# Ethane, bromo-: Human health tier II assessment

**13 February 2015**

## CAS Number: 74-96-4



## 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 | Bromoethane<br>Ethyl Bromide<br>Bromic ether<br>Monobromoethane<br>Hydrobromic ether |
| Structural Formula |  |
| Molecular Formula | C2H5Br |
| Molecular Weight (g/mol) | 108.97 |
| Appearance and Odour (where available) | Colourless to yellow liquid with an ether-like odour |
| SMILES | C(C)Br |

# Import, Manufacture and Use

## Australian

No specific Australian use, import, or manufacturing information has been identified.

## International

The following international uses have been identified through the European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; the Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV); the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and international assessments (World Health Organisation (WHO)).

The chemical has reported commercial uses including:

- as a refrigerant; and
- in gasoline ethylation.

The chemical has reported site-limited use as a solvent in organic synthesis.

The chemical has reported non-industrial uses as:

- an intermediate for pharmaceuticals; and
- as a grain and fruit fumigant.

# 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
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

# Existing Work Health and Safety Controls

## Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R20/22 (acute toxicity)
- Carc. Cat. 3; R40 (carcinogenicity)

### Exposure Standards

#### Australian

The chemical has an exposure standard of 22 mg/m$^3$ (5 ppm) time weighted average (TWA).

#### International

The following exposure standards are identified (Galleria Chemica).

TWA of:

- 22 mg/m$^3$ (5 ppm) in Canada (Alberta, British Columbia, Saskatchewan), Denmark, Iceland, Indonesia, Ireland, Norway, South Africa, Spain, Switzerland and the United States of America (USA) (California);
- 50 mg/m$^3$ in Poland and Hungary;
- 223 mg/m$^3$ (50 ppm) in Canada (Quebec); and
- 890 mg/m$^3$ (200–250 ppm) in Canada (Yukon), Estonia, France, Mexico, the Phillipines, Taiwan and the USA (Hawaii, Minnesota, Tennessee, Vermont, Washington).

Short-term exposure limits (STEL) of:

- 1110 mg/m$^3$ (250 ppm) in Canada (Yukon), Greece, South Africa and the USA (Hawaii, Minnesota, Tennessee, Vermont, Washington).
- 50–100 mg/m$^3$ in Poland and Hungary; and
- 7 ppm in Canada (Saskatchewan).

## Health Hazard Information

### Toxicokinetics

Animal studies have shown that the chemical is rapidly absorbed through the lungs following inhalation exposure. Absorption can also occur through the gastrointestinal tract and the skin. Following absorption, the chemical is distributed throughout the body to the brain and the liver in rabbits and mice. In rats, most of the chemical was excreted unchanged in exhaled air (70 % of dose), urine and faeces within 5–11 hours following oral gavage (WHO, 2002; HSDB).

In a study in rats the chemical, administered subcutaneously, was conjugated by glutathione-*S*-transferase to form the metabolite ethylmercapturic acid, which was excreted in the urine. Enzymatic dehalogenation, mediated by glutathione or cysteine, was shown to occur in rat liver cells, in vitro. The chemical was also observed to bind and inhibit cytochrome P450 activity in phenobarbital-induced rats, which could lead to cellular damage (IARC, 1991; WHO, 2002; HSDB).

Following acute inhalation exposure in anaesthetised patients, a lingering garlic odour in the breath has been associated with the chemical for several days postexposure (WHO, 2002; HSDB).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). The available data (median lethal dose (LD50) <2000 mg/kg bw) support this classification

The oral LD50 was reported to be 1350 mg/kg bw in rats (HSDB).

### Dermal

Only limited data are available, indicating the chemical has low acute dermal toxicity.

In a poorly-documented acute dermal toxicity study, the chemical (details not available) was placed in contact with the skin of one rabbit for six hours. No signs of toxicity were reported (WHO, 2002).

### Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification.

The four-hour median lethal vapour concentration (LC50) was 4681 ppm (20.8 mg/L) in rats and 2723 ppm (12.1 mg/L) in mice. Central nervous system (CNS) effects (hyperactivity and incoordination) and dyspnoea were reported in rats (WHO, 2002).

### Observation in humans

In humans, neurotoxicity was reported as the most common effect following acute exposure to high concentrations of the chemical. Symptoms include CNS depression, headache, dizziness, fainting, apathy, lethargy, delirium, stupor, memory loss and mental confusion, speech and visual impairment, paralysis and ataxia (US EPA, 1992).

The chemical also caused acute respiratory congestion, hepatic and renal effects (jaundice, haematuria and fatty degeneration of tissues) in workers (NTP, 1989). The exposure levels have not been quantified.

Past widespread use of the chemical as a general anaesthetic has stopped due to its irritating effects on the respiratory tract, and damage to the liver and kidneys. It has even been reported to cause several deaths (NTP, 1989).

