinces and territories of Canada who make mortality data available to Statistics Canada under federal–provincial agreements is gratefully acknowledged.
replaced by the modelled rate in order to incorporate exposure to butadiene. The formula describing the probability of survival up to age \( i \) is given by:

\[
S_i = \exp \left[ -\sum_{j=1}^{n} h_j^* - h_j + h_j g_j \right]
\]

(3)

where \( h_j^* \) and \( h_j \) are the Canadian mortality rates due to all causes and due to leukaemia at age \( j \), respectively, and \( g_j = g(D_j) \) is the excess risk at age \( j \).

Substituting equation (2) into (1), the lifetime probability of death due to leukaemia is given by:

\[
P(D(70); 70) = \sum_{i=1}^{70} h_i g_i S_{i-1}
\]

where 1–70 years is the standard lifetime for a human.

**Cancer potency (TC)**

The TC is computed by determining the exposure \( D(t) \) at which the excess risk is equal to 0.01. That is,

\[
P(D(t); t) - P(0; t) = 0.01
\]

If a constant exposure \( d \) is assumed for an individual from birth to age 70 years, then \( d(t) = d \ ppm \) and the cumulative exposure \( D(t) = d \times 70 \) ppm-years. The TC is then the ambient exposure level \( d \) (in ppm) at which the excess risk equals 0.01 at \( t = 70 \) years.

**Lagged exposure analysis**

In separate analyses, exposures were lagged by \( n = 2, 5, 10, 15, 20, \) and 25 years to determine if the models would provide better fits if the most recent \( n \) years of exposure were ignored. An \( n \)-year lag was achieved by resetting an individual’s cumulative exposure at each year to be equal to the exposure he had accumulated \( n \) years prior. In so doing, the last \( n \) years of exposure do not affect the probability of developing leukaemia. The data were first stratified on unlagged cumulative exposure, and then the individual exposures were lagged. Thus, the number of strata remains constant when using different lag periods, and models with different lags may be directly compared (Preston et al., 1987).

**Validation study**

To assess the predictive power of the exposure–response models, a validation study was performed in which individuals in the cohort were divided randomly into two groups. The models were fit separately to both groups, and then a likelihood ratio test was performed to determine if the estimated parameters were equal. The process of dividing and fitting was repeated 1000 times to characterize the variability due to the random splitting process. If the models provided consistent fits, then the likelihood ratio test would be expected to reject at a rate equal to the desired significance level of the test (i.e., at a significance level of 0.05, the fitted parameters should be significantly different in 1 in 20 times). If the tests are significant more often than this, the confidence in the predictive power of the models is reduced.

**Results**

**Exposure–response modelling**

Four different exposure–response models were examined and are presented in Table A-2. These models are identical to those fitted in the Delzell et al. (1995) report except that model 2 is more general and flexible than the square root model used by those authors. Preliminary analysis indicated that all stratification variables except race significantly affected the model fit. Since race was only marginally insignificant, all variables were used to stratify the data prior to model fitting.

The four models were fitted while stratifying on race, age, calendar year, years since hire, and styrene exposure. The results of the model fitting are displayed in Table A-2. (Note: A smaller deviance roughly indicates a better fit.) A graphic representation of the data and the fitted models is shown in Figure A-1. Judging from the model deviances and the shape of the curves relative to the data, especially in the low-dose region, model 1 provides the best fit to the data.

For purposes of comparison, the same models were fitted using the median exposure as per the Delzell et al. (1995) report. These analyses indicated that there is little difference between using mean or median exposures. Models including age as a multiplying factor of \( e^{70 \cdot t} \) instead of as a stratification variable were also fitted, but these models did not fit as well. Since cumulative exposure and years since hire may be confounded, their interaction was examined. The interaction was not significant for any of the models. The same models were refitted excluding the largest exposure group (200+ ppm-years), but this did not significantly affect any of the parameter estimates. The four models were also refitted allowing for different background rates for control and exposed populations. Different background rates might be necessary in occupational studies where lifetime non-exposed workers may differ fundamentally from exposed workers as a result of differences in jobs and work areas. Results of this analysis indicated that different background rates are not necessary for these data.

The parameter estimates obtained in the present analysis are also not significantly different from those presented in the Delzell et al. (1995) report. The differences in parameter estimates are likely due to the different levels used in the stratification variables. Table A-2 compares the parameter estimates obtained in this analysis with those of the Delzell et al. (1995) report.
Table A-2: Parameter estimates and model deviances for each of four models fit to mean cumulative exposure per person-year for Delzell et al. (1995) study and comparison with parameter estimates from Delzell et al. (1995) analyses.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter estimates</th>
<th>Standard error</th>
<th>Deviance</th>
<th>Parameter estimates from Delzell et al. (1995) study</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) RR = (1 + dose)(^{b})</td>
<td>&quot; = 0.2850 SE(&quot;(^{b})) = 0.0976</td>
<td>171.5</td>
<td>&quot; = 0.2028</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>2) RR = 1 + (\delta_{\text{base}})</td>
<td>&quot; = 0.3999 SE(&quot;(^{b})) = 0.2733</td>
<td>172.0</td>
<td>&quot; = 0.5000(^{b})</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>$ = 0.4558$ SE($\delta$) = 0.8222</td>
<td></td>
<td></td>
<td>$ = 0.1293$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) RR = (e^{\delta_{\text{base}}\delta})</td>
<td>$ = 0.0029$ SE($\delta$) = 0.0014</td>
<td>176.7</td>
<td>$ = 0.0041$</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>4) RR = 1 + (\delta_{\text{base}}\delta)</td>
<td>$ = 0.0099$ SE($\delta$) = 0.0065</td>
<td>174.7</td>
<td>$ = 0.0068$</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) p-value of likelihood ratio test of equality of parameters.
\(^{b}\) For the Delzell et al. (1995) analysis, " was fixed at 0.5, and only $ was estimated.

