2-Propen-1-ol: Human health tier II assessment

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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

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Acronyms & Abbreviations

Chemical Identity

Synonyms	allyl alcohol 2-propenyl alcohol 3-hydroxypropene vinylcarbinol
Structural Formula	
Molecular Formula	C3H6O
Molecular Weight (g/mol)	58.08
Appearance and Odour (where available)	Colourless liquid with a pungent, mustard-like odour.
SMILES	C(=C)CO

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, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; and the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited uses, including:

- for manufacturing allyl compounds (allyl esters, diallyl phthalate), glycerol, acrolein and epichlorohydrin;
- to produce plastic lenses and silicone surfactants (NTP, 2006);
- to produce resins, polymers and plasticisers
- as an intermediate for manufacturing war gas and fire retardants; and
- as a denaturant for ethanol.

The chemical has reported non-industrial use as an intermediate in the pharmaceutical industry and contact pesticide for weed seeds and certain fungi.

Restrictions

Australian

Allyl alcohol is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 7 (SUSMP, 2017).

Schedule 7 chemicals are described as 'Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply'. Schedule 7 chemicals are labelled with 'Dangerous Poison'. The chemical is listed with condition 1 'Not to be available **except** to authorised or licensed persons' under appendix J of the SUSMP (SUSMP, 2017).

International

The content of free allyl alcohol is restricted in the manufacture of allyl esters in perfumes. Allyl esters are specified as 'should only be used when the level of free allyl alcohol in the ester is less than 0.1%. This recommendation is based on the delayed irritant potential of allyl alcohol' (IFRA, 2017).

As a poisonous substance, the chemical is listed in a broad range of categories in Galleria Chemica such as:

- Canada Environmental Emergency Regulations - Part 2 Substances Hazardous when Inhaled;
- China List of Extremely Toxic Chemicals;

- EU Annex I to Directive 67/548/EEC—Classification and Labelling of Dangerous Substances;
- International Global Organic Textile Standard - Limit values for residues in additional fibre materials and accessories;
- Japan Poisonous and Deleterious Substances Control Law;
- United Nations Consolidated List of Products Whose Consumption and/or Sale Have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments; and
- US the Collaborative on Health and the Environment (CHE) Toxicant and Disease Database.

It is also restricted based on potential use in chemical warfare:

US Department of Homeland Security Chemical Facility Anti-Terrorism Standards - Chemicals of Interest.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the HCIS (Safe Work Australia):

- Acute toxicity – category 3; H331 (Toxic if inhaled); H311 (Toxic in contact with skin; and H301 (Toxic if swallowed)
- Skin irritation – category 2; H315 (Causes skin irritation)
- Eye irritation – category 2; H319 (Causes serious eye irritation)
- Specific target organ toxicity (single exposure) – category 3; H335 (May cause respiratory irritation)

Exposure Standards

Australian

The chemical has an exposure standard of 4.8 mg/m^3 (2 ppm) time weighted average (TWA) and 9.5 mg/m^3 (4 ppm) short-term exposure limit (STEL) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica):

A TWA of

- 4.8–5.4 mg/m^3 (2 ppm) in Canada (Quebec and Yukon), Denmark, Egypt, Europe, Phillipines, Singapore, South Africa, Switzerland, United Kingdom and the United States of America (USA) (Hawaii, Minnesota, Tennessee, Vermont and Washington); and
- 1.2–2.4 mg/m^3 (0.5–1 ppm) in Canada (Alberta, British Columbia and Saskatchewan), China, Japan, Malaysia and USA (California).

A STEL in different countries such as

- 9.5–14 mg/m^3 (4–5 ppm) in Canada (Quebec and Yukon), Egypt, Europe, Mexico, Sweden, United Kingdom and the USA (Hawaii, Minnesota, Tennessee, Vermont and California); and
- 1.5–4.8 mg/m^3 (2 ppm) in China, France and Canada (Saskatchewan).

Health Hazard Information

Toxicokinetics

The chemical is absorbed rapidly following oral administration. In rats administered a single oral dose of 120 mg/kg bw, a mean concentration in blood of 9–15 µg/mL was observed at 15–120 minutes after administration. The chemical can also be absorbed through intact skin in toxic and even lethal concentrations (HSDB).

