2-Oxetanone: Human health tier II assessment

13 February 2015

CAS Number: 57-57-8

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.

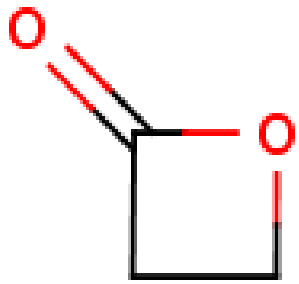
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	beta-propiolactone 1,3-propiolactone 3-hydroxypropionic acid lactone 3-propanolide hydracrylic acid beta-lactone
Structural Formula	
Molecular Formula	C3H4O2
Molecular Weight (g/mol)	72.06
Appearance and Odour (where available)	Colourless liquid with a slightly sweet odour
SMILES	C1(=O)CCO1

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 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 various international assessments (International Agency for Research on Cancer (IARC) (1999); National Toxicology Program (NTP) (2014).

The chemical has reported site-limited use as an intermediate in manufacturing fine chemicals including acrylic acid and esters.

The chemical has reported non-industrial uses including:

- in pharmaceuticals; and

- in food additives (as a component of adhesives).

The most recent data suggest that the chemical is no longer used in manufacturing acrylic acid (NTP, 2014).

Restrictions

Australian

The chemical is a restricted carcinogen for all uses under the *Work, Health and Safety Act 2011* (WHS, 2011).

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.

The chemical is also 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 as follows: the chemical 'shall not be placed on the market, or used, as substance, as constituent of other substances, or, in mixture, for supply to the general public when the individual concentration in the substance or mixture is equal to or greater than 0.1 %'.

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):

- T+; R26 (acute toxicity)
- Xi; R36/38 (irritation)
- Carc. Cat. 2; R45 (carcinogenicity)

Exposure Standards

Australian

The chemical has a time weighted average (TWA) exposure standard of 1.5 mg/m^3 (0.5 ppm) (Safe Work Australia).

International

The chemical has a TWA of 1.5 mg/m^3 (0.5 ppm) in many countries including Canada, Greece, Iceland, Indonesia, Ireland, Norway, Spain, Singapore, Switzerland and the United States of America (USA) (Galleria Chemica).

The American Conference of Governmental Industrial Hygienists (ACGIH) also recommends an 8-hour threshold limit value (TLV) of 1.5 mg/m^3 (IARC, 1999).

Health Hazard Information

Toxicokinetics

The chemical is rapidly metabolised and excreted in mammals (details not available). The main metabolite is lactic acid.

The chemical is readily soluble in water and the main hydrolysis product is hydracrylic acid. The chemical's degradation products (not specified) are reported to be 5–10 times less toxic than the chemical (CRI, 2004).

As a possible result of its rapid degradation in water and plasma, the chemical has mostly local action at the initial site of exposure (CRI, 2004) as has been observed in animal experiments (see **Genotoxicity** and **Carcinogenicity**).

Acute Toxicity

Oral

The chemical is considered to have high acute oral toxicity, warranting hazard classification.

The median lethal dose (LD50) in rats was reported to be approximately 50–100 mg/kg bw (HSDB; REACH). Reported signs of toxicity included twitching, gasping, convulsing and collapsing (HSDB).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T+; R26) in the HSIS (Safe Work Australia). The available data support this classification.

A median lethal concentration (LC50) of 25 ppm/6-hours (73 mg/m^3/6-hours) in rats was reported (RTECS).

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical was applied (once or several times) to the skin of Swiss male mice at various doses for up to two weeks (0.8–20 mg in acetone or 0.8–5 mg in corn oil or 15–100 mg undiluted chemical). All doses of the undiluted chemical, applied only once, caused moderate to severe skin irritation in 20–100 % of animals (no irritation scores were available). Application of 20 mg in acetone, once or twice within two weeks caused the most serious skin effects including erythema, heavy crusting, hair loss and scarring in 60–100 % of animals. All animals treated with the chemical at 2.5–10 mg in acetone for three times a week showed moderate to severe skin reactions. The study results indicate that 80 % of animals treated with the chemical at 5 mg in corn oil for three times a week showed serious skin effects (Palmes et al., 1962).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia). The limited data available support this classification. The available information is not sufficient to consider whether a higher hazard classification should be warranted.

Instillation of the chemical to the eye in rabbits caused immediate pain, graying of the cornea, miosis (constriction of the pupil) and corneal opacity that could be permanent (CRI, 2004; HSDB; REACH). Details of the study, including irritation scores, were not available.

Sensitisation

Skin Sensitisation

The chemical is considered to be a strong skin sensitiser based on the positive results seen in a single local lymph node assay (LLNA), warranting hazard classification.

In an LLNA, groups of mice (strain and number unspecified) were treated with daily applications of the chemical at concentrations of 0.025, 1 or 2.5 % on the dorsum of both ears for three days, resulting in a stimulation index (SI) of 1.5, 13 and 19.9 respectively (Ashby et al., 1995). The effective

concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was reported to be 0.15 %, indicating a strong potency for skin sensitisation (Ashby et al., 1995, cited in Gerberick et al., 2005).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical is considered to be genotoxic, warranting hazard classification.

The chemical is an alkylating agent that can form carboxyethyl derivatives and adducts with polynucleotides and DNA. The chemical showed positive results in most in vitro and in vivo tests, including in both somatic cells and germ cells (IARC, 1999).