Figure A-1. Observed rate ratios and fitted curves for leukaemia in Delzell et al. (1995) study.

Cancer potency (TC\(_{01}\))

The TC\(_{01}\)s were calculated for each model using the lifetable methods described above, and the resulting ambient occupational exposures per person-year were converted to environmental exposures by assuming that the exposures occurred for 8 h/day, 240 days/year. This amounts to multiplying the TC\(_{01}\) by:

\[
\frac{8 \ h}{24 \ h} \times \frac{240 \ days}{365 \ days}
\]

To convert the ambient exposures from ppm to mg/m\(^3\), the TC\(_{01}\)s are further multiplied by 2.21, the conversion factor for butadiene. The occupational and equivalent environmental TC\(_{01}\)s are presented in Table A-3. Environmental TC\(_{01}\)s for each of the four models ranged from 1.4 to 4.3 mg/m\(^3\). TC\(_{01}\)s calculated excluding the largest exposure group were slightly smaller, ranging from 0.6 to 1.6 mg/m\(^3\), while those calculated on the basis of median exposures were similar, ranging from 0.4 to 5.0 mg/m\(^3\).

TC\(_{01}\)s were also calculated using the parameter estimates from the Delzell et al. (1995) report and are compared with the TC\(_{01}\)s developed here in Table A-3. They ranged from 3.1 to 14.3 mg/m\(^3\).

Lagged exposure analysis

The same four models were fitted when exposures were lagged by 2, 5, 10, 15, 20, and 25 years. The resulting model fits are displayed in Table A-4. Since the deviances are similar for each lag period, this analysis indicates that lagging exposures does not dramatically improve the fit of any of the four models. In fact, TC\(_{01}\)s for all four models and all lag periods ranged from 0.8 to 4.3 mg/m\(^3\).

Validation study

With respect to model validation, the p-values for the tests of equality of the parameters are displayed in Table A-5. If the models were providing consistent fits between the two halves, the proportion of p-values less than the significance level of ** would be **. The results of the simulation study indicate that the test is rejecting more often than would be expected if the
models were providing the same fits to both halves of the data. For model 1, the test was rejected at a significance level of 1% in 7.4% of the runs, whereas a rejection rate of 1% of the runs would be expected if the model was fitting consistently. The results of this analysis reduce the confidence in the power of the models to predict leukaemia mortality rates.

**Summary**

It is noteworthy that the choice of the exposure–response model does not have a large impact on the resulting TC\(_s\), as indicated in Table A-3, the values are similar, ranging from 1.4 to 4.3 mg/m\(^3\). However, if a best model must be chosen, it would be model 1, owing to the smaller deviance (Table A-2), the shape of the curve relative to the data in the low-dose region (Figure A-1), and the fact that it has one fewer parameter than model 2, which provides a similar fit. The TC\(_s\) for model 1 is 1.7 mg/m\(^3\).

It is difficult, though, to assess how well any of these models truly describes the data. It is noted that the plot in Figure A-1 provides only a rough indication of the shape of the data, since each point on the plot is an average of data in many strata. The results of the validation study reduce confidence in the ability of the models to predict leukaemia mortality.

The choice of exposure lag does not greatly improve the fit of any of the four models, and it does not affect the resulting TC\(_s\). Including all lagged models, the range of TC\(_s\) is still from 0.8 to 4.3 mg/m\(^3\).

For comparison with these values, potency estimates were also calculated on the basis of the recent case–control study of styrene-butadiene rubber workers by Matanoski et al. (1997). Although workers were from plants subsumed in the Delzell et al. (1995) study, exposure was independently characterized. Treating the odds ratio presented by these authors as a rate ratio (since leukaemia is a rare disease) and using their model and parameter estimates as well as the same lifetime methods described above, the TC\(_s\), for environmental exposure was calculated to be 0.4 mg/m\(^3\). It is reassuring, therefore, that this value is only slightly lower than the estimates derived on the basis of the Delzell et al. (1995) cohort study data.

