2-Propenal: 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.

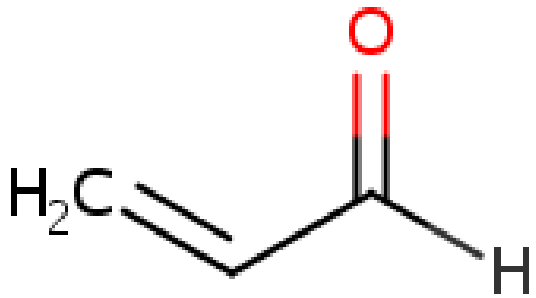
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	acrolein acrylaldehyde allyl aldehyde prop-2-enal
Structural Formula	
Molecular Formula	C3H4O
Molecular Weight (g/mol)	56.06
Appearance and Odour (where available)	Colourless or yellowish liquid with an acrid, pungent odour.
SMILES	C(=O)C=C

Import, Manufacture and Use

Australian

The chemical is commercially produced by vapour phase oxidation of propylene in the presence of bismuth molybdate-based catalysts. During this reaction, the major by-products produced are acrylic acid and carbon oxides, and the minor by-products are acetaldehyde, acetic acid, formaldehyde, and polyacrolein (ATSDR, 2007). Naturally occurring acrolein may be generated from the combustion of organic materials during forest fires, or from combustion of artificial materials such as tobacco products, plastics, and refined vehicle fuels. Cooking oils can also generate acrolein. A small amount of acrolein may also be generated from fermentation and ripening processes (ATSDR, 2007).

The chemical is not commercially produced in Australia. It is mainly imported from the United States of America (USA) (APVMA, 2002).

The National Pollutant Inventory (NPI) holds data for all sources of acrolein emissions in Australia. The following use information was listed on NPI:

The chemical has reported commercial and site-limited use including as:

- an intermediate for manufacturing plastics and colloidal forms of metal; and
- an additive in perfumes.

In the past, acrolein was used in military poison gas mixtures.

The chemical has reported non-industrial use as a herbicide in irrigation channels to control algae and submerged weed growth.

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; the OECD High Production Volume chemical program (OECD HPV), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (Canadian Environment Protection Authority (Health Canada, 2000); US EPA, 2003).

The chemical has reported commercial uses, including:

- to promote cross-linking of protein collagen in leather tanning (US EPA, 2003);
- as a tissue fixative for histological samples (US EPA, 2003);
- controlling the formation of slime in paper manufacture (US EPA, 2003);
- as a warning agent in methyl chloride refrigerants;
- as an active ingredient to scavenge hydrogen sulfide from produced fluids in petroleum operations by oil companies (Health Canada, 2000); and
- to solubilise ferrous sulfide deposits that obstruct wells, tanks and barrels (Health Canada, 2000).

The chemical has reported site-limited uses, including:

- as an intermediate for manufacturing plastics, polymers, epoxides, colloidal forms of metal and perfumes; and
- in organic synthesis of acrylic acid, glycerol, glutaraldehyde, and pyridines.

The chemical has reported non-industrial use in pharmaceuticals, as an aquatic biocide/herbicide and in making an animal feed additive (DL-methionine).

The chemical was used as a tear gas under the name Papite in World War I (HSDB).

Although the chemical is listed as an additive in perfumes in NPI, its not listed as such in the International Fragrance Association (IFRA, 2017).

There is currently no documented use of the chemical either as a cosmetic in the Compilation of the Ingredients used in Cosmetics in United States (CIUCUS, 2011), or as a domestic use in the Household Products Database.

Restrictions

Australian

Acrolein 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).

The use of the chemical in pesticides is restricted in Schedule 4 of the Agricultural and Veterinary (Agvet) Chemicals Code Regulations 1995 (APVMA, 2017).

International

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

- Canada Environmental Protection Act (CEPA) 1999 - Schedule 1 Toxic Substances List;
- Catalogue of China Strictly Controlled Toxic Chemicals for Import and Export;
- EU Annex I to Directive 67/548/EEC—Classification and Labelling of Dangerous Substances;
- International Aerospace Environmental Group (IAEG) Aerospace and Defence Declarable Substances List;
- International Global Oragnic Textile Standard - Limit values for residues in additional fibre materials and accessories;
- Japan Poisonous and Deleterious Substances Control Law;
- US OSHA List of Highly Hazardous Chemicals, Toxics and Reactives; and
- US World Doctors Association (WDA) List of Banned Medicines and Substances.