## Corrosion / Irritation

### Respiratory Irritation

The chemical has been reported to be a respiratory irritant in animals. Lung irritation was observed in guinea pigs exposed to the chemical vapour at 3200 ppm (14.3 mg/L) for nine hours and the animals died within 1–5 days (HSDB).

Respiratory irritation has also been observed in humans (see **Observation in humans** below). However, the information available is not sufficient to warrant hazard classification.

### Skin Irritation

Based on the limited information available, the chemical is not expected to be a skin irritant.

The chemical produced no skin irritation when applied on the skin of one rabbit in a sealed chamber for six hours (WHO, 2002). No details were available.

### Eye Irritation

Only limited data are available.

Repeated dose inhalation toxicity studies have indicated that the chemical vapours were irritating to the eyes of rats and mice at 1600 ppm (7200 mg/$m^3$) (see **Repeat dose toxicity: Inhalation**).

Human observations have included evidence of eye irritation when exposed to high concentrations (HSDB) (see **Observation in humans** below).

### Observation in humans

The chemical has been reported to be an eye irritant causing conjunctival hyperaemia and haemorrhages in the conjunctiva in humans. Volunteers exposed to the chemical at a concentration of 6500 ppm (29 mg/L) for five minutes developed mild eye irritation and the effects were immediate when exposed to a higher concentration (12000 ppm, 53 mg/L) (HSDB).

Former use of the chemical as a human anaesthetic caused respiratory irritation and fatalities due to respiratory or cardiac arrest (HSDB). The doses that elicited these effects in humans were not reported.

## Sensitisation

### Skin Sensitisation

No data are available.

The chemical has an alert for protein binding according to the OECD Quantitative Structure Activity Relationship (QSAR) application toolbox. The alert is for nucleophilic substitution to alkyl halides. The electron-deficient carbon attracts nucleophiles and reacts with proteins via substitution by a protein amino group on the carbon, with subsequent halide ion displacement (Roberts et al., 2007).

QSAR modelling using OASIS–TIMES resulted in a negative prediction for the chemical for skin sensitisation. However, this prediction was out of the applicability domain of the model and, therefore, the prediction's reliability was uncertain.

## Repeated Dose Toxicity

### Oral

No data are available.

### Dermal

No data are available.

### Inhalation

Based on the available data, the chemical is not considered to cause severe effects following inhalation exposure, unless at high concentrations.

In an inhalation study (OECD Test Guideline (TG) 413), Fischer 344 (F344) rats and B6C3F1 mice (n = 10/sex/dose) were exposed to the chemical vapour at 0, 100, 200, 400, 800 or 1600 ppm (0, 450, 900, 1800, 3600 or 7200 mg/m$^3$), six hours/day, five days/week for 14 weeks. Deaths occurred at the highest concentration (1600 ppm) in rats and in mice at ≥400 ppm. At the highest concentration, both species exhibited neurological effects (ataxia, dyspnoea, tremors), thigh muscle atrophy, decreased body weights, reproductive effects (testes atrophy in male rats and uterus atrophy in female rats and mice) and eye irritation. At concentrations of ≥800 ppm, the effects observed were decreased ovary sizes and corpora lutea numbers (in female mice) and decreased liver to body weight ratios (in female rats). Pathological results at 1600 ppm revealed haemosiderosis of the spleen and depletion of bone-marrow haematopoietic cells in the rats. The no observed adverse effect concentration (NOAEC) was established as 400 ppm (1800 mg/m$^3$) in rats and 200 ppm (900 mg/m$^3$) in mice (US EPA, 2002; WHO, 2002; HSDB).

In an inhalation study (OECD TG 412), rats and mice (n = 5/sex/dose) exposed to the chemical vapour for 14 days died before the end of the study at concentrations ≥2000 ppm (9000 mg/m$^3$). Before dying, the animals displayed dyspnoea and prostration, and male rats were lacrimating. Dose-related inflammation of the nasal turbinates, trachea and lungs were observed at 1000 ppm and 2000 ppm in both species and the no observed adverse effect level (NOAEL) was established as 500 ppm (2300 mg/m$^3$) (US EPA, 2002; WHO, 2002).

In a 104-day combined chronic/carcinogenicity study (OECD TG 451) in rats and mice (n = 50/sex/dose), no compound-related non-neoplastic toxicity effects were observed up to vapour concentrations of 400 ppm (1800 mg/m$^3$), other than an increased incidence of conjunctivitis in female rats and reduced survival in female mice at 400 ppm (US EPA, 2002; WHO, 2002).

### Observation in humans

The chemical was reported to cause CNS effects, which included staggering gait, finger tremor, muscular weakness and speech disorders, following repeated exposure for a long duration (HSDB).

