1,3-Dioxane, 5-bromo-5-nitro-: Human health tier II assessment

05 February 2016

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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.

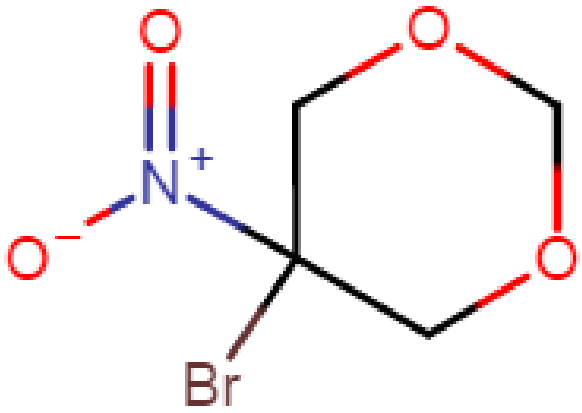
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	5-bromo-5-nitro-1,3-dioxane bronidox
Structural Formula	
Molecular Formula	C4H6BrNO4
Molecular Weight (g/mol)	211.998
Appearance and Odour (where available)	Insoluble white crystallic powder.
SMILES	C1(Br)(N(=O)=O)COCOC1

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: Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and various international assessments (Cosmetic Ingredient Review (CIR), and Danish Environmental Protection Agency (Danish EPA)).

The chemical has reported cosmetic use as a preservative in various rinse-off personal care products (shampoos, bath oils, bath soaps and detergents), and hair dyes and colours.

The chemical has reported domestic uses, including:

- in cleaning or washing agents; and
- for surface treatment (floor polishes).

The chemical has reported non-industrial uses, including in pesticides and preservatives.

Restrictions

Australian

No known restrictions have been identified.

International

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

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’);
- EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed for use in cosmetic products under specific conditions: at a maximum concentration in ready for use preparation of 0.1 %. Avoid formation of nitrosamines);
- New Zealand Cosmetic Products Group Standard - Schedule 7: Preservatives Cosmetic Products May Contain with Restrictions; and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex VI Part 1: List of preservatives allowed for use in cosmetic products (at a maximum authorised concentration of 0.1 %, in rinse-off products only. Avoid formation of nitrosamines).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 3 mg/m^3 time weighted average (TWA) in Russia.

Health Hazard Information

The primary metabolite of the chemical is 2-bromo-2-nitropropane-1,3-diol, also known as bronopol (NICNASa). The chemical can be synthesised from a reaction of bronopol and paraformaldehyde. The antimicrobial mode of action of this chemical is the same as, or similar to those of bronopol and formaldehyde. Therefore, toxicological data for bronopol and formaldehyde has been considered for this chemical assessment (CIR, 1990).

The antimicrobial effect of the chemical is attributed to its ability to oxidise protein thiol groups contained in mercaptoamino acids to disulfides, subsequently inhibiting enzyme activity and microbial growth (CIR, 1990).

Toxicokinetics

Animal studies have shown that the chemical can be absorbed orally and dermally. No inhalation studies are available. Dermal absorption in rats, rabbits and man is around 10–40 % when applied to the skin (EC SCC, 1987).

The chemical is metabolised in rats and rabbits to form 2-bromo-2-nitropropane-1,3-diol (bronopol, a nitrosating agent), 2-nitro-1,3-propanediol, and 2-nitroethanol, together with formaldehyde. Therefore, the chemical may act as a nitrosating agent, reacting with amines and amides to form nitrosamines or nitrosamides (CIR, 1990).

In an in vitro study, the chemical was incubated with urine, faeces, stomach juices, or intestinal fluids. The results showed that the degradation of the chemical to its various metabolites can occur not only in the acidic medium of the stomach but in other organs as well, following absorption (CIR, 1990). Eventually, the chemical degradation pathway follows the bronopol pathway, leading to formaldehyde release (Paulus, 1993; NICNAS).

In a dermal study in humans, the chemical was applied as a cream at 1.85–2.50 g to male volunteers. After 24 hours, the chemical was excreted unchanged or as its metabolites in urine at 10.8 to 75.3 % of the applied dose (CIR, 1990). No further details are provided.

In rats, the chemical or its metabolites were excreted in the urine and faeces at 44.1, 17, or 56 % of the oral, dermal or intraperitoneal (i.p.) doses, respectively, within four days (CIR, 1990).