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 Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – category 1; H330 (Fatal if inhaled), category 2; H300 (Fatal if swallowed), category 3; H311 (Toxic in contact with skin);
- Skin corrosion – category 1; H314 (Causes severe skin burns and eye damage); and
- AUH071 (Corrosive to the respiratory tract).

Exposure Standards

Australian

The chemical has an exposure standard of 0.23 mg/m^3 (0.1 ppm) time weighted average (TWA) and 0.69 mg/m^3 (0.3 ppm) short-term exposure limit (STEL) (HCIS).

International

The following exposure standards are identified (Galleria Chemica):

A TWA of 0.12–0.25 mg/m^3 (0.05–0.10 ppm) in different countries such as Canada (Quebec and Yukon), Denmark, Egypt, Germany, Greece, Iceland, India, Japan, Singapore, South Africa, Switzerland, United Kingdom and the United States of America (USA).

A STEL of 0.25–0.80 mg/m^3 (0.1–0.3 ppm) in different countries such as Canada (Quebec and Yukon), France, Hungary, Sweden, Mexico, India, Ireland, Poland, United Kingdom and the USA (Hawaii, Minnesota, Tennessee, Vermont and Washington).

Health Hazard Information

Acrolein is a reactive unsaturated aldehyde that exists as a highly volatile clear or yellow liquid. Due to its highly reactive nature, acrolein is a point of contact irritant rather than systematically toxic. As a result, effects in both humans and animals primarily involve sensory irritation and respiratory system effects.

Toxicokinetics

Following oral administration in rats, the chemical is well absorbed at low dose levels (2.5 mg/kg bw), however polymerisation occurs at higher dose levels (15 mg/kg bw) which reduces the rate of absorption. Dermal and inhalation absorption is predicted to be high. The irritant and corrosive properties of the chemical do not allow assessment of dermal absorption (EURAR, 2001; CLH, 2011).

Following inhalation exposure to atmospheres containing the vapour of the chemical (400–600 mg/m^3, 172–258 ppm) in dogs, total respiratory tract retention was high (81–84 %) and appeared to be independent of concentration (EURAR, 2001; US EPA, 2003). When administered via inhalation, the chemical is retained primarily in the upper respiratory tract (nose, throat and trachea) due to its reactive nature (US EPA, 2003).

Following oral administration of ^{14}C-acrolein in rats, the highest concentration of the radiolabel was found in the liver. Excretion was predominantly via urine, then in exhaled air (mainly as $^{14}CO_2$) and faeces. Elimination of the metabolites was observed within 48 hours of dosing in rats, at ~70–80 % following oral administration and 11–22 % following inhalation exposure (EURAR,

2001). As the chemical is rapidly metabolised, it is unlikely to bioaccumulate in the body (Health Canada, 2000). Radiolabel acrolein was also detected in the milk of lactating goats, indicating that in utero exposure of the developing foetus is possible (CLH, 2011).

The major metabolic pathways involve oxidation/hydrolysis and conjugation with glutathione (GSH). The chemical is very reactive and binds primarily at the application site. In vivo, conjugation readily occurs with glutathione (GSH) or other thiol-containing molecules to form adducts, thus, leading to GSH depletion and oxidative stress. The conjugate is excreted in rat urine as mercapturic acid metabolites (3-hydroxypropylmercapturic acid (3-HPM) and 2-carboxyethylmercapturic acid (CEMA)) (EURAR, 2001; NTP, 2006; HSDB).

In vitro, the chemical is oxidised by rat liver aldehyde dehydrogenase (ALDH) to acrylic acid. Incubation with rat liver or lung microsomes and NADPH yielded glycidaldehyde and its hydration product glyceraldehyde. These metabolites have not been demonstrated in an in vivo metabolic pathway of acrolein (EURAR, 2001).

The chemical is also capable of reacting nonenzymatically with sulfhydryl groups via Michael additions, which is proposed to contribute to cytotoxic effects if reactions with critical intracellular sulfhydryl groups occur (NTP, 2006).

The chemical may be produced in the body. It is a metabolite of allyl alcohol, allylamine, spermine, and spermidine, and is formed during lipid peroxidation. It can also be formed following exposure of the skin lipid triolein to ultraviolet (UV) radiation. The chemical has been detected in plaque deposits associated with atherosclerosis and Alzheimer’s disease (AEP, 2011).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 2’ and hazard statement ‘Fatal if swallowed’ (H300) in the HCIS (Safe Work Australia). The available data support this classification (EURAR, 2001; CLH, 2011; HSDB).