Pregnant workers (n = 262) exposed to the chemical vapour (duration not stated) had early and late pregnancy toxaemias. However, they were also exposed to other chemicals (HSDB).

## Genotoxicity

Only limited data are available. The chemical is an alkylating agent and is directly mutagenic in bacteria and mammalian cells in vitro. However, no appropriate in vivo studies are available to determine the genotoxic potential of the chemical.

The chemical gave mixed results in several in vitro assays (WHO, 2002; CalEPA, 2012; HSDB):

- positive in bacterial reverse mutation assay in *Salmonella typhimurium* strains TA1535 and TA100, with or without metabolic activation;
- weakly positive in a *Saccharomyces cerevisiae* gene mutation test, with or without metabolic activation, and induced DNA deletions in a deletion recombination assay in *S. cerevisiae*; and
- reported increased incidences of sister chromatid exchanges (SCE) but not chromosome aberrations and micronuclei in Chinese hamster ovary (CHO) cells

The chemical gave negative results in a sex-linked recessive lethal test in *Drosophila melanogaster* at concentrations up to 0.9 mg/m$^3$ (WHO, 2002).

### Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the HSIS. The available data support this classification.

The International Agency for Research on Cancer (IARC) concluded that the chemical is ‘not classifiable as to its carcinogenicity to humans (Group 3)’. The IARC (1999) stated that 'there were no relevant epidemiological data for the chemical and only limited evidence was available in laboratory animals for carcinogenicity'.

In a carcinogenicity study conducted by the National Toxicology Program (NTP), rats and mice were exposed to the chemical vapour at 0, 100, 200 or 400 ppm (0, 450, 900 or 1800 mg/m$^3$), six hours/day, five days/week for 103 weeks. There was clear evidence of carcinogenicity in female mice, with dose-related increases of rare uterine tumours (adenomas, adenocarcinomas or squamous cell carcinomas), reaching statistical significance at ≥200 ppm. Some adenocarcinomas metastasised to other organs and were proposed to have contributed to the high mortality rate. At the highest dose, increased incidences of nasal and alveolar epithelial hyperplasia were observed in rats, and in male mice. In male mice, marginally increased incidences of alveolar/bronchiolar carcinomas and combined adenomas or carcinomas were observed at ≥200 ppm. Male rats developed (non-statistically significant) increased phaeochromocytomas of the adrenal gland and granular cell neoplasms at 100 ppm (450 mg/m$^3$), and pulmonary adenomas and carcinomas at 200 ppm (900 mg/m$^3$). Effects in female rats were considered ‘equivocal evidence of carcinogenic activity’, with marginally increased incidences of granular cell tumours of the brain, and lung adenomas at 400 ppm (NTP, 1989; IARC, 1991; WHO, 2002).

In a screening assay, mice (n = 10/sex/dose) were injected intraperitoneally with the chemical (in tricaprylin) at doses of 0, 1200, 3000 or 6000 mg/kg bw/day, three times/week for eight weeks. Mice given tricaprylin (n = 160) served as controls. Lung tumours were observed in 34/154, 4/19, 4/16 and 6/20 for the combined (male and female) control, low-, mid- and high-dose groups, respectively. This short-term study did not show any treatment-related increase in carcinogenicity (IARC, 1991; WHO, 2002).

### Reproductive and Developmental Toxicity

Only limited data are available. The information available is sufficient to indicate that the chemical could be reproductively and developmentally toxic, but it is insufficiently characterised.

No reproductive and developmental studies have been conducted in animals. However, in a 14-week inhalation toxicity study (see **Repeat dose toxicity: Inhalation**) severe testicular atrophy in male rats was observed at concentrations of 7200 mg/m$^3$. Decreased ovary sizes and the number of corpora lutea were observed in female mice at the same concentration (WHO, 2002; HSDB).

### Other Health Effects

#### Neurotoxicity

Neurological symptoms were reported in acute and repeated dose inhalation toxicity studies in both animals and humans following exposure to high concentrations of the chemical (see **Acute toxicity: Inhalation** and **Repeat dose toxicity: Inhalation**). Clinical symptoms of neurotoxicity were observed at 7200 mg/m$^3$ in rats and mice. Former use of the chemical as a surgical anaesthetic has caused neurological effects, including CNS depression in humans.

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects through oral and inhalation exposure; and
- systemic long-term effects (carcinogenicity).

The chemical may also cause systemic effects on reproductive organs at high concentrations.

### Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

### Occupational Risk Characterisation

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

Based on the available data, the hazard classification in the HSIS is considered appropriate.

## NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

### Regulatory Control

#### 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 and environmental hazards.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)* | Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332) |
| Carcinogenicity | Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)* | Suspected of causing cancer - Cat. 2 (H351) |

[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 consumers

Products containing the chemical should be used according to the instructions on the label.

## 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 could 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;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; 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 help meet 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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