The chemical is rapidly oxidised by hepatic alcohol dehydrogenase (ADH) to acrolein, which is responsible for its hepatotoxicity. Administration of hepatotoxic doses of allyl alcohol caused necrosis in periportal regions of the liver lobule in rodents. Prior treatment with ADH inhibitors significantly reduced the hepatotoxicity of allyl alcohol. Preventing the detoxification of acrolein has also been shown to enhance the hepatotoxicity of allyl alcohol (NTP, 2006). Acrolein is subsequently oxidised by liver aldehyde dehydrogenase (ALDH) to acrylic acid, then excreted in the urine after glutathione conjugation as 3-hydroxypropylmercapturic acid (3-HPM). An oral dose of 64 mg/kg bw of the chemical resulted in about 28 % urinary 3-HPM (OECD, 2013; HSDB).

In the presence of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) and liver and lung microsomes, the chemical and acrolein can be oxidised to glycidol and glycidaldehyde, respectively. Glycidol may be converted to glycerol by epoxide hydrolase (OECD, 2013).

Metabolism to acrolein in humans has been identified in a case study. A man died within 100 minutes of ingesting of the chemical and 7.2 mg/L acrolein was detected in the blood, bile and urine. Acrolein-induced cardiotoxicity was presumed to be the cause of death (REACH).

The chemical is also produced endogenously, via enzymatic hydrolysis of allyl esters in the stomach, liver and blood (Auerbach et. al., 2008).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic if swallowed’ (H301) in the HCIS (Safe Work Australia). The available data support this classification (HSDB; REACH).

The reported median lethal doses (LD50) values are:

- 64–105 mg/kg bw in rats;
- 85–96 mg/kg bw in mice; and
- 52–72 mg/kg bw in rabbits.

Reported signs of toxicity in rats include apathy along with anxiety, lacrimation, tremors, coma and diarrhoea. Gross pathology revealed oedema and congestion of the lungs, visceral congestion, mucous in the intestinal tract, liver discolouration with some necrosis and swollen discoloured kidneys. Similar pathological observations were reported in rabbits (REACH).

Dermal

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic in contact with skin’ (H311) in the HCIS (Safe Work Australia). The available data support an amendment to this classification (see **Recommendation** section).

The reported dermal LD50 values in rabbits are 45 and 89 mg/kg bw (HSDB; REACH).

In a primary acute dermal toxicity study (OECD TG 402) in male albino rabbits, the primary observation reported was apathy and flushing of the skin. Other toxicity effects included aggresiveness, ataxia, convulsions and diarrhoea. Histopathological observations included lung congestion, effects on the liver (congestion and necrosis of the periportal sinusois and central pallor), and kidneys (heme casts and cloudy swelling). The dermal LD50 was 89 mg/kg bw (REACH).

Inhalation

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic if inhaled’ (H331) in the HCIS (Safe Work Australia). The available data support an amendment to this classification (see **Recommendation** section).

In an acute inhalation study (OECD TG 403), the reported median lethal concentrations (LC50) in Sprague Dawley (SD) rats for 1-, 4-, and 8-hour exposures to vapours of the chemical were >400 ppm (0.95 mg/L), >100 ppm (0.24 mg/L) and >50 (0.12 mg/L) ppm, respectively. Observed clinical toxicity signs in all groups included gasping, reddened ears, forelimbs and/or hindlimbs, and red or clear substance around the mouth and on ventral abdominal or urogenital surfaces. Microscopic findings were of increasing severity with time and included reversible nasal cavity changes (indicative of primary irritation), olfactory epithelium degeneration, chronic inflammation and haemorrhage (REACH; OECD, 2013).

An LC50 in SD rats of >0.53 mg/L for a 4 hour exposure (as mist) was reported in another acute inhalation study (OECD TG 403). Clinical toxicity signs such as emaciation, sedation, loose stool and soiled fur were reported in one male, but disappeared by seven days after exposure (OECD, 2013).