The reported median lethal doses (LD50) values are:

- 10.3–46 mg/kg bw in rats; and
- 13.9–40 mg/kg bw in mice

Reported signs of toxicity in rats included lethargy, decreased motor activity, tremor, hypothermia and respiratory distress. Mice further displayed squinted eyes, rough coat, hunched posture and piloerection. At necropsy, haemorrhagic stomach and intestine were observed in both species, and reddening of the lungs was seen in mice (EURAR, 2001; CLH, 2011).

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 this classification.

The dermal LD50 value in rabbits was reported between 164 to 1022 mg/kg bw depending upon the vehicle used and concentration of the chemical applied. The dermal LD50 for undiluted acrolein in rabbits was reported at 562 mg/kg bw. Clinical signs of toxicity included severe pain and hyperactive behaviour initially, followed by lethargy, respiratory distress, cyanosis, ulceration, oedema and haemorrhage of the dermis and skin discolouration. At necropsy, pulmonary effects such as red spots and collapsed lung were observed from vapourisation and inhalation of the chemical (CLH, 2011; EURAR, 2001).

Inhalation

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 1’ and hazard statement ‘Fatal if inhaled’ (H330) in the HCIS (Safe Work Australia). The available data support this classification.

The reported median lethal concentration (LC50) values are (EURAR, 2001; REACH):

- 16–150 mg/m^3 (vapours) for four hours in rats;
- 58 mg/m^3 for four hours in hamsters; and
- 151 mg/m^3 (vapours) for six hours in mice.

Reported signs of toxicity included eye and nose irritation, respiratory difficulties (mouth breathing, decreased respiration rate, audible respiration), body weight loss and lung and liver discolouration. Examination of the lungs revealed congestion, haemorrhages, fibrin deposition and necrosis (EURAR, 2001).

In addition to overt toxicity, several indicators of oxidative stress were reported in rats exposed to 1 ppm (2.3 mg/m^3) for 4 hours, including reduced lung levels of ascorbic acid and alpha-tocopherol, reduced glutathione and thiols, and increased superoxide dismutase activity (ATSDR, 2007).

Observation in humans

Available human case studies or exposure data mainly involve irritation (see **Irritation** section).

Human case reports of acute acrolein inhalation exposures (concentration not stated) have shown severe effects including high fever, dyspnoea, coughing, foamy expectoration, cyanosis, pulmonary oedema and death. Volunteers treated with 10 % acrolein in ethanol topically showed irritation, papillary oedema, polymorphonuclear infiltrates and epidermal necrosis after 48 hours (ATSDR, 2007).

In 1 case report, 2 young boys died from lung damage after being exposed for 2 hours to smoke from an overheated fryer. However, co-exposure to other components of the smoke may have contributed to this outcome (AEP, 2011).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with hazard category ‘Skin corrosion Category 1’ and hazard statement ‘Causes severe skin burns and eye damage’ (H314) in the HCIS (Safe Work Australia). The available animal and human data support this classification.

In animals, ~1 % solutions of the chemical was reported to cause serious eye and skin damage (CICAD, 2002).

In a skin irritation study, the chemical (0.5 mL) was applied on intact and abraded skin of New Zealand White (NZW) rabbits (n = 6) for 24 hours. Erythema and oedema were scored at 24 and 72 hours after exposure. During exposure, 2 animals died. Oedema up to grade 4 was observed in 1 animal. Effects were not reversible in 3 out of 4 survivors after 14 days, and were reported to become progressively severe (US EPA, 2003; CDPR, 2015).

In an eye irritation study, the chemical at 0.5 mL was severely irritating in NZW rabbits (n = 9) when applied on the lower lids with observation up to 7 days. Complete corneal opacity, deepened folds, congestion or swelling of the iris, and crimson red, swollen conjunctivae were reported. These effects were not reversible after 7 days. The reported scores were corneal opacity = 4; iris lesion = 2; redness of conjuctivae = 4; and chemosis of conjunctivae = 2 (CLH, 2011).

Exposure to the vapour of the chemical at concentrations between 1.9 and 2.6 ppm for 4 hours caused slight eye irritation in rabbits. No irritation was observed when rabbits were exposed to 0.6 ppm (1.4 mg/m^3) up to 30 days (EURAR, 2001).