The chemical produced positive in vitro results in:

- gene mutation tests in bacterial systems (e.g. strains of *Salmonella typhimurium*);
- mitotic gene conversion, aneuploidy and mutations in yeast;
- cell transformation and gene mutation in human cells; and
- chromosomal aberrations and sister chromatid exchange (SCE) in mammalian cells (IARC, 1999).

The following positive results were observed in vivo with the chemical:

- gene mutations in the stomach and the liver of Muta^{TM} mouse, which received an oral dose of 150 mg/kg bw/day (Brault et al., 1996 cited in IARC, 1999);
- chromosomal aberrations in bone marrow cells of Sprague Dawley (SD) and Long Evans rats treated intravenously at 100 mg/kg bw/day (Rees et al., 1979 cited in IARC, 1999);
- micronuclei in splenocytes of CD-1 male mice treated with a single intraperitoneal (i.p.) dose of 53.7 mg/kg bw/day (Benning et al., 1994 cited in IARC, 1999);
- chromosomal aberrations in oocytes and embryos of mice treated with a single i.p. dose of 2 mg/kg bw/day (Santalo et al., 1987 cited in IARC, 1999);
- micronuclei in hepatocytes and spermatids of CD-1 mice treated with two i.p. doses of 27 mg/kg bw/day and a single i.p. dose of 54 mg/kg bw/day, respectively (Cliet et al., 1989 and Cliet et al., 1993 both cited in IARC, 1999);
- sex-linked recessive lethal mutation in male *Drosophila melanogaster* injected or fed with 720 ppm of the chemical and heritable translocations in flies fed with 1800 ppm of the chemical (Kortselius, 1979 cited in IARC, 1999); and
- sex-linked recessive lethal mutation and heritable translocations in *D. melanogaster* fed with 250 and 3000 ppm of the chemical, respectively (Woodruff et al., 1984 cited in IARC, 1999).

In the sex-linked recessive lethal mutation and heritable translocation tests reported above by Kortselius (1979), the recessive lethal frequency was higher after injection than after oral administration, and heritable translocations were induced only by injection. These differences were reported to be due to the chemical's instability in aqueous feeding solutions and its degradation in vivo, which restricts the activity of the chemical mainly to the site of application (Kortselius, 1979).

A couple of mouse bone marrow micronucleus tests gave negative results. However, the sensitivity of these tests were reported to be 'insufficient to detect unstable compounds' compared with micronucleus tests in other systems (Cliet et al., 1989 and Cliet et al., 1993).

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.

The IARC has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on sufficient evidence for carcinogenicity in animal testing (IARC, 1999) as described below, while it is 'reasonably anticipated to be a human carcinogen' by the National Toxicology Program (NTP, 2014).

Weekly oral administration of the chemical to female SD rats at 10 mg for 487 days induced squamous cell carcinomas of the forestomach in 3/5 rats compared with none in the control animals (Van Duuren et al., 1966 cited in IARC, 1974).

In a six-week inhalation study, SD rats (n = 50) were exposed (whole body) to the chemical at 10 ppm (30 mg/m^3), six hours/day for five days/week. The mortality-corrected incidence of nasal cancer was 60 %, 480 days after the start of exposure. After 720 days, all rats exposed to the chemical developed nasal cancer, compared with none in the control group (Snyder et al., 1986, cited in IARC, 1999).

Ten albino mice were painted weekly with a 2.5 % solution of the chemical for 52 weeks. One mouse died, after five weeks. Five animals exhibited papillomatas (benign epithelial tumours) after 27 applications, resulting in malignant tumours in two mice. Four surviving animals were left three weeks after the end of treatment, and were killed because of their poor general condition (Roe & Glendenning, 1956).

In another experiment, 20 mice received five weekly dermal applications of 5 % or 10 % of the chemical in order to produce moderate ulceration and scabbing. The applications were continued weekly, for a further 35 weeks at a 2.5 % concentration. One mouse in which scarring persisted, developed three malignant tumours by week seven. Another mouse with no scar developed a papilloma during week 22 that turned malignant by week 31. The authors concluded that the few tumours that developed mostly became malignant tumours very shortly after their first appearance (Roe & Glendenning, 1956).

Reproductive and Developmental Toxicity

Only limited data are available and, therefore, no conclusion can be made on reproductive or developmental toxicity of the chemical.

In a fertility study, male Wistar rats were treated (i.p. injections) with the chemical at 20 mg/kg bw/day for five days before mating. No evidence of infertility of the males was noted during the six weeks following treatment (Jackson et al., 1959).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include

- systemic long-term effects (carcinogenicity and mutagenicity); and
- systemic acute effects (acute toxicity from oral and inhalation exposure).

The chemical can also cause skin and eye irritation and skin sensitisation.

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

This chemical is a restricted carcinogen in Australia, which means a person conducting a business or undertaking (PCBU) at a workplace must apply in writing to the regulator for authorisation to use, handle or store the chemical at the workplace.

The above existing control measures are adequate to protect workers from risks during handling the chemical.

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

NICNAS Recommendation

This chemical is a restricted carcinogen in Australia under the Work Health Safety Regulations 2011. Suppliers of this chemical and PCBUs using this chemical have specific obligations to protect the safety of workers using, handling or storing the chemical (WHS, 2011).

The information about the status of the chemical as a restricted carcinogen under the Work Health Safety Regulations 2011 should be included in the Australian Inventory of Chemical Substances (AICS) according to section 13(1)(b) of the *Industrial Chemicals (Notification and Assessment) Act 1989*.

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) Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
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;
- 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;
- 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[s] 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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Last update 13 February 2015

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