In another study (non-guideline), the LC50s in male Long Evan rats for 1-, 4-, and 8-hour exposures to the vapour of the chemical were 1060, 165 and 76 ppm (1.90–2.13, 0.30–0.33, 0.14–0.15 mg/L), respectively. Lacrimation, tremors, coma and diarrhoea (proceeding death) were observed. Histopathological observations were similar to the acute dermal study in rabbits (OECD, 2013; REACH). The 4-hour LC50 (165 ppm, 0.30 mg/L) in this study is within the classifications for a Category 1. However, the 4-hour no observed adverse effect concentration (NOAEC) from the guideline studies was 100 ppm (0.23 mg/L) in one study, and a LC50 of >0.5 mg/L in another study, which is more appropriate for a Category 2 classification (REACH).

Observation in humans

In a case report, a 55-year old man who ingested the chemical (estimated maximum dose of 212 g) died within 100 minutes. Observations at autopsy included bloody, reddish fluid in the mouth, larynx, oesophagus and trachea, and inflammation and congestion in the mucous membranes of the trachea, stomach and duodenum. Pungent green-black fluid was found in the stomach and all internal organs emitted a strong pungent odour (OECD, 2013).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with hazard category ‘Specific target organ toxicity (single exposure) – category 3; H335 (May cause respiratory irritation)' in the HCIS (Safe Work Australia). The available data in animals and in humans (see **Observation in Humans** section) support this classification.

In mice, the chemical induced a very rapid decrease in the respiratory rate due to sensory irritation, reaching a plateau within the first 10 minutes. The sensory irritating responses ceased very rapidly when treatment was terminated. Concentrations required to depress respiratory rates by 50 % (RD50) within the first 10 minutes, and for the mean value of the period from 21–30

minutes due to sensory irritation were calculated to be 9.24 mg/m^3 (3.9 ppm) and 11.4 mg/m^3 (4.8 ppm), respectively. No pulmonary irritation was observed at the RD50 value (OECD, 2013).

Skin Irritation

The chemical is classified as hazardous with hazard category 'Skin irritation – category 2' and hazard statement 'Causes skin irritation' (H315) in the Safe Work Australia. The available data in humans (see **Observation in Humans** section) support this classification.

In a primary dermal irritation study, the undiluted chemical (0.5 mL) was applied occlusively to the intact and abraded skin of 3 New Zealand White (NZW) male rabbits for 24 hours. Slight erythema was observed in 1 animal and no reactions were observed in the other 2. The chemical was considered to be slightly irritating to the skin (OECD, 2013).

Eye Irritation

The chemical is classified as hazardous with hazard category 'Eye irritation – category 2' and hazard statement 'Causes serious eye irritation' (H319) in the HCIS (Safe Work Australia). The available data in animals (conjunctival and corneal damage) and in humans (see **Observation in Humans** section) support this classification.

In a primary eye irritation study, the undiluted chemical (0.1 mL) was found to be irritating to the eyes of 6 New Zealand White male rabbits when applied for 4 hours. The mean scores at 24, 48 and 72 hours for erythema, chemosis, and corneal opacity were 2.89, 1.23 and 2.09, respectively (IUCLID, 2016).

In another eye irritation study in male albino rabbits (using the Draize test method), the chemical instilled at 0.05 mL for 48 hours caused reversible conjunctival redness, iridial injection and corneal opacity that persisted for at least 48 hours post-exposure (IUCLID, 2016).

Observation in humans

Reported toxicity effects for allyl alcohol include eye discomfort at 5 ppm, and corneal necrosis and temporary blindness at 25 ppm (NTP, 2006). Exposure to air that is moderately contaminated with the chemical (concentration not stated) causes excessive secretion of tears, pain behind the eyes, sensitivity to light and blurring of vision. However, despite effects persisting for several hours, neither increased sensitivity nor tolerance developed for the above effects (HSDB).

The vapour and liquid of the chemical is reported to be intensely irritating to the skin and mucuous membranes. Contact with the liquid causes delayed-onset skin irritation and burns. Additionally, skin absorption leads to deep pain which may be due to muscle spasm (NTP, 1991).