**Tumorigenic concentrations based on data from studies in experimental animals**

Estimates of carcinogenic potency were calculated on the basis of the incidences of malignant lymphomas, histaicytic sarcomas, cardiac haemangiosarcomas, alveolar/bronchiolar adenomas or carcinomas, hepatocellular adenomas or carcinomas, squamous cell papillomas or carcinomas of the forestomach, adenomas or carcinomas of the Harderian gland, granulocytic cell tumours of the ovaries, and adenocarcinomas, carcinomas, or malignant mixed tumours of the mammary gland observed in B6C3F\(_1\) mice in the chronic bioassay conducted by the NTP (1993) and the mammary gland tumours, pancreatic exocrine adenomas, Leydig cell tumours, 2ymbl gland carcinomas, thyroid follicular cell adenomas or carcinomas, and uterine sarcomas in Sprague-Dawley rats reported by Hazleton Laboratories Europe Ltd. (1981a). (The tumour incidence data for each of the sites considered are presented in Tables 2 and 3.)

<table>
<thead>
<tr>
<th>Model</th>
<th>Occupational TC(_s) (mg/m(^3))</th>
<th>Environmental TC(_s) (mg/m(^3))</th>
<th>Delzell et al. (1995) analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) RR = (1 + dose) (^t)</td>
<td>7.8</td>
<td>1.7</td>
<td>14.3</td>
</tr>
<tr>
<td>2) RR = 1 + $dose (^{t})</td>
<td>6.5</td>
<td>1.4</td>
<td>6.4</td>
</tr>
<tr>
<td>3) RR = $dose (^t)</td>
<td>19.8</td>
<td>4.3</td>
<td>3.1</td>
</tr>
<tr>
<td>4) RR = 1 + $dose (^t)</td>
<td>13.8</td>
<td>3.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

In the NTP study, mice were exposed to 0, 6.25, 20, 62.5, 200, or 625 ppm (0, 13.8, 44.2, 138, 442, or 1383 mg/m\(^3\)) butadiene for 6 h/day, 5 days/week, for 103 weeks. Survival of mice decreased with increasing exposure concentration; therefore, to minimize the effect of the high mortality rate, the poly-3 adjusted data (Bailer & Portier, 1988; Porter & Bailer, 1989) presented in the NTP (1993) report were used in these calculations. For some tumour types, the adjusted data still demonstrated downward curvature at the highest concentration. In these cases, the high exposure group was excluded in the determination of the TC\(_s\). The TC\(_s\)s were calculated for these end points by first fitting a multistage model to the data. The multistage model is given by:

\[
P(D_i) = 1 - e^{-q_0 - q_1 d - ... - q_k d^k}
\]

where \(d_i\) is dose, \(k\) is the number of dose groups in the study minus one, \(P(D_i)\) is the probability of the animal developing a tumour at dose \(d_i\) and \(q_0, i = 1, ..., k\) are parameters to be estimated.

The models were fitted using GLOBAL82 (Howe & Crump, 1982), and a chi-square lack of fit test was performed for each model fit. The degrees of freedom for this test are equal to \(k\) minus the number of \(q\)s whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. The lower confidence limits presented are approximate, based on output from GLOBAL82. Results from the model fitting are displayed in Table A-6. Plots of the data and the fitted models are shown in Figure A-2.

TC\(_s\)s were determined as the doses D (in mg/m\(^3\)) that satisfy

\[
\frac{P(D) - P(0)}{1 - P(0)} = 0.05
\]

and then adjusted by multiplying by:

\[
\frac{6h/day \times 5 days/week \times wweeks}{24h/day \times 7 days/week \times 104 weeks \{104 weeks\}^2}
\]

where, in the first term, which ammortizes the dose to be constant over the lifetime of a mouse, \(w\) is the duration of the experiment (103 weeks). The second factor was suggested by Peters et al. (1984) and corrects for an experiment length that is unequal to the standard lifetime. Since tumours develop much more rapidly later in life, a greater than linear increase in the tumour rate is expected when animals are observed for tumours longer than their standard lifetime (or the reverse, when animals are observed for a period shorter than their standard lifetime). (Application of this factor does not impact greatly on the final values, since it is very close to one.) The selected TC\(_s\) values for this study and their 95% lower confidence limits (LCLs) are presented in Table A-6 and range from 2.3 mg/m\(^3\) (95% LCL = 1.7 mg/m\(^3\)) to 1.1 ppm (95% LCL = 0.79 ppm) for Harderian gland tumours in males to 99 mg/m\(^3\) (95% LCL = 23 mg/m\(^3\)) or 45 ppm (95% LCL = 10 ppm) for malignant lymphomas in males.
Table A-4: Parameter estimates and model deviances for each of four lagged-exposure models fitted to median cumulative exposure per person-year.

