1,3-Butadiene: Human health tier II assessment

22 November 2013

CAS Number: 106-99-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

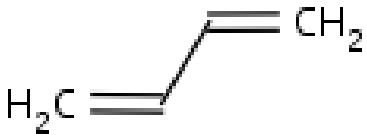
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	.alpha.,.gamma.-Butadiene Biethylene Bivinyl Erythrene Pyrrolylene
Structural Formula	
Molecular Formula	C4H6
Molecular Weight (g/mol)	54.09
Appearance and Odour (where available)	Colourless gas, mildly aromatic or gasoline-like odour.
SMILES	C(=C)C=C

Import, Manufacture and Use

Australian

Under a mandatory call for information, the total reported volume of the chemical was 325,700 tonnes (NICNAS, 2000). It is also listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a reported volume of 10,000 to 99,999 tonnes and reported use in producing rubber and plastics (NICNAS, 2006).

The National Pollutant Inventory (NPI) holds data for all sources of the chemical in Australia (NPI).

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; and eChemPortal: the US Agency of Toxic Substances and Disease Registry Report, the European Union Risk Assessment Report and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

The chemical has reported site-limited use including:

- producing synthetic rubber (used to manufacture automotive tyres and tyre products);
- producing plastics such as acrylics, high impact polystyrene and acrylonitrile butadiene styrene (ABS) resin plastics, nylon and neoprene;
- producing resins;
- processing petroleum;
- as a chemical intermediate in producing some fungicides; and
- in manufacturing latex adhesives and paints.

Small levels of 1,3-butadiene are found in petrol and other hydrocarbon refinery streams. The chemical is also present in smoke from cigarettes as well as bush and woodfires. It is reported to be present in trace amounts in elastomeric flashing cement and adhesive pastes (US Household Products Database).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (the cosmetic ingredient "Hotlist").

Existing Work Health and Safety Controls

Hazard Classification

F+; R12

Carc. Cat. 1; R45

Muta. Cat. 2; R46

Exposure Standards

Australian

The chemical has an exposure standard of 10 mg/m³ (22 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 1–4.4 mg/m³ (0.5–2 ppm) in different countries such as USA, Canada, Sweden and South Africa. Denmark, Greece and the UK had an exposure limit (TWA) of 10 mg/m³ (22 ppm).

Health Hazard Information

Due to the gaseous nature of the chemical under normal conditions of exposure, data on exposure routes other than inhalation are scarce and unlikely to relate to actual conditions of human exposure.

Toxicokinetics

1,3-Butadiene is absorbed through the lungs in animals and humans. There are no data for absorption by mouth or skin exposure but, as it is a gas, it is reasonable to assume that uptake by these two routes would be minor compared with inhalation. After inhalation, the substance is widely distributed throughout the body. The first step in the metabolic pathway is the formation of epoxybutene. Further metabolism of epoxybutene to butenediol, diepoxybutane, and erythritol can occur. Excretion of 1,3-butadiene and its metabolites is mainly in the urine or breath (OECD, 1996).

Evaluation of the relevance of adverse health effects observed in laboratory animals to human health by inhalation is complicated by large species differences in the metabolism of 1,3-butadiene. The metabolism of 1,3-butadiene in humans and laboratory animals involves the same enzymatic pathways; however, there are notable quantitative differences in the production and detoxification of several reactive metabolites. Mice are the most sensitive species. For example, in one study reported by ATSDR, an exposure of mice to 1 ppm of the chemical resulted in levels of a reactive metabolite that were 50 times higher than in rats and 1,000 times higher than in humans under similar conditions. Although the mode of action has not been elucidated for all toxicological end points, there are strong data to support the reactive metabolites as the causative agents for the ovarian atrophy, cancer, and genotoxic effects observed in laboratory animals (ATSDR, 2012).

Acute Toxicity

Oral

This chemical has low acute toxicity following oral exposure (OECD, 1996).

Dermal

No data are available.