A group of volunteers (n = 24) were exposed to the chemical for 5 minutes, 1 to 3 times per week. No cases of pulmonary discomfort or noticeable effect on the central nervous system were reported. Immediate eye irritation occurred and was reported as 'not more than slight' until exposure level reached 25 ppm (60 mg/m^3). Nasal mucosa irritation was at least moderate in 4 out of 7 subjects at 12.5 ppm (30 mg/m^3) (OECD, 2013).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not expected to have skin sensitisation potential.

In a guinea pig maximisation test study (OECD TG 406), male Hartley guinea pigs (n = 20) were intradermally induced with the chemical at 1 % in water. This was followed by topical exposure to the chemical at 2.5 % in water for 48 hours, one week after

the injections. After a 21-day non-treatment period, the animals were challenged with occlusive patches of undiluted chemical for a 24-hour period. Observations were made at 24 and 48 hours. None of the treated animals showed a positive dermal response (OECD, 2013; REACH).

Observation in humans

The chemical causes skin, eye and respiratory irritation (see **Irritation** section), but no allergic responses were reported.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is considered to cause serious damage to health from repeated oral exposure and classification is warranted (see **Recommendation** section).

The effects observed in the repeat dose oral studies indicate that the liver and forestomach in rats and mice are the primary target sites, with mice being less sensitive to toxicity than rats. Forestomach effects may be due to primary irritation (REACH). Hepatotoxicity was evident at ≥25 mg/kg bw/day in rats and is stated to be due to biotransformation to acrolein (see **Toxicokinetics** section) (NTP, 2006). A sex difference in hepatotoxicity in rats was reported to be correlated with the greater alcohol dehydrogenase activity in female rats than in male rats (Auerbach et. al., 2008; NTP, 2006).

In a 14-week repeat dose oral toxicity study (OECD TG 408), Fischer 344 (F344/N) rats were administered the chemical (via gavage) at 0, 1.5, 3, 6, 12 or 25 mg/kg bw/day. In the rat study, 1 female in the 6 mg/kg bw/day group died. Male rats had a significant increase in absolute liver weights at the highest dose, and in relative liver weights at ≥6 mg/kg bw/day. Histopathological observations in rats included a statistically significant increase in the incidence of forestomach squamous epithelial hyperplasia in both sexes at ≥6 mg/kg bw/day, and significantly increased incidences of bile duct hyperplasia and liver periportal hypertrophy in females at 25 mg/kg bw/day. The oestrous cycles of female rats at 25 mg/kg bw/day were affected, with an extended dioestrous and smaller metoestrous phases. The no observed adverse effect level (NOAEL) in rats was 3 mg/kg based on histopathological effects seen at 6 mg/kg bw/day. The NOAEL in mice was 6 mg/kg bw/day based on forestomach squamous epithelial hyperplasia seen at 12 mg/kg bw/day. (NTP, 2006; REACH).

In a 14-week repeat dose oral toxicity study, allyl alcohol was administered to B6C3F1 mice (via gavage, 10 male and female per group) at dose levels of 0, 3, 6, 12, 25 or 50 mg/kg bw/day for 5 days a week for 14 weeks. Effects observed at 50 mg/kg bw/day included decreased mean body weight gain of males (compared to controls), haemosiderin pigmentation (one male, one female), and granulomatous inflammation and hepatocyte necrosis (one female). Significant increases in the incidence of liver portal cytoplasmic vacuolisation (compared to controls) were observed in males (50 mg/kg bw/day) and in females (25 mg/kg). Significantly increased incidences of forestomach squamous epithelial hyperplasia were observed in treated groups at 12, 25 and 50 mg/kg. Prolonged oestrous cycle was observed in some animals at all dose groups, but this effect was not considered to be significant. The NOAEL was 6 mg/kg based on forestomach squamous epithelial hyperplasia at 12 mg/kg bw/day (NTP, 2006; REACH).

In two studies in rats (Long-Evans and Wistar strains), the chemical was administered in drinking water at concentrations up to 1000 ppm for 13–15 weeks. The main effects observed were increased relative kidney and liver weights at ≥200 ppm (~19.2 mg/kg bw/day) in males and at ≥100 ppm (~9.6 mg/kg bw/day) in females. The NOAELs in these studies were 50 ppm in Wistar rats (mean intake equivalent of 6.2 mg/kg bw/day in females and 4.8 mg/kg bw/day in males) and 100 ppm in Long-Evans rats (11.6 mg/kg bw/day in males, 13.2 mg/kg bw/day in females) (OECD, 2013; IUCLID, 2016).