Dogs and monkeys appeared to be more sensitive towards irritation than rodents to the chemical. Lacrimation, blinking or closed eyes were observed during intermediate duration exposure to 3.7 ppm, but none of these changes were reported in guinea pigs and rats exposed for the same duration (ATSDR, 2007).

Respiratory Irritation

The chemical is classified as hazardous with hazard category 'Corrosive to the respiratory tract (AU071)' in the HCIS (Safe Work Australia). Acute and repeated dose inhalation toxicity studies in rats showed irritation to the respiratory system and damage to the nasal and tracheal epithelium. Exposure to a low concentrations (0.25 ppm) caused mild nasal epithelial dysplasia, necrosis and focal basal cell metaplasia (ATSDR, 2007).

Sensory irritation of the upper respiratory tract was observed in animals after inhalation exposure. Decreased respiratory rates were observed at 1–3 ppm (2.3–6.9 mg/m^3). Mice were reported to be more sensitive than rats. The concentration required to reduce respiratory rates by 50 % (RD50) was 2.4–6.6 mg/m^3 in mice and 9.2–13.7 mg/m^3 in rats (EURAR, 2001; US EPA, 2003; ATSDR, 2007).

Exposure of Syrian golden hamsters to 6 ppm (14 mg/m^3) of the chemical for four hours caused >50 % exfoliation of ciliated cells in the bronchi, and the cells were observed to be pale and swollen at 24 and 48 hours post-exposure. Areas of irregular epithelium with early stratification and hyperplasia were observed after 96 hours. The chemical depleted sensory neuropeptides (calcitonin-gene related peptide (CGRP) and substance P) in the trachea of rats exposed to 22–249 ppm (51–571 mg/m^3) for 10 minutes (US EPA, 2003).

In vitro studies conducted in tissues from several animal species including sheep, chickens and cows showed that the chemical induced significant reduction in ciliary movement in the upper respiratory tract (CICAD, 2002).

Other

Irritation of the gastrointestinal mucosa appeared to be the primary effect following oral exposure. Acute and intermediate duration exposure to high doses (>2 mg/kg) cause increasingly severe irritation effects in the stomach, including epithelial hyperplasia, ulceration, haemorrahage, and oedema of the stomach mucosa. Species differences in gastrointestinal sensitivity were reported (ATSDR, 2007).

Observation in humans

Many human exposure studies are available. Effects following oral or inhalation exposure to the chemical have been consistently observed at the site of contact (stomach or respiratory tract) (CICAD, 2002). Exposure to the vapour or liquid forms of the chemical causes inflammation and irritation of the skin and eyes, mucous membranes and respiratory tract, progressing into delayed pulmonary oedema, chronic respiratory disease, skin and corneal burns and sensitisation dermatitis. Ingestion causes severe mouth and gastrointestinal tract irritation (HSDB).

Irritation is reported to be concentration and time dependent. In various human exposure studies, minor eye irritation (perceived as rapid-onset stinging of the eyes and increased blinking) was reported at 0.1–0.3 ppm. A lowest observed adverse effect level (LOAEL) of 0.34 mg/m^3 for eye irritation was suggested, with sensory irritation persisting 10 minutes after exposure. Rapid onset of nose and throat irritation and reduced breathing rate was reported following acute exposure to 0.3 ppm. A 5 minute exposure to 1 ppm (2.3 mg/m^3) of vapour caused lacrimation, marked eye, nose and throat irritation. At 3 ppm (7 mg/m^3), the chemical is a severe pulmonary irritant and powerful lachrymogen, affecting the conjunctivae and mucous membranes of the upper respiratory tract. At higher concentrations it causes lung injury; a 10 minute exposure to 350 mg/m^3 is lethal. Respiratory difficulties may persist for at least 18 months following exposure (ATSDR, 2007; HSDB).

Humans appear to adapt to eye irritation at low levels of vapour exposure, as a study reported increasing eye irritation up to 40 minutes in volunteers exposed to a constant level of acrolein vapours for 60 minutes, but no further increase in discomfort thereafter (ATSDR, 2007).

In a human patch test, volunteers were exposed to the chemical at concentrations of 0.01, 0.1, 1 and 10 % in ethanol (duration not stated). Positive skin reactions were observed in 6 out of 48 subjects at 1 % concentration, with 4 of the 6 exhibiting serious oedema and bullae and the other 2 with erythema. At the highest concentration (10 %), all subjects showed severe skin effects

including bullae, necrosis, inflammatory cell infiltration and papillary oedema. No adverse effects were observed at ≤0.1 % (CICAD, 2002; CLH, 2011).

