2-Oxetanone, 4-methyl-: Human health tier II assessment

13 February 2015

CAS Number: 3068-88-0

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.

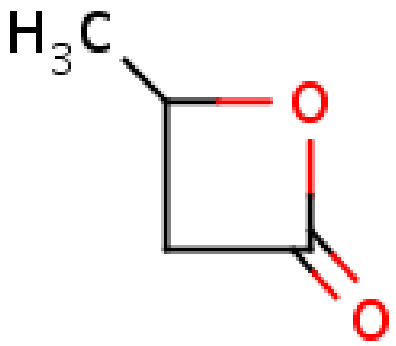
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	beta-butyrolactone 3-hydroxybutanoic acid, beta-lactone 3-hydroxybutyric acid lactone 4-methyloxetan-2-one
Structural Formula	
Molecular Formula	C4H6O2
Molecular Weight (g/mol)	86.09
Appearance and Odour (where available)	Liquid with acetone-like odour
SMILES	C1(=O)CC(C)O1

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 and the International Agency for Research on Cancer (IARC):

The chemical has reported site-limited uses including as:

- a solvent for polymers; and
- an intermediate for chemical manufacture (IARC, 1999).

Restrictions

Australian

No known restrictions have been identified for the chemical.

International

The chemical is listed on the EU REACH Regulation (EC) No 1907/2006—Annex XVII—Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles (Galleria Chemica).

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 for the chemical.

International

The Office of Environmental Health Hazard Assessment (OEHHA) lists the chemical on the California Proposition 65 list with a no significant risk level (NSRL) of 0.7 μg/day.

Health Hazard Information

When data for the chemical being assessed are not available, health hazard information for 2-oxetanone (CAS No. 57-57-8) has been included in this report, where appropriate. Similar to the chemical being assessed, it is a 4 carbon ring that is a strong alkylating agent due to its potential for bond breaking between the carbon and oxygen atoms. Therefore 2-oxetanone is considered to be a suitable analogue for the chemical.

Acute Toxicity

Oral

The limited information indicates that the chemical has low acute oral toxicity.

Median lethal dose (LD50) values of 17000 mg/kg bw and 17.2 mL/kg bw in rats were reported (Galleria Chemica).

Dermal

The limited information available indicates that the chemical has low acute dermal toxicity.

Dermal LD50 values of >20000 mg/kg bw and >20 mL/kg bw in rabbits were reported (Galleria Chemica).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the limited available data, the chemical causes skin irritation, although the data are not sufficient to determine whether classification is appropriate.

In an open skin irritation test in rabbits, 500 mg of the chemical applied to the skin caused moderate skin reactions (Galleria Chemica). Details of the test or irritation scores were not available.

The analogue chemical, 2-oxetanone (CAS No. 57-57-8), is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia).

Eye Irritation

No data are available for the chemical.

The analogue chemical, 2-oxetanone (CAS No. 57-57-8) is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia).

Sensitisation

Skin Sensitisation

No data are available for the chemical. However, its structure indicates a likely alkylating ability similar to the analogue 2-oxetanone, which is a strong skin sensitiser (Ashby et al., 1995; NICNAS).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The limited available data are not sufficient to make a conclusion on genotoxicity, in the context of the carcinogenicity data of the chemical (i.e. carcinogenicity observed locally at the site of administration only; see **Carcinogenicity** section) and the genotoxicity of the close analogue. The analogue chemical 2-oxetanone (CAS No. 57-57-8) was considered to be genotoxic (NICNAS).

The following in vitro tests were reported:

- a mutagenicity test (microsome assay) in *Salmonella typhimurium* without metabolic activation was positive (McCann et al., 1975);
- a mutagenicity test (*umu* test, measuring the induction of the SOS response) in *S. typhimurium* TA1535/pSK1002 found that 0.1 mL of the chemical (in 2.5 mL total volume) induced an approximate 3-fold increase in *umu* gene expression (Nakamura et al., 1987); and
- a DNA damage test using calf thymus DNA as the substrate found that a concentration of 100 mM of the chemical significantly increased deoxyribonuclease activity (approximately 20 %) (Melzer, 1967).

The following in vivo tests gave mixed results:

- a micronucleus assay in bone marrow polychromatic erythrocytes from male ddY mice treated with the chemical twice at doses of 0, 375, 750, 1200 and 1500 mg/kg bw via intraperitoneal (ip) injection was positive at the highest dose, but responses were marginal or negative in peripheral

blood reticulocytes (Morita et al., 1997); and

- a micronucleus assay in bone marrow polychromatic erythrocytes from male ddY mice treated with the chemical twice at doses of 0, 375, 750, 1200 and 1500 mg/kg bw via intavenous injection was negative (Morita et al., 1997).

The analogue 2-oxetanone (CAS No. 57-57-8) also showed positive results in most in vivo tests, in both somatic and germ cells (IARC, 1999).

Carcinogenicity

Based on the available data the chemical is considered to be carcinogenic in rodents, warranting hazard classification (see **Recommendation** section). Although the chemical has shown carcinogenic effects at the site of contact, closely paralleling 2-oxetanone (NICNAS), the available data are not sufficient to recommend a higher hazard classification in the absence of human data.

The IARC has classified the chemical as 'Possibly carcinogenic to humans' (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animals (IARC, 1999).

In a carcinogenicity study, female Sprague Dawley (SD) rats (n = 5) were orally gavaged with the chemical at 100 mg/animal, once a week for up to 492 days. Squamous cell carcinomas were observed in the forestomach of 3/5 animals compared with none in the control group (IARC, 1976).

In three dermal carcinogenicity studies in female ICR/Ha Swiss mice, 0.1 mL of a 10 % solution (in benzene or acetone) of the chemical was applied to the shaved dorsal skin until death. Skin carcinomas developed in 21/30 mice in the first study and in 16/30 in the second study, where benzene was used as the vehicle. No tumours were reported in control mice in the first study (no details of controls in the second study). In the third study, where acetone was used as the vehicle, 1/40 mice developed skin carcinomas (IARC, 1976). It is not clear whether benzene was primarily responsible for the tumours, or whether the choice of solvent affects the delivery of the chemical to the skin.

In mice that received 0.1 or 0.2 or 10 mg of the chemical, and in rats that received 100 mg of the chemical via subcutaneous injection (weekly or up to three times per week for four weeks, or until death), there was an increased incidence of local sarcomas, local fibrosarcomas or local saquamous cell carcinomas, compared with no tumours in control animals (IARC, 1976).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are systemic long-term effects (carcinogenicity).

No data are available on systemic acute or repeated dose effects, and local effects such as eye and skin irritation, and skin sensitisation. The chemical structure indicates a likely alkylating ability similar to 2-oxetanone, which is a strong skin sensitiser (NICNAS). The precautions that should be used to protect against the likely carcinogenic effect should preclude significant exposure.

Public Risk Characterisation

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

Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal 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 available data support classifying the chemical as a hazardous substance (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided the recommended 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]
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 industry

Control measures

Control measures to minimise the risk from oral and dermal 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;
- 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;
- 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.

References

Approved criteria for classifying hazardous substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

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