In a reproductive toxicity study, rats were administered the chemical by gavage at up to 40 mg/kg bw/day. All effects were observed at the highest dose (40 mg/kg bw/day), and only in parental animals. Observed effects included salivation, decreased locomotor activity, irregular respiration, lacrimation and loose stools, rough surface of the liver, enlargement and yellowish patches on the liver of females, and forestomach thickening in males. Histopathological observations included atrophy of the thymus and luteal cell hypertrophy in the ovary of females, and liver effects (necrosis, fibrosis, bile duct proliferation, hypertrophy and brown pigment deposition in perilobular hepatocytes and diffuse clear cell changes) in both sexes. Hyperplasia of squamous epithelium in the forestomach was observed in males. The NOAEL for general toxicity was 8 mg/kg bw/day (OECD, 2013; REACH).

Repeat dose oral toxicity studies of acrolein in animals have not shown any systemic effects. Observed effects are mainly local and are considered secondary to irritation/corrosivity. No hepatotoxicity effects are reported, due to the highly reactive nature of acrolein which makes it an irritant at the point of contact rather than a systemic toxicant (NICNAS). Allyl alcohol is less reactive and would be more bioavailable and widely distributed to the tissues prior to metabolism to acrolein (Auerbach, et. el., 2008).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is hazardous to rats following repeated inhalation exposure at high concentrations. However, human exposure did not result in pulmonary discomfort at concentrations up to 25 ppm (see **Observations In Humans** section), and the primary or immediate effects observed were irritation.

In a 12-week repeat dose inhalation study (OECD TG 413), male Long-Evans rats (n = 10/group) were exposed (wholebody) to the vapours of the chemical at nominal concentrations of 0, 0.0024, 0.0047, 0.012, 0.047, 0.095, 0.142, 0.237 or 0.355 mg/L (0, 1, 2, 5, 20, 40, 60, 100 or 150 ppm), 7 hours/day, 5 days/week. At 150 ppm 10/10 animals died within 10 exposures, at 100 ppm 6/10 animls died within 46 exposures and at 60 ppm 1/10 animals died after 4 days of exposure. For rats treated at 150 ppm, livers appeared haemorrhagic and lungs were pale and spotted, although the kidneys appeared normal. Microscopic examination revealed slight lung and liver congestion. Clinical signs observed with increasing severity from 40 ppm included gasping, severe depression, nasal discharge, eye irritation and corneal opacity. At 20 ppm, significantly decreased body weight gain was observed. At 40 and 60 ppm, significantly increased relative lung and kidney weights were observed. The no observed adverse effect concentration (NOAEC) was stated as 0.012 mg/L (5 ppm) based on decreased body weight gain at 20 ppm (OECD, 2013). However, decreased weight gain was reported as ‘uncertain biological significance’ although it was statistically significant. Therefore, the NOAEC was proposed as 0.047 mg/L (20 ppm) (based on increased lung weight observed at 0.095 mg/L (40 ppm)) (IUCLID, 2016; REACH).

A series of repeat dose inhalation trials were conducted in dogs, rats, rabbits and guinea pigs, 7 hours/day, 5 days/week for 5 weeks, or for 6 months at 2 or 7 ppm. Observations include severe irritation of the eyes and mucous membranes at 7 ppm, but not at 2 ppm. Exposure to 7 ppm of the chemical for 6 months also caused cloudy swelling and focal necrosis of the liver, kidney necrosis of convoluted tubules and proliferation of interstitial tissues. However, these effects are reported as 'mild and reversible' (HSDB).

Observation in humans

Case studies in humans with regard to exposure to the chemical are primarily acute or immediate effects (see **Acute Toxicity** section).