Acute Toxicity

Oral

The available information indicates that the chemical has moderate acute oral toxicity in animals. Therefore, hazard classification is warranted.

The median lethal dose (LD50) is 455 mg/kg bw in rats and 590 mg/kg bw in mice. The chemical is reported to affect the central nervous system of animals, causing tremor, convulsions and excitement (CIR, 1990).

Dermal

Based on a briefly reported study in rabbits, the chemical is considered to have moderate acute toxicity.

The Danish EPA has reported that this chemical has a dermal LD50 of 2.5 mg/kg bw in rats at 24 hours (Danish EPA, 2007). However, no details are available and this value is not stated in other safety data sheets and risk assessments.

On rabbit skin, 500 mg/kg bw of the chemical in olive oil caused death in 24 hours (EC SCC, 1987).

No adverse dermal effects were observed in rabbits at a chemical concentration of 0.5 % in a 24-hour study. However, skin necrosis was observed in the skin of hairless mice when a concentration of more than 0.5 % of the chemical was applied (CIR, 1990) (see **Irritation**).

Inhalation

No data are available.

Corrosion / Irritation

Corrosivity

While no guideline studies are available for the chemical, corrosive effects were observed on the skin of mice and rats at a chemical concentration ≥0.5 %. Based on the available data hazard classification is warranted.

Skin effects

The chemical did not cause any dermal effects in rabbits, when applied repeatedly to the skin, or as a single 24-hour patch at a concentration of 0.5 % (CIR, 1990).

The chemical was applied to the skin of hairless mice in vaseline and two creams at concentrations of 0.1 and 0.5 % every day for 3–5 days, at 1 % every day for 2–3 days, or as a single application of 2.5 %. No effects were observed at 0.1 %. However, necrosis was observed in the skin of 1–5 mice in each group at ≥0.5 %. The same authors conducted a similar study in rats at chemical concentrations of 0.1 % or 0.5 % up to five days. At 0.5 % concentration of the chemical, sloughing of the skin was observed in 3-5 rats in each group (CIR, 1990).

Eye effects

In an eye irritation study with limited documentation, instillation of a 0.05 % solution of the chemical in carboxymethylcellulose in rabbit eyes over two weeks was not irritating. A single application of 0.1 % solution of the chemical did not produce significant irritation. However, a single application solution of the chemical at 0.5 % produced a strong eye irritation response in rabbits. These effects were reversible (EC SCC, 1987; CIR, 1990).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical was not a sensitiser or a photosensitiser in animal studies. However, mixed results have been obtained in humans case studies. The available data are not sufficient to warrant hazard classification.

In a skin sensitisation maximisation test, guinea pigs were intradermally administered the chemical (0.1 mL) at 0.1 % concentration into the shoulder, followed by topical exposure to 2.5 % for 24 hours on day 8. After a 14-days non-treatment period, the animals were challenged epicutaneously at 2.5 % concentration. Skin reactions were observed at 24, 48, and 72 hours after challenge. 'No adverse reactions' were noted. The results indicate that the chemical was not a sensitiser in this test (CIR, 1990).

In a photosensitisation test, guinea pigs were exposed to a non-irritating and non-sensitising concentration level of 0.05 % solution of the chemical in propylene glycol. The solution was applied as 10 occlusive patches to the backs of guinea pigs, six hours/day for 14 days. A 10 minute exposure to UV light was conducted following the second and fifth applications. After five days, the animals were challenged with occlusive patches twice in a 24 hour period, and observations were made at 15 minutes, 24 or 72 hours. Mild irritation occurred at the test areas, attributed to skin fatigue, but ‘there was no evidence of increased irritation due to photosensitivity at challenge between the test and control animals’ (CIR, 1990).

Observation in humans

A 24-hour patch test was conducted with 40 patients with the chemical at 0, 0.1 or 0.5 % concentrations in vaseline and two creams. Reactions were observed in one patient to vaseline alone, and one patient to a cream alone. Eleven out of the remaining 38 patients showed positive reactions to at least one of the formulations containing the chemical (CIR, 1990).

In another study, three out of 114 volunteers showed skin reactions to a shampoo containing 0.1 % of the chemical, used at least once a week for six weeks. However, no positive skin sensitisation reactions were observed in these three subjects to the chemical (CIR, 1990). A concentration of 0.05 % in a cream formulation applied daily for 21 days did not cause irritation (EC SCC, 1987).