Sensitisation

Respiratory Sensitisation

No data are available.

Skin Sensitisation

Based on the available data, skin sensitisation potential is indicative but not definitive. The sensitisation potential of the chemical at high concentrations cannot be ruled out.

In a poorly reported guinea pig maximisation test (similar to OECD TG 406), female guinea pigs were intradermally induced with the chemical at 0.01 % in water, followed by topical exposure at 2.5 %, and a topical challenge phase at 0.5 %. Skin reactions were scored on a scale of 0.5, 1, 2 and 3. Positive skin reactions were reported in 7/15 test animals and in one control animal at a score of 0.5. The authors defined 0.5 as patches of redness and non-confluent, which equates to a score of 1 according to the description in the OECD guidelines. The available data is insufficient to warrant classification for sensitisation (EURAR, 2001; CLP, 2001).

Repeated Dose Toxicity

Oral

Based on the available data, no systemic effects were observed. Reported effects were mainly local and were considered secondary to irritation/corrosivity; therefore, not relevant for classification.

The primary effects observed in animal studies were in the forestomach. No hepatotoxicity was reported. Stomach lesions were observed in Fischer 344 (F344) rats but not in Sprague Dawley (SD) rats, and may relate to differences in strain sensitivity (US EPA, 2003).

In a 14-week repeat dose oral gavage study conducted by the NTP, F344 rats (n = 10/sex/dose) were administered the chemical at 0, 0.75, 1.25, 2.5, 5 or 10 mg/kg bw/day, and B6C3F1 mice (n = 10/sex/dose) were administered 0, 1.25, 2.5, 5, 10 or 20 mg/kg bw/day. At the highest doses, mortalities occurred in most of the rats and in all mice. In rats, observed effects at the highest dose included significantly decreased body weight gain, clinical toxicity effects (abnormal breathing, eye or nasal discharge, ruffled fur, thinness and lethargy), significantly decreased absolute and relative thymus weights and gross lesions in the forestomach and glandular stomach. Microscopically, increased incidences of forestomach squamous epithelial hyperplasia were observed in males at ≥5 mg/kg bw/day and in females at ≥2.5 mg/kg bw/day, and increased incidences of glandular stomach haemorrhage in the 10 mg/kg bw/day groups. The no observed adverse effect level (NOAEL) was 2.5 mg/kg bw/day and 1.25 mg/kg for males and females, respectively (NTP, 2006).

In the mouse study, there was no change in body weight gain. Effects observed at the highest dose included gross lesions (red or white discolouration) in the forestomach and glandular stomach (females), significantly increased incidences of glandular stomach haemorrhage (both sexes), and glandular stomach inflammation and epithelial necrosis (females). Microscopic examinations revealed forestomach squamous epithelial hyperplasia at ≥2.5 mg/kg bw/day. The NOAEL was 1.25 mg/kg bw/day (NTP, 2006).

In a standard 90-day oral gavage study in SD rats (n = 30/sex/dose), no mortalities or treatment-related toxicity were observed at doses up to 5 mg/kg bw/day. A 2-year oral gavage study in SD rats and an 18-month study in mice did not show any treatment-related clinical signs of toxicity or any significant histopathological changes at doses up to 2.5 mg/kg bw/day in rats and 4.5 mg/kg bw/day in mice. The study otherwise resulted in early mortality in rats (0.5 mg/kg bw/day), which was considered

significant even after it was proposed to be due to dosing errors (US EPA, 2003; CLH, 2011). The disparity in effects observed between the NTP study and this study could be is due to the use of a thickening agent in the dosing vehicle for the NTP study, increasing the gastrointestinal residence time and hence, the toxicity of the chemical (ATSDR, 2007).

In a non-guideline study, beagle dogs administered the chemical in gelatin capsules up to 2 mg/kg bw/day for 12 months did not show treatment-related effects. Transient vomiting was reported at ≥0.5 mg/kg bw/day, possibibly from ingestion of the capsule. This effect decreased over time, suggesting that tolerance developed for this method of administration. (CICAD, 2002; ATSDR, 2007; CLH, 2011).

Dermal

Based on the available data, the dermal effects observed are primarily due to irritation and systemic toxicity is not expected.