In a case study, groups of volunteers (mean age of 22) were exposed to the chemical at 0.78, 6.25, 12.5 or 25 ppm, 1 to 3 times/week for 5 minutes, over 50 days. The volunteers were in apparent good health before and during the exposure period, and were under supervision of a physician. There were no cases of pulmonary discomfort or effects on the central nervous system. Eye irritation was immediate, but was not more than slight until the concentration reached 25 ppm. At 12.5 ppm, nose irritation was at least moderate for 4 out of 7 subjects. At 6.25 ppm, olfactory cognition was regarded as more than moderate for 2 of 5 subjects (HSDB).

Genotoxicity

The available data indicate both positive and negative results in in vitro assays which may be due to conversion to the mutagen acrolein. Positive results reported in in vitro studies (chromosomal changes, gene mutation) were not replicated in in vivo studies. Overall, the results do not indicate mutagenic potential for the chemical.

The following results were reported in various in vitro assays (OECD, 2013; REACH):

- in bacterial reverse mutation assays in *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538), positive results were seen in TA100 (without metabolic activation) and in TA1535 (with metabolic activation);
- negative in bacterial forward mutation assay with *Streptomyces coelicolor* (resistant to streptomycin);
- negative in point mutation assay in fungi, *Aspergillus nidulans* (resistance to 8-azaguanine);
- positive in gene mutation assay in V79 cells (Chinese hamster lung cells that are resistant to 6-thioguanine);
- positive in a chromosome aberration test (OECD TG 473) in human peripheral lymphocytes at concentrations up to 581 µg/mL, with or without metabolic activation; and
- positive in a cell gene mutation test (OECD TG 476) in mouse lymphoma L5178Y cells when tested up to cytotoxic concentrations (581 µg/mL), with metabolic activation.

Under certain experimental conditions, the chemical was considered to potentially induce base-substitution mutations (typically detected by *S. typhimurium* strains TA1535 and TA100), which may reflect conversion to acrolein. Positive results in cultured human lymphocytes are proposed to be due to clastogenic activity as a consequence of acrolein release. However, this effect was not observed in another study with acrolein in Chinese hamster ovary (CHO) cells, indicating strong cytotoxicity of acrolein may have prevented observation of clastogenicity in that study (REACH).

Negative results were reported in the following in vivo studies (NTP, 2006; REACH):

- two micronucleus studies in F344 rats and B6C3F1 mice (OECD TG 474). The chemical did not significantly increase micronucleated erythrocytes in the bone marrow of male rats administered the chemical intraperitoneally (i.p.) at doses up to 40 mg/kg bw, and did not increase the frequencies of micronucleated normochromatic erythrocytes (NCEs) in the peripheral blood of male or female mice administered the chemical at doses up to 50 mg/kg bw/day for 14 weeks. There were no effects on the percentage of polychromatic erythrocytes (PCEs) (NTP, 2006);
- a liver micronucleus test (comparable to OECD TG 474) in young male F344 rats. Doses up to approximately half of LD50 did not produce significant increases in micronucleated cell frequencies in hepatocytes or peripheral blood erythrocytes;
- in an unscheduled DNA synthesis (UDS) assay (OECD TG 486), no DNA damage leading to repair synthesis was found in the liver of male SD rats following oral administration at 16 or 32 mg/kg bw; and
- a dominant lethal test (OECD TG 478) in SD rats at 25 mg/kg bw/day up to 15 weeks.

The metabolite, acrolein, is an alkylating agent and; therefore, a direct-acting mutagen for bacteria. Acrolein was not mutagenic in vivo. It induced gene mutations and sister chromatid exchanges in vitro, but was negative in chromosome aberrations tests in mammalian cells in vitro. Positive results for the in vitro tests were generally observed in a narrow, near lethal, dose range (NICNAS).

Carcinogenicity

Based on the available data for the chemical and its metabolite acrolein, the chemical does not have carcinogenic potential.

In a carcinogenicity study with limited documentation, F344 rats were administered the chemical in drinking water at 300 mg/L (total dose of 3.2 g) for 106 weeks, with observation for a further 17–26 weeks (until natural death). There were no increased incidences of neoplastic changes (liver, adrenal cortex, pituitary and leukaemia) compared with the controls in male rats. There was an increased occurrence of hepatic nodules/carcinomas seen in females (6/20) compared to the controls (2/20) that was considered to be biologically significant. Overall, there was no evidence of carcinogenicity in male rats and equivocal evidence for carcinogenicity in the females (IUCLID, 2016).