<table>
<thead>
<tr>
<th>Model</th>
<th>Lag</th>
<th>Parameter estimates</th>
<th>Standard error</th>
<th>Deviance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) $RR = (1 + \text{dose})^t$</td>
<td>None</td>
<td>$t = 0.2850$</td>
<td>SE($t$) = 0.0976</td>
<td>171.5</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>$t = 0.2852$</td>
<td>SE($t$) = 0.0982</td>
<td>171.6</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>$t = 0.2883$</td>
<td>SE($t$) = 0.0995</td>
<td>171.6</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>$t = 0.3064$</td>
<td>SE($t$) = 0.1034</td>
<td>171.1</td>
</tr>
<tr>
<td></td>
<td>15 years</td>
<td>$t = 0.2955$</td>
<td>SE($t$) = 0.1079</td>
<td>172.4</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>$t = 0.2891$</td>
<td>SE($t$) = 0.1141</td>
<td>173.6</td>
</tr>
<tr>
<td></td>
<td>25 years</td>
<td>$t = 0.2898$</td>
<td>SE($t$) = 0.1334</td>
<td>175.4</td>
</tr>
<tr>
<td>2) $RR = 1 + \text{dose}^t$</td>
<td>None</td>
<td>$t = 0.3999$</td>
<td>SE($t$) = 0.2733</td>
<td>172.0</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>$t = 0.3992$</td>
<td>SE($t$) = 0.2739</td>
<td>172.0</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>$t = 0.4024$</td>
<td>SE($t$) = 0.2737</td>
<td>172.0</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>$t = 0.4245$</td>
<td>SE($t$) = 0.2755</td>
<td>171.4</td>
</tr>
<tr>
<td></td>
<td>15 years</td>
<td>$t = 0.4835$</td>
<td>SE($t$) = 0.3397</td>
<td>172.6</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>$t = 0.4270$</td>
<td>SE($t$) = 0.3558</td>
<td>173.9</td>
</tr>
<tr>
<td></td>
<td>25 years</td>
<td>$t = 0.2960$</td>
<td>SE($t$) = 0.2833</td>
<td>175.3</td>
</tr>
<tr>
<td>3) $RR = e^{\text{dose}t}$</td>
<td>None</td>
<td>$t = 0.0029$</td>
<td>SE($t$) = 0.0014</td>
<td>176.7</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>$t = 0.0029$</td>
<td>SE($t$) = 0.0015</td>
<td>176.8</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>$t = 0.0031$</td>
<td>SE($t$) = 0.0015</td>
<td>176.7</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>$t = 0.0034$</td>
<td>SE($t$) = 0.0016</td>
<td>176.4</td>
</tr>
<tr>
<td></td>
<td>15 years</td>
<td>$t = 0.0035$</td>
<td>SE($t$) = 0.0018</td>
<td>177.0</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>$t = 0.0033$</td>
<td>SE($t$) = 0.0022</td>
<td>178.2</td>
</tr>
<tr>
<td></td>
<td>25 years</td>
<td>$t = 0.0033$</td>
<td>SE($t$) = 0.0022</td>
<td>178.2</td>
</tr>
<tr>
<td>4) $RR = 1 + \text{dose}^t$</td>
<td>None</td>
<td>$t = 0.0099$</td>
<td>SE($t$) = 0.0065</td>
<td>174.7</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>$t = 0.0102$</td>
<td>SE($t$) = 0.0067</td>
<td>174.7</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>$t = 0.0109$</td>
<td>SE($t$) = 0.0072</td>
<td>174.6</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>$t = 0.0137$</td>
<td>SE($t$) = 0.0089</td>
<td>173.8</td>
</tr>
<tr>
<td></td>
<td>15 years</td>
<td>$t = 0.0158$</td>
<td>SE($t$) = 0.0016</td>
<td>174.1</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>$t = 0.0179$</td>
<td>SE($t$) = 0.0129</td>
<td>175.7</td>
</tr>
<tr>
<td></td>
<td>25 years</td>
<td>$t = 0.0179$</td>
<td>SE($t$) = 0.0129</td>
<td>175.7</td>
</tr>
</tbody>
</table>

Estimates of carcinogenic potency were also calculated based on the results of the bioassay in Sprague-Dawley rats (Hazleton Laboratories Europe Ltd., 1981a). In this study, rats were exposed to 0, 1000, or 8000 ppm (0, 2212, or 17 696 mg/m³) for 6 h/day, 5 days/week, for 105 (males) or 111 (females) weeks. A high mortality rate was observed at the higher concentration; therefore, this exposure group was excluded from the analysis, except for the potency estimates for pancreatic exocrine adenomas in males (for this end-point, exclusion of the high-exposure group would have resulted in the exposure–response relationship curving downwards). As for mice, a multistage model was fit to the data for rats using GLOBAL82 and adjusted to account for study duration ($w$) by multiplying by:

$$\frac{6\text{h/day} \times 5\text{days/week} \times w\text{weeks}}{24\text{h/day} \times 7\text{days/week} \times 104\text{weeks}}\times \left(\frac{w\text{weeks}}{104\text{weeks}}\right)^2$$

where the duration of the experiment was 105 weeks for males and 111 weeks for females. The exposure–response curves and estimated adjusted TC₀ values based on this study in rats are presented in Figure A-3 and Table A-6, respectively. The
Table A-5: Model validation p-values for Deziel et al. (1995) study.