In a subchronic dermal toxicity study (OECD TG 410), NZW rabbits (n = 10/sex/dose) were exposed to the chemical at 0, 7, 21 or 63 mg/kg bw/day for 21 days. Dermal application at ≥7 mg/kg bw/day resulted in local irritation which increased in severity with dose and duration. Slight to moderate erythema and oedema were observed at 7 or 21 mg/kg bw/day. Oedema was more pronounced at the highest dose. Dose-dependent increased incidences of nasal mucous discharge, interstitial pneumonia and lethargy were reported in all treated groups. Lung toxicity was stated to be a result of inhalation of the volatile chemical. No specific systemic toxicity was observed in this study (CLH, 2011).

Inhalation

Many non-guideline studies for the chemical have been conducted in rats, rabbits, guinea pigs, hamsters, dogs and monkeys, with rats being the most sensitive species. These studies had limitations in their protocol or reporting. Overall, the observed effects are similar to that observed upon acute exposure, including pulmonary inflammation, and lesions in the respiratory tract and nasal cavity. Lung effects were considered to result from repeated exposure to an irritant or corrosive atmosphere (CLH, 2011). No classification is recommended.

In several studies ranging from 62–90 days, rats were exposed (whole-body) to the chemical at concentrations ranging from 0.4 ppm (0.9 mg/m^3) to 4.9 ppm (9.2 mg/m^3). At the highest dose, significant mortality was observed. Histopathological changes in the respiratory tract (destruction and hyper- and metaplasia of the epithelial lining and inflammatory alterations) were observed with increasing severity at all doses. Histopathological changes in the lungs included bronchiolar necrosis at 1.4 ppm, and sloughing, bronchiolar oedema and focal pulmonary oedema at 4 ppm. Increased relative organ weights (lung, heart, kidneys and adrenals) was observed at 4.9 ppm. An elevated expiratory flow rate was observed in the low dose group. A dose-related decrease in body weight gain and increased severity of respiratory tract lesions (squamous cell metaplasia in the nasal cavity) were observed at all doses, while body weight change was not significant in the low dose groups. The NOAEC was determined as <0.4 ppm (<0.9 mg/m^3) (EURAR, 2001; CLH, 2011).

In a repeat dose inhalation study, rats, hamsters and rabbits were exposed (whole-body) to vapours of the chemical at 0.4, 1.4 or 4.9 ppm (0.9, 3.2 or 11.2 mg/m^3) for 62 days. Rats were the most sensitive species and effects observed are summarised above. Rabbits and hamsters did not show adverse effects at 0.4 ppm. At the highest dose, clinical toxicity effects included laboured breathing and sneezing, salivation and nasal discharge, decreased body weights, increased relative organ weights (lung, hearts and kidneys), significant increased erythrocyte count, haemoglobin content and number of lymphocytes. Histopathological changes (inflammatory changes in the nasal cavity and respiratory tract) were observed from 1.4 ppm. The NOAECs for rabbits and hamsters were determined as 0.4 ppm (0.9 mg/m^3) (EURAR, 2001; CLH, 2011).

Several short-term inhalation studies (up to 3 days, up to 1.7 ppm) in rats were conducted to study the biochemical and histopathological changes in the respiratory and olfactory epithelium of the nose and in free lung cells. Effects were examined at the microscopic level and included cell proliferation in nasal and tracheal epithelium and concentration-dependent increase in the proportion of DNA-synthesising cells, olfactory degeneration and necrosis, ulceration and basal cell hyperplasia of the respiratory epithelium (EURAR, 2001; CICAD, 2002; US EPA, 2003).

One 13-week repeat dose inhalation study in F344 rats was conducted at lower concentrations at 0, 0.05, 0.14, 0.5, 1.4 or 4.2 mg/m^3, 6 hours/day, 5 days/week and involved a more extensive examination of the nasal cavity. The NOAECs were

established as 0.5 mg/m^3 for the respiratory epithelium and 1.4 mg/m^3 for the olfactory epithelium, based on neuronal loss at 4.2 mg/m^3 (AEP, 2011). Computational fluid dynamic modelling revealed that although the reported NOAEC for the respiratory epithelium was lower, olfactory epithelium lesions arise at a lower delivered tissue dose suggesting that the ofactory epithelium is more sensitive to the effects of inhaled acrolein than the respiratory epithelium (OEHHA, 2008).

A few short-term studies in mice reported moderately severe lesions in the respiