1,2-Oxathiolane, 2,2-dioxide: Human health tier II assessment

13 February 2015

CAS Number: 1120-71-4

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.

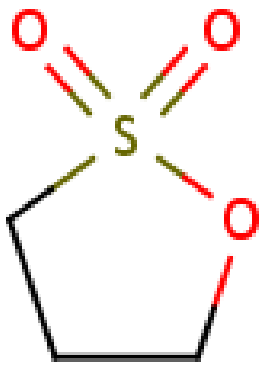
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,3-propanesultone 3-hydroxy-1-propanesulfonic acid gamma-sultone 1-propanesulfonic acid-3-hydroxy-gamma-sultone 1,2-oxathiolane-2,2-dione
Structural Formula	
Molecular Formula	C3H6O3S
Molecular Weight (g/mol)	122.14
Appearance and Odour (where available)	White crystalline solid or colourless liquid (above 31 degrees C), with foul odour when heated
SMILES	C1CCOS1(=O)=O

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; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited use including as:

- an intermediate for manufacturing sulfopropylated substances such as detergents, lathering agents and bacteriostats to confer water solubility and anionic characteristics;
- a corrosion inhibitor for mild (untempered) steel;
- a precursor for manufacturing aqueous polyurethane dispersions and light sensitive dyes for photographic and radiographic film;

- an additive for electrolysis; and
- a solvent in sealed electrical batteries and electrical accumulators.

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;
- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles—Limits for basic polymers;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1.

The chemical is not recommended for use in consumer products (REACH).

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):

- Carc. Cat. 2; R45 (carcinogenicity); and
- Xn; R21/22 (acute toxicity).

Exposure Standards

Australian

No specific exposure standards are available.

International

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) as low as possible for exposure by all routes (HSDB).

The National Institute for Occupational Safety and Health (NIOSH) recommends that exposure be limited to the lowest feasible concentration, as the chemical is a potential occupational carcinogen (HSDB).

Health Hazard Information

Toxicokinetics

The chemical is a highly reactive alkylating agent, capable of interacting with DNA and proteins (SCOEL, 2013).

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 support a higher classification (see **Recommendation** section).

In studies conducted similarly to the Organisation of Economic Cooperation and Development Test Guideline (OECD TG) 401, the median lethal dose (LD50) was reported to be between 100 and 200 mg/kg bw in rats and 400 mg/kg bw in mice (OTS, 1992 cited in REACH).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available data support this classification.

Using a standard method of testing (details not available), the LD50 was reported to be 660 mg/kg bw in rabbits (MAK, 1985 cited in REACH).

When the chemical was tested in 12 guinea pigs by applying the undiluted chemical at 0.1–20 mL/kg bw (equivalent to 140–2800 mg/kg bw) under a dermal cuff, an LD50 between 700 mg/kg bw and 1400 mg/kg bw was reported (OTS, 1992 cited in REACH).

Inhalation

The chemical is considered to have moderate acute inhalation toxicity, warranting hazard classification (see **Recommendation** section).

In a study equivalent to OECD TG 403 in six rats (n = 3/dose), with whole body inhalation exposure to the chemical vapour at doses of 1.3 mg/L or 2.14 mg/L for six hours, the median lethal concentration (LC50) was determined to be between 1.3 mg/L and 2.14 mg/L (260 ppm and 425 ppm). There were no deaths in the low dose group. In the high dose group, 2/3 animals died after 24 hours and the last animal died on day eight (OTS, 1992 cited in REACH).

Corrosion / Irritation

Skin Irritation

The chemical is considered to be a skin irritant, warranting hazard classification (see **Recommendation** section).

In two studies, guinea pigs were exposed to the undiluted chemical by applying 0.1–20 mL in a cuff or 10 drops to an open area. In the first study (n = 12), moderate to gross oedema and necrosis over the entire patch and erythema (score = 3) at the perimeter of the patch were observed on days 1–3. Erythema (score = 2) at the periphery of the patch was observed on day six and scattered scarring with little or no hair was reported after two weeks. In the second study (n = 3), erythema (score = 2–3) and slight to moderate oedema were observed at 24 and 48 hours post application, but the effects were minimal by one and two weeks after exposure. The chemical was reported to be irritating to the skin (OTS, 1992 cited in REACH).

Eye Irritation

The chemical is considered to be a serious eye irritant, warranting hazard classification (see **Recommendation** section).

In an eye irritation study in one rabbit, one drop of the undiluted chemical was found to be highly irritating with conjunctivitis and corneal opacity observed at 24, 48 and 72 hours post application. The oedema reversed completely, but the erythema was still slight and corneal opacity was not reversed within the 14-day observation period (OTS, 1992 cited in REACH).

Although the eye irritation scores were not available and the observation period was not continued up to day 21 (according to OECD TG 405 for eye irritation), since the corneal effects were not reversible by day 14, the chemical is considered to be a serious eye irritant.

Sensitisation

Skin Sensitisation

The chemical is not considered to cause skin sensitisation.

The chemical was tested in a guinea pig maximisation test equivalent to OECD TG 406. Dunkin-Hartley guinea pigs (n = 5) were exposed to 1 % of the chemical via an intradermal injection and 1 % of the chemical one week later via a topical application for 48 hours (induction phase). Two weeks after

induction, they were challenged topically (closed patch or open application) with 2 % or 0.1 % of the chemical for 24 hours. No skin reactions were observed in guinea pigs at 24 and 48 hours after challenge (Morikawa et al., 1978 cited in REACH).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

A derived no effect level (DNEL) of 0.1 µg/kg bw/day was reported based on workers exposed to the chemical long-term via the dermal route (Galleria Chemica).