<table>
<thead>
<tr>
<th>Model</th>
<th>Proportion of p-values greater than 0.1</th>
<th>Proportion of p-values greater than 0.05</th>
<th>Proportion of p-values greater than 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) RR = (1 + dose)</td>
<td>0.074</td>
<td>0.167</td>
<td>0.252</td>
</tr>
<tr>
<td>2) RR = 1 + dose</td>
<td>0.084</td>
<td>0.19</td>
<td>0.286</td>
</tr>
<tr>
<td>3) RR = e^dose</td>
<td>0.08</td>
<td>0.188</td>
<td>0.264</td>
</tr>
<tr>
<td>4) RR = 1 + dose</td>
<td>0.103</td>
<td>0.214</td>
<td>0.303</td>
</tr>
</tbody>
</table>

* p-value of likelihood ratio test of equality of parameters fitted to each half of the data.

concentrations of butadiene estimated to be associated with a 5% increased incidence of tumours ranged from 6.7 mg/m$^3$ (95% LCL = 4.7 mg/m$^3$) or 3.0 ppm (95% LCL = 2.1 ppm) to 4872 mg/m$^3$ (95% LCL = 766 mg/m$^3$) or 2203 ppm (95% LCL = 346 ppm) for tumours of the mammary gland and Zymbal gland in female rats, respectively. Although the available data for analysis of exposure–response were more limited for rats than for mice, it is interesting to note the similarity in estimates of potency for mammary gland tumours (i.e., 6.7 mg/m$^3$ in both species).

Based on modelling (using THC; Howe, 1995a) of the incidence of micronucleated polychromatic erythrocytes in B6C3F1 mice exposed to butadiene for up to 15 months in the NTP bioassay, BMC$_{05}$ for somatic cell mutations were very similar to the lower end of the range of the TC$_{05}$s for tumour induction.

**Benchmark concentrations for ovarian atrophy in mice**

Benchmark concentrations (BMC$_{05}$s) for ovarian atrophy were derived on the basis of the chronic bioassay conducted by the NTP (1993) in which B6C3F1 mice were exposed to concentrations of 0, 6.25, 20, 62.5, 200, or 625 ppm (0, 13.8, 44.2, 138, 442, and 1383 mg/m$^3$) butadiene for up to 2 years. There was a concentration-related increase in the incidence as well as the severity of ovarian atrophy, as summarized in Table A-7.

The exposure–response relationship for ovarian atrophy from this study was quantified by fitting the following model to the dose–response data (Howe, 1995b):

$$P(d) = \begin{cases} 
q_0 + (1-q_0) \left[1-e^{-q_1(d-d_0)} \cdots - q_k(d-d_0)^k \right] & \text{if } d \leq d_0 \\
q_0 + (1-q_0) \left[1-e^{-q_1(d-d_0)} \cdots - q_k(d-d_0)^k \right] & \text{if } d > d_0 
\end{cases}$$

where $d$ is dose, $k$ is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing the effect at dose $d$, and $q_i > 0$, $i = 1, \ldots, k$ and $d_0$ are parameters to be estimated. The models were fit using THRESH (Howe, 1995b), and the BMC$_{05}$s were calculated as the dose $D$ that satisfies:

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to $k$ minus the number of $q$’s whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit.

The BMC$_{05}$ was then amortized to be constant over the standard life of a mouse by multiplying by:
Table A-6: Carcinogenic potency estimates (TC⁰₅s) of butadiene based on results of bioassays in experimental animals.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC⁰₅ (mg/m³)</td>
<td>95% LCL (mg/m³)</td>
</tr>
<tr>
<td><strong>Mice (from NTP, 1993)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar/bronchiolar adenomas or carcinomas</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Histiocytic sarcomas</td>
<td>12</td>
<td>8.4</td>
</tr>
<tr>
<td>Cardiac haemangiosarcomas</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td>Forestomach squamous cell papillomas or carcinomas</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Ovarian granulosa cell tumours</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mammary gland adenocanthomas, carcinomas, or malignant mixed tumours</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hepatocellular adenomas or carcinomas</td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Harderian gland adenomas or carcinomas</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Malignant lymphomas</td>
<td>99</td>
<td>23</td>
</tr>
<tr>
<td><strong>Rats (from Hazleton Laboratories Europe Ltd., 1981a)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary gland adenomas or carcinomas</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pancreatic exocrine adenomas</td>
<td>597</td>
<td>316</td>
</tr>
<tr>
<td>Leydig cell tumours</td>
<td>161</td>
<td>96</td>
</tr>
<tr>
<td>Thyroid follicular cell adenomas or carcinomas</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Uterine sarcomas</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zymbal gland carcinomas</td>
<td>1023</td>
<td>905</td>
</tr>
</tbody>
</table>

a. Values have been adjusted for lifetime exposure.
b. Chi-squared goodness of fit statistic.
c. Degrees of freedom.
d. p-value of goodness of fit test (p-value < 0.05 indicates significant lack of fit).
e. Values for malignant lymphomas presented here only for comparison; potency estimates for these tumours not considered relevant to humans due to the greater sensitivity of these mice to induction of this effect associated with the presence of an endogenous retrovirus.
Figure A-2: Exposure-response analysis for butadiene-induced tumours in mice
Figure A-2 (continued).
Figure A2 Continued.

- Forestomach tumors, females
- Harderian gland tumors, males
- Forestomach tumors, males
- Granulosa cell tumors, females

*TC$_{50}$ unadjusted for lifetime dosing
Fig A-2 (continued).
Figure A-3: Exposure-response analysis for butadiene-induced tumours in rats
Figure A-3 (continued).
### Table A-7: Incidence and severity of ovarian atrophy observed in 2-year bioassay in mice (NTP, 1993).