Inhalation

The chemical has low acute toxicity following a single inhalation exposure (OECD, 1996). The ATSDR reported a study that determined LC50 values of 122,000 and 129,000 ppm for mice and rats exposed for two and four hours respectively (ATSDR, 2012).

Observation in humans

The limited data available indicate that it has low acute toxicity to humans (OECD, 1996).

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The chemical does not exhibit skin irritation (OECD, 1996).

Eye Irritation

No data are available.

Observation in humans

Dermal contact with liquid 1,3-butadiene causes a sensation of coldness followed by a sensation of burning, which results from pressurised 1,3-butadiene rapidly expanding from a liquid to gas state (NIOSH, 2005). Although this may cause frostbite, it is specific to an unusual exposure scenario and is not a toxicological endpoint. However, the possible toxic effects from dermal absorption of such a concentrated dose of 1,3-butadine are unknown. High gas concentrations may cause mild skin irritation (NIOSH, 2005; ATSDR, 2012).

In a study reported by the ATSDR, workers exposed to 1,3-butadiene gas during rubber manufacture complained of irritation to the eyes, nasal passages, throat, and lungs. In some, coughing, fatigue, and drowsiness developed. All symptoms disappeared when workers ceased to be exposed to the gas. The associated exposure levels were not reported (ATSDR, 2013).

Sensitisation

Respiratory Sensitisation

There are no reports of respiratory sensitisation (OECD, 1996).

Skin Sensitisation

There are no reports of skin sensitisation (OECD, 1996).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

The ATSDR reported a number of repeated dose inhalation toxicity studies in rats and mice using different doses and time periods. These effects were generally seen at higher doses than the effects seen in cancer, reproductive and developmental toxicity studies (see these sections for more information).

Effects in mice include precancerous lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes. Non-neoplastic lesions of the liver (necrosis) in mice and of the kidney in rats were observed in chronic studies. In mice, repeated dose exposures resulted in decreases in red blood cell counts and haemoglobin concentration, progressing to macrocytic megaloblastic anaemia, decreases in spleen and thymus weight, and depressed splenic cellularity. However, these types of effects were not seen in rats or human studies (ATSDR, 2012).

Genotoxicity

The chemical is classified as hazardous—Category 2 mutagenic substance—with the risk phrase ‘May cause heritable genetic damage’ (T; R46) in HSIS (Safe Work Australia). The available data support this classification.

The chemical is genotoxic to bacterial cells in vitro (with metabolic activation). A number of in vivo studies demonstrate that it is mutagenic to somatic and germ cells in the mouse but only mutagenic to somatic cells in the rat (ATSDR, 2012; IARC, 2012). The metabolites epoxybutene and diepoxybutane are mutagenic in somatic cells in the mouse and/or hamster, and in the germ cells of mice and rats. There is some evidence that the chemical causes genetic damage in humans, but the findings are inconsistent and overall the potential for human genotoxicity cannot be excluded (OECD, 1996; IARC, 2012).

Carcinogenicity

The chemical is classified as hazardous—Category 1 carcinogenic substance—with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The IARC has classified the chemical as 'carcinogenic to humans (Group 1)', based on sufficient evidence in both humans and animals that it causes cancer. There is sufficient evidence that it causes cancer of the haematolymphatic organs in humans and

strong evidence that this operates by a genotoxic mechanism (IARC, 2012).

The carcinogenicity of 1,3-butadiene has been studied in rats and mice, and there is a marked species difference in susceptibility. In the mouse, 1,3-butadiene is a multi-organ carcinogen. In the rat, the available study shows, even at high exposure concentrations, a lower tumour frequency and fewer tumour types, mainly of a benign nature. The tumour types suggest hormonal influences may play a role in the rat carcinogenic response, and thus a non-genotoxic mechanism may underlie the tumour formation (OECD, 1996).