A DNEL of 0.32 µg/m^3 was reported based on workers exposed to the chemical long-term via the inhalation route (Galleria Chemica).

Genotoxicity

Based on the available data, the chemical is considered to have genotoxic potential, warranting hazard classification (see **Recommendation** section). However, no germ cell data are available to consider a higher classification for genotoxicity.

The International Agency for Research on Cancer (IARC) reported that the chemical showed positive results for mutagenicity in bacteria, and positive clastogenicity results in rodent and human cells. It also induced DNA strand breaks in brain cells of rats (IARC, 1999).

The following in vitro tests gave mostly positive results:

- a bacterial reverse mutation assay (equivalent to OECD TG 471) without metabolic activation showed positive results in *Salmonella typhimurium* strains TA 1535 and TA 100, but negative results in *S. typhimurium* strains TA 1536, TA 1537, TA 98 and TA 1538 (Simmon, 1979 cited in REACH and IARC,1999);
- a bacterial reverse mutation assay (equivalent to OECD TG 471) without metabolic activation showed positive results in *S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, TA 102 and TA 97 (Khudoley et al., 1987 cited in REACH);
- a mammalian chromosome aberration test (equivalent to OECD TG 473) using Chinese hamster lung (CHL) Don cells without metabolic activation showed 6 %, 22 % and 94 % cells with aberrations at doses of 0.0313 mg/mL, 0.0625 mg/mL and 0.125 mg/mL, respectively (Ishidate et al., 1977 cited in REACH and IARC,1999);
- a micronucleus test (non guideline study) in primary astrocyte cell cultures prepared from brain cells of 4–5 day old Sprague Dawley (SD) rats, showed significantly increased frequencies of micronucleated cells at doses of 0.08, 0.16 and 0.31 mM of the chemical (Ooida et al., 2000 cited in REACH); and
- chromosomal aberration tests and sister chromatid exchange (SCE) assays in both CHL fibroblasts and human lymphocytes showed positive results (IARC, 1999).

Two in vivo assays gave positive results:

- a micronucleus assay (equivalent to OECD TG 474) in male CD-1 mice treated with the chemical twice (24 hours apart) via intraperitoneal injections at doses of 9, 18, 36 or 72 mg/kg bw showed significantly increased proportions of micronucleated reticulocytes at the two highest doses (Morita et al., 1997 cited in REACH); and
- an alkaline elution assay in SD rats treated with a single dose of the chemical at 31 mg/kg bw via intraperitoneal injection showed DNA fragmentation (increased rates of SCE) in brain cells (IARC, 1999; SCOEL, 2013).

Carcinogenicity

The chemical is classified as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The available data support this classification. Although epidemiological data from workers exposed to the chemical from the 1950s to the 1970s have been analysed in 2012–13, the information available is not sufficient to warrant a higher carcinogenicity classification.

The IARC has classified the chemical as possibly carcinogenic to humans (Group 2B) (IARC, 1999). The chemical was reported to be carcinogenic in rats by all routes of exposure, 'producing tumours at various sites including the brain and mammary gland' (IARC, 1999). The chemical also produced local tumours in mice following dermal application and subcutaneous injection (IARC, 1999).

In rats following oral, subcutaneous or intravenous dosing with the chemical at doses ranging from 10–166 mg/kg bw as one injection, or repeat injections once weekly or twice weekly for 13–60 weeks; and in mice following subcutaneous or dermal administration of the chemical at 0.6, 2.5 or 25 % w/v as one injection or repeat injections twice weekly for one year, a variety of tumours have been reported. These included tumours of the brain or nervous system, mammary gland, small intestine, kidneys, skin, lungs and leukaemia (IARC, 1974; IARC, 1999).

In 55 male workers exposed to the chemical in Germany in the 1950s, 1960s and 1970s, there were 20 cases of various neoplasms reported, with a mean tumour latency period of about 31 years. The reported tumours included glioblastoma (brain), intestinal malignancies (including a duodenal carcinoma where the human incidence is very rare), a malignant schwannoma (an extremely rare nerve-related tumour), haematopoietic/lymphatic (blood) malignancies, renal cell (kidney) carcinoma and lung cancers. Quantification of exposure levels to the chemical or simultaneous exposure to other chemicals (with the exception of limited information for three workers) or smoking status was not available (Bolt & Golka, 2012; SCOEL, 2013). The confounding factors do not allow a clear conclusion as to carcinogenicity of the chemical in humans to be determined.

Reproductive and Developmental Toxicity

Only limited data are available. Therefore, it is not possible to draw a conclusion on reproductive and developmental toxicity of the chemical.

In a non-guideline study, pregnant BD rats were injected intravenously with a single dose of the chemical (70 mg/kg bw, n = 1; 60 mg/kg bw, n = 2; 20 mg/kg bw n = 4) on gestation day 15. There were no tumours in the dams until their natural death. Offspring of dams that were exposed to the highest dose died soon after birth and had severe abnormalities, particularly with their paws. In offspring of dams that were exposed to the intermediate and lowest doses, 4/14 and 3/25 (respectively) died from malignancies from day 177 to day 709 (IARC, 1974; REACH). This route of administration is not relevant for human exposure.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity and mutagenicity); and systemic acute effects from oral, dermal and inhalation exposure. The chemical can also cause skin and eye irritation.

Public Risk Characterisation

Given the site-limited use 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 systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and 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.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (see **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

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	Toxic if swallowed (T; R25) Harmful in contact with skin (Xn; R21)* Toxic by inhalation (T; R23)	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[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 oral, dermal, ocular and 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[s], if valid techniques are available to monitor the effect on the worker's health;
- 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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