In two poorly reported studies, male hamsters (n = 20) were administered the chemical via gavage at doses of 2 mg/week for 48 weeks. No tumours in the forestomach or pancreas were observed. Adenomas or carcinomas of the adrenal cortex were observed in four out of 13 survivors. In another study, male and female hamsters (n = 20/group) were administered (gavage) the chemical for 60 weeks. The incidence of tumours did not increase significantly compared with controls (HSDB).

For acrolein, lifetime gavage carcinogenicity studies in rats and mice did not report treatment-related increases in tumour incidence. Incidences of mammary neoplasms and neoplastic pancreatic lesions were observed to occur within historical limits

and were not considered to be dose related. Inhalation studies in rats and hamsters were inadequate for determining carcinogenicity (NICNAS).

Reproductive and Developmental Toxicity

Based on the data available for the chemical and its metabolite acrolein, the chemical is not significantly toxic to reproduction or development. Effects on the offspring are secondary to parental toxicity.

In a reproductive and developmental toxicity study (OECD TG 421), the chemical was administered (gavage) to SD rats (n = 12/sex/dose) at 0, 2, 8 or 40 mg/kg bw/day during the pre-mating and mating periods to parental males; and during the pre-mating, mating, gestation and until day 3 of lactation. No effects on testes or epididymis weight, or histopathological changes in testes, epididymis, prostate or seminal vesicle were observed in males. At the highest dose in females, mean oestrous cycle was significantly prolonged with an extended dioestrous phase. Total litter loss occurred in 1 dam between birth and day 4 post parturition and was considered secondary to maternal toxicity. No effects on other reproductive parameters (such as the mating index, fertility index, numbers of corpora lutea or

implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behaviour) were observed. The NOEALs for reproduction were determined as 40 mg/kg bw/day for males, and 8 mg/kg bw/day for females and offspring (REACH; OECD, 2013).

In a developmental study (OECD TG 414), groups of SD rats (n = 25/dose) were administered (gavage) the chemical at 0, 10, 35 or 50 mg/kg bw/day on gestation days (GD) 6–19. At ≥35 mg/kg bw/day, maternal toxicity was observed and included mortalities, clinical toxicity, significant decrease in mean body weight gain and food consumption, increased liver weights and macroscopic liver findings. One female at 10 mg/kg bw/day displayed yellow areas in the liver. Gravid uterine weights were not significantly affected. Dose-related increases in post-implantation loss were observed at ≥35 mg/kg bw/day. Severe maternal toxicity was observed with total litter loss including evidence of significant liver toxicity. However, there were no treatment-related increases in malformation rates or incidence of variations. The maternal LOAEL is 10 mg/kg bw/day and the developmental NOAEL is 10 mg/kg bw/day based on post-implantation losses at 35 mg/kg bw/day (OECD, 2013; REACH).

In a developmental toxicity study (OECD TG 414), NZW rabbits were dosed with the chemical at 0, 5, 10 or 20 mg/kg bw/day on GD 7–28. At the highest dose, maternal toxicity (mortalities, clinical toxicity, decreased mean body weight gains and food consumption) was observed. Increased abortion was seen at 20 mg/kg bw/day. Foetal weights at the highset dose were significantly decreased compared with controls. However, no treatment-related foetal malformations or developmental variations were observed. The NOAEL for maternal and developmental toxicity was 10 mg/kg bw/day (REACH).

Studies on acrolein did not show effects on reproductive parameters in animals. Developmental effects were only seen at dose levels that resulted in maternal toxicity (NICNAS).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (repeated dose toxicity to the liver);
- systemic acute effects (acute toxicity from oral, dermal and inhalation exposure); and
- skin, eye and respiratory irritation.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. The chemical is currently listed on Schedule 7 of the SUSMP and is only available to authorised or licensed persons. Hence, the public risk from this chemical is

not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might 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 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 HCIS (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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301)* Fatal in contact with skin - Cat. 2 (H310) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)* Causes skin irritation - Cat. 2 (H315)* May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)*

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)

[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, 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 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;
- 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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