Numerous epidemiological studies of multiple occupational cohorts, including one encompassing 15,000 workers, have associated a higher incidence of haemato-lymphopoietic cancer mortality among exposed workers. Although most of these workers were co-exposed to other organic compounds, including styrene, benzene, and dithiocarbamates, multivariate analysis suggested that the estimates of 1,3-butadiene exposure provided the best correlation with the rates of lympho-haematopoietic cancers (ASTDR, 2012).

Reproductive and Developmental Toxicity

There is sufficient evidence of reproductive and developmental effects seen in animals to classify the chemical as a reproductive and developmental toxicant (Category 3)—Category 1B under GHS (refer to the Recommendation Section).

The reproductive and developmental effects are the most sensitive effects observed in rodents, apart from the carcinogenic effects. The ATSDR describes a number of studies in rats and mice that found reproductive and developmental effects following inhalation exposures to the chemical.

Serious lesions of reproductive tissues in male and female mice have arisen from intermediate- and chronic-duration exposures of the chemical. Ovarian atrophy, including complete loss of oocytes, follicles, and corpora lutea, occurred in mice exposed to 200 ppm for 9 months and as low as 6.25 ppm for 2 years (ATSDR, 2012).

Developmental effects include significant reductions in foetal weight and increased foetal deaths following exposures greater than or equal to 200 ppm. The lowest-observed-adverse-effect level (LOAEL) identified for one study was 12.5 ppm, when male mice were mated with unexposed females, resulting in increased late foetal death, exencephaly, and skull abnormalities of foetuses. When exposed to concentrations up to 8,000 ppm 1,3-butadiene for 6 hours/day, 5 days/week during GDs 6–15, Sprague-Dawley (SD) rats showed signs of dose-related maternal and foetal toxicity (including major skeletal defects). Similar effects were found in the foetuses of groups of mice exposed to 20 and 1,000 ppm (ATSDR, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, reproductive toxicity and developmental toxicity). The chemical may also cause harmful effects to the kidneys and liver following repeated exposure through inhalation.

Public Risk Characterisation

Exposures from industrial sources are expected to be much lower than ambient exposures from cigarette smoke, petrol fumes, bush and wood fires. Thus, the chemical is not considered to pose an unreasonable risk to public health from industrial uses of butadiene.

Occupational Risk Characterisation

Given the critical health effects and provided that the controls for handling and using the chemical to ensure low worker exposure are implemented, its use is unlikely to elicit local or acute toxicity effects.

During product use, inhalation exposure of workers to the chemical could occur. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical, systemic, long-term health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise inhalation exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) has adequate information to determine appropriate controls.

The control measures put in place to minimise the carcinogenic risk should adequately control risks associated with all of the health hazards documented above.

The data available support an amendment to the hazard classification in HSIS (refer to the Recommendation section).

The current Australian exposure standard of 22 mg/m³ (10 ppm) TWA may require reconsideration. Although Greece, the UK and Denmark have the same exposure standard as Australia, international exposure standards are mostly in the range of 1 mg/m³ (0.5 ppm) to 4.4 mg/m³ (2 ppm), which is significantly less than the current Australian level.

NICNAS Recommendation

The chemical is classified as a Category 1 carcinogen (HSIS) and has an exposure standard for workplace use. However, not all of the potential health effects of the chemical are covered by the current classification and it should be expanded as detailed in the occupational health and safety section below.

Although the chemical has a current exposure standard of TWA 22 mg/m³ (10 ppm), this is higher than that specified in most of the other juristrictions.

A Tier III assessment may be necessary to provide further information as to whether the current exposure controls and other standards are appropriate to offer adequate protection to workers and the public.

Regulatory Control

Public Health

Apart from its presence in petrol, the chemical is not expected to be present in consumer products as it is only permitted to be used as a reactant to manufacture other chemicals.

The existing regulatory controls are considered adequate.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)*	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 1 - May cause cancer (T; R45)*	May cause cancer - Cat. 1A (H350)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62) Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging fertility - Cat. 2 (H361f) Suspected of damaging the unborn child - Cat. 2 (H361d)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing
- zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and
- continue to do so;
- minimising manual processes and work tasks through automating processes; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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