In a case study, a man patch-tested daily with 0.25 % (occlusively) for 21 days showed progressively increased irritation after about six to eight applications (EC SCC, 1987).

Repeated Dose Toxicity

Oral

Limited data are available. Based on the available information, the chemical was not harmful up to a concentration of 50 mg/kg bw/day. Data are not sufficient to warrant hazard classification.

In a repeated dose toxicity study, rats (10 animals/sex/dose) were administered (gavage) the chemical at doses of 0, 10, 50 or 100 mg/kg bw/day, five times/week for 17 weeks. After six to seven weeks, the highest dose was increased to 200 mg/kg bw/day. Some rats (amount not stated) administered the highest dose (200 mg/kg bw/day) died within a few days. At doses ≤50 mg/kg bw/day, no changes in body weight, haematological parameters, and urine composition were observed between the treated and control groups. Some rats in these groups developed mild irritation of the stomach mucous membrane, slight growth depression and decreased kidney function (extent not stated). At higher doses, eosinophilic and round cell infiltration in the heart was found, with hypoxic myocardial changes at the highest dose (200 mg/kg bw/day) (EC SCC, 1987; CIR, 1990).

In another repeated dose toxicity study, rats were administered (gavage) the chemical at doses of 0, 10, 50 or 100 mg/kg bw/day for six weeks, and observed for a further nine weeks. No effects were observed up to 50 mg/kg bw/day (EC SCC, 1987). No other details are available.

Dermal

The chemical did not cause any adverse dermal effects when applied repeatedly to the skin of rabbits at a concentration of 0.5 % and to the skin of hairless mice and rats at 0.1 % (see **Irritation**). Skin necrosis was observed in mice at concentrations ≥0.5 % and skin sloughing in rats at 0.5 %.

Inhalation

No data are available.

Genotoxicity

Based on the limited data available, the chemical is not considered to be genotoxic.

Only Ames tests and one in vivo mammalian bone marrow assay are available.

The chemical gave negative results in bacterial reverse mutation assays in several strains (TA1535, TA1537, TA1538, TA98 and TA100) of *Salmonella typhimurium* at concentrations up to 35 ppm (pure), or 10 % in propylene glycol, with or without metabolic activation (CIR, 1990).

In an in vivo micronucleus assay, mice were injected (i.p.) with the chemical at 20 mg/kg bw, followed by a second dose 24 hours later. The chemical did not significantly increase the number of micronuclei (CIR, 1990).

The primary metabolite of the chemical, bronopol is not considered to be genotoxic based on available in vitro and in vivo studies (NICNASa).

Carcinogenicity

No carcinogenicity studies are available for the chemical.

The chemical and its metabolite bronopol are effective nitrosating agents, reacting with amines or amides to form potentially carcinogenic nitrosamines (see **Toxicokinetics**). However, the metabolite bronopol is not considered to be carcinogenic based on long-term studies in rats and mice (NICNASa).

The chemical also metabolises to formaldehyde (see **Toxicokinetics**), which is a category 2 carcinogen on the HSIS. However methanol, which also metabolises to endogenous formaldehyde is not considered to be carcinogenic (NICNASb).

Reproductive and Developmental Toxicity

Limited data are available. The chemical does not show specific developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

In a developmental toxicity study, groups of pregnant Sprague Dawley (SD) rats were orally administered the chemical at doses of 0, 5, 15 or 45 mg/kg bw/day on gestation days (GD) 6–15. Maternal toxicity effects including ataxia, piloerection, decreased activity, and dyspnoea were observed at all doses. Mortalities occurred for one dam in the mid-dose group and four in the high-dose group. Foetal effects included increased resorption rate after implantation and increased retardation at the highest treated dose only. The maternal NOAEL for the chemical was <5 mg/kg bw/day. The observed foetal effects appear to be secondary to the severe maternal toxic effects at the highest dose of the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects (acute toxicity from oral and dermal exposure); and
- local effects (corrosivity).

Public Risk Characterisation

The general public could be exposed through the skin when using cosmetic or domestic products containing the chemical. However, based on current use information reported by the CIR (CIR, 2011), concentration in these products (at 0.04 %) is not considered to be sufficiently high to cause effects. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, oral, dermal and ocular exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular 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.

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

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2015).

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 in contact with skin (Xn; R21)	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1C (H314)

[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 oral, dermal and ocular 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 that 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;
- 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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