<table>
<thead>
<tr>
<th>Exposure level (ppm)</th>
<th>Number of animals examined</th>
<th>All severities</th>
<th>Minimal severity</th>
<th>Mild severity</th>
<th>Moderate severity</th>
<th>Marked severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>49</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6.25</td>
<td>49</td>
<td>19</td>
<td>0</td>
<td>15</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>48</td>
<td>32</td>
<td>1</td>
<td>23</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>62.5</td>
<td>50</td>
<td>42</td>
<td>3</td>
<td>18</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>50</td>
<td>43</td>
<td>0</td>
<td>9</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>625</td>
<td>79</td>
<td>69</td>
<td>0</td>
<td>19</td>
<td>47</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table A-8: Benchmark concentrations for ovarian atrophy.

<table>
<thead>
<tr>
<th>Ovarian atrophy</th>
<th>BMC&lt;sub&gt;50&lt;/sub&gt; (ppm)</th>
<th>95% LCL on BMC&lt;sub&gt;50&lt;/sub&gt; (ppm)</th>
<th>BMC&lt;sub&gt;50&lt;/sub&gt; (mg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>95% LCL on BMC&lt;sub&gt;50&lt;/sub&gt; (mg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>Chi-square df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All severities</td>
<td>2.5</td>
<td>1.9</td>
<td>5.6</td>
<td>4.1</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>All severities, excluding top two dose groups</td>
<td>0.25</td>
<td>0.20</td>
<td>0.57</td>
<td>0.44</td>
<td>7.0</td>
<td>2</td>
</tr>
<tr>
<td>Moderate/marked severity</td>
<td>4.3</td>
<td>3.4</td>
<td>9.6</td>
<td>7.6</td>
<td>37.1</td>
<td>4</td>
</tr>
<tr>
<td>Moderate/marked severity, excluding top dose group</td>
<td>1.4</td>
<td>1.1</td>
<td>3.1</td>
<td>2.5</td>
<td>2.2</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure A-4: Exposure–response analysis for ovarian atrophy in mice (* BMC<sub>90</sub> and BMCL<sub>90</sub> unadjusted for lifetime dosing).

Figure A-5: Exposure–response analysis for ovarian atrophy in mice excluding two highest dose groups (* BMC<sub>90</sub> and BMCL<sub>90</sub> unadjusted for lifetime dosing).
Figure A-6: Exposure–response analysis for moderate/marked ovarian atrophy (* BMC\text{bio} and BMCL\text{bio} unadjusted for lifetime dosing).

Figure A-7: Exposure–response analysis for moderate/marked ovarian atrophy, excluding high-dose group (* BMC\text{bio} and BMCL\text{bio} unadjusted for lifetime dosing).
**1,3-BUTADIENE**

**CAS No:** 106-99-0  
**RTECS No:** EI9275000  
**UN No:** 1010 (stabilized)  
**EC No:** 601-013-00-X

*Divinyl*  
*Vinylethylene*  
*C₂H₆ / CH₂=CH–CH₂*  
*Molecular mass: 54.1*

<table>
<thead>
<tr>
<th>TYPES OF HAZARD/EXPOSURE</th>
<th>ACUTE HAZARDS/SYMPTOMS</th>
<th>PREVENTION</th>
<th>FIRST AID/FIRE FIGHTING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRE</strong></td>
<td>Extremely flammable.</td>
<td>NO open flames, NO sparks, and NO smoking.</td>
<td>Shut off supply; if not possible and no risk to surroundings, let the fire burn itself out; in other cases extinguish with water spray, powder, carbon dioxide.</td>
</tr>
<tr>
<td><strong>EXPLOSION</strong></td>
<td>Gas/air mixtures are explosive.</td>
<td>Closed system, ventilation, explosion-proof electrical equipment and lighting. Prevent build-up of electrostatic charges (e.g., by grounding) if in liquid state.</td>
<td>In case of fire: keep cylinder cool by spraying with water.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>AVOID ALL CONTACT! AVOID EXPOSURE OF (PREGNANT) WOMEN!</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>ON CONTACT WITH LIQUID: FROSTBITE.</td>
</tr>
<tr>
<td>Eyes</td>
<td>Redness. Pain. Blurred vision. See Skin.</td>
</tr>
<tr>
<td>Ingestion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPILLAGE DISPOSAL</th>
<th>PACKAGING &amp; LABELLING</th>
</tr>
</thead>
</table>
| Evacuate danger area! Consult an expert! Ventilation. NEVER direct water jet on liquid. Remove all ignition sources. Chemical protection suit including self-contained breathing apparatus. | F+ Symbol  
T Symbol  
R: 45-12  
S: 53-45  
Note: D  
UN Hazard Class: 2.1 |
| Do not transport with food and feedstuffs. |

<table>
<thead>
<tr>
<th>EMERGENCY RESPONSE</th>
<th>STORAGE</th>
</tr>
</thead>
</table>
| Transport Emergency Card: TEC (R)-20G41  
NFPA Code: H2; F4; R2 | Fireproof. Cool. Separated from food and feedstuffs. |
<table>
<thead>
<tr>
<th>IMPORTANT DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical State; Appearance</td>
</tr>
<tr>
<td>COLOURLESS COMPRESSED LIQUEFIED GAS, WITH CHARACTERISTIC ODOUR.</td>
</tr>
<tr>
<td>Physical dangers</td>
</tr>
<tr>
<td>The gas is heavier than air and may travel along the ground; distant ignition possible. As a result of flow, agitation, etc., electrostatic charges can be generated. The vapours are uninhibited and may form polymers in vents or flame arresters of storage tanks, resulting in blockage of vents.</td>
</tr>
<tr>
<td>Chemical dangers</td>
</tr>
<tr>
<td>The substance can under specific circumstances (exposure to air) form peroxides, initiating explosive polymerization. The substance may polymerize due to warming with fire or explosion hazard. Shock-sensitive compounds are formed with copper and its alloys (see Notes). The substance decomposes explosively on rapid heating under pressure. Reacts vigorously with oxidants and many other substances, causing fire and explosion hazard.</td>
</tr>
<tr>
<td>Occupational exposure limits</td>
</tr>
<tr>
<td>TLV: (as TWA) 2 ppm; A2 (ACGIH 1999). MAK: class 2 (1999)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHYSICAL PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point: -4°C</td>
</tr>
<tr>
<td>Melting point: -109°C</td>
</tr>
<tr>
<td>Relative density (water = 1): 0.6</td>
</tr>
<tr>
<td>Solubility in water: none (0.1 g/100 ml)</td>
</tr>
<tr>
<td>Vapour pressure, kPa at 20°C: 245</td>
</tr>
<tr>
<td>Relative vapour density (air = 1): 1.9 3,47 (1.87)</td>
</tr>
<tr>
<td>Flash point: -76°C</td>
</tr>
<tr>
<td>Auto-ignition temperature: 414°C</td>
</tr>
<tr>
<td>Explosive limits, vol% in air: 1.1-16.3</td>
</tr>
<tr>
<td>Octanol/water partition coefficient as log Pow: 1.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENVIRONMENTAL DATA</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piping material for this gas must not contain over 63% of copper. Use of alcoholic beverages enhances the harmful effect. The odour warning when the exposure limit value is exceeded is insufficient.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADDITIONAL INFORMATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>LEGAL NOTICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information</td>
</tr>
</tbody>
</table>

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RÉSUMÉ D’ORIENTATION


Le 1,3-butadiène (No CAS 106-99-0) résulte de la combustion incomplète de certains produits lors de processus naturels ou d’activités humaines. C’est également un produit chimique industriel principalement utilisé pour la préparation de polymères, notamment du polybutadiène et des caoutchoucs et latex styrène-butadiène ou des élastomères acrylonitrile-butadiène. Le 1,3-butadiène pénètre dans l’environnement avec les gaz d’échappement des véhicules à essence ou à gazole, lors de l’utilisation de combustibles à d’autres fins que le transport, de la combustion de la biomasse ou encore lors de son utilisation sur des sites industriels.

Le 1,3-butadiène ne persiste pas dans l’environnement mais il est néanmoins répandu dans tout le milieu urbain du fait de la présence généralisée des sources de combustion où il prend naissance. C’est dans les villes et à proximité immédiate des installations industrielles que sont mesurées les concentrations atmosphériques les plus fortes.

L’exposition de la population générale au 1,3-butadiène est due principalement à sa présence dans l’air extérieur ou intérieur. Comparativement, la contribution des autres véhicules, comme les aliments ou l’eau de boisson, reste négligeable. En revanche, celle de la fumée de tabac peut être importante.

Le métabolisme du 1,3-butadiène se révèle être de même nature d’une espèce à l’autre, mais il y a néan-
Les effets sanitaires du 1,3-butadiène et le mode d’action de ce composé ont été étudiés en détail, mais d’importants travaux de recherche continuent de lui être consacrés afin de tenter de lever les incertitudes qui subsistent dans la base de données.

Il existe, entre l’exposition au 1,3-butadiène sur le lieu de travail et certaines leucémies, une corrélation qui répond à plusieurs des critères d’une relation de cause à effet. L’étude la plus vaste et la plus exhaustive effectuée jusqu’ici, et qui a porté sur une cohorte de travailleurs employés dans de multiples usines, a mis en évidence un parallélisme entre une augmentation constatée de la mortalité par leucémie et l’exposition cumulée estimative au 1,3-butadiène dans les industries produisant des élastomères styrène-butadiène. La correction pour tenir compte de l’exposition au benzène et au styrène n’a pas fait disparaître cette corrélation, qui se manifestait d’ailleurs le plus fortement dans les sous-groupes potentiellement les plus exposés. On a également observé une corrélation entre l’exposition au 1,3-butadiène et les leucémies lors d’une étude cas-témoins menée indépendamment de l’enquête précédente sur une population de travailleurs en grande partie identique. Par contre, on n’a pas constaté d’augmentation de la mortalité par leucémie chez des travailleurs employés à la production de butadiène monomère mais non exposés simultanément à certaines des autres substances présentes dans l’industrie des élastomères styrène-butadiène, en dépit d’éléments d’appréciation limités concernant la possibilité d’une association avec la mortalité par lymphosarcomes ou réticulosarcomes dans certains sous-groupes.

Au vu des données épidémiologiques et toxicologiques, le 1,3-butadiène est cancérogène pour l’Homme et pourrait également être génotoxique. Le pouvoir cancérogène (concentration qui entraîne uneaugmentation de 1% de la mortalité par leucémie) a été évalué à 1,7 mg/m³ et le mieux conduit sur des travailleurs exposés. Cette valeur correspond à l’extrémité inférieure de la série de concentrations tumorigènes déterminée par des études sur des rongeurs. Le 1,3-butadiène présente également une toxicité génésique chez les animaux de laboratoire. Ce potentiel toxique peut s’évaluer par la concentration de référence de 1,3-butadiène obtenue dans le cas des effets ovariens et qui est égale à 0,57 mg/m³.

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RESUMEN DE ORIENTACIÓN

Este CICAD sobre el 1,3-butaeni, preparado por la Dirección General de Higiene del Medio del Ministerio de Salud del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la Ley Canadiense de Protección del Medio Ambiente (CEPA). El objetivo de las evaluaciones sanitarias de las sustancias prioritarias en el marco de la CEPA es valorar los efectos potenciales de la exposición indirecta en el medio ambiente general para la salud humana. En este examen se utilizaron los datos obtenidos hasta el final de abril de 1998. La información relativa al carácter del examen colegiado y a la disponibilidad del documento original se presenta en el apéndice 1. La información sobre el examen colegiado de este CICAD figura en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Helsinki (Finlandia) del 26 al 29 de junio de 2000. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0017) para el 1,3-butaeni, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El 1,3-butaeni (CAS Nº 106-99-0) se produce por una combustión incompleta en procesos naturales y actividades humanas. Es también un producto químico industrial que se utiliza fundamentalmente en la producción de polímeros, en particular polibutaeni, cauchos y látex de estireno-butaeni y cauchos de nitrilo-butaeni. El 1,3-butaeni se incorpora al medio ambiente a partir de las emisiones de los gases de escape de los vehículos con motor de gasolina y diésel, de la combustión de combustibles fósiles no utilizados en el transporte, de la combustión de biomasa y de usos industriales sobre el terreno.

El 1,3-butaeni no es persistente, pero sí ubicuo en el medio ambiente urbano, debido a la presencia generalizada de sus fuentes de combustión. Las concentraciones atmosféricas más altas se han medido en el aire de las ciudades y en las cercanías de fuentes industriales.

La población general está expuesta al 1,3-butaeni fundamentalmente mediante el aire del ambiente y de los espacios cerrados. En comparación, otros medios, entre ellos los alimentos y el agua de bebida, contribuyen de manera insignificante a la exposición a él. El humo del tabaco puede producir cantidades significativas de 1,3-butaeni.

El metabolismo del 1,3-butaeni parece ser cualitativamente semejante en todas las especies, aunque hay diferencias cuantitativas en los metabolitos.
La asociación entre la exposición al 1,3-butadieno en el entorno de trabajo y la leucemia cumple varios de los criterios tradicionalmente establecidos para la causalidad. En el estudio más amplio y completo realizado hasta el momento, utilizando una cohorte de trabajadores de diversas instalaciones, la mortalidad por leucemia aumentó con una exposición acumulativa estimada al 1,3-butadieno en la industria del caucho de estireno-butadieno; esta asociación se mantuvo tras el control de la exposición al estireno y al benceno y alcanzó la intensidad máxima en los subgrupos con el mayor potencial de exposición. Análogamente, en un estudio de casos y testigos independiente basado prácticamente en la misma población de trabajadores se observó una asociación entre la exposición al 1,3-butadieno y la leucemia. Sin embargo, no se produjo un aumento de la mortalidad a causa de la leucemia en los trabajadores de la producción de monómeros de butadieno que no estaban simultáneamente expuestos a algunas de las otras sustancias presentes en la industria del caucho de estireno-butadieno, aunque en algunos subgrupos se obtuvieron pruebas limitadas de asociación con la mortalidad por linfosarcoma y reticulosarcoma.

Los datos epidemiológicos y toxicológicos disponibles demuestran que el 1,3-butadieno es carcinogénico, y también puede ser genotóxico, para las personas. Se calculó una potencia carcinogénica (concentración que produce un aumento del 1% de la mortalidad por leucemia) de 1,7 mg/m³, sobre la base de los resultados de la mayor investigación epidemiológica bien realizada en trabajadores expuestos. Este valor es semejante al nivel más bajo de la gama de concentraciones tumorigénas determinadas a partir de los estudios realizados con roedores. El 1,3-butadieno indujo también toxicidad reproductiva en animales experimentales. Como medida de su potencia para inducir efectos reproductivos, se obtuvo una concentración de referencia de 0,57 mg/m³ para la toxicidad ovárica en los ratones.

Aunque se han investigado a fondo los efectos en la salud asociados con la exposición al 1,3-butadieno y el mecanismo de acción para la inducción de estos efectos, se siguen realizando numerosas investigaciones sobre esta sustancia, a fin de tratar de abordar algunas de las incertidumbres asociadas con la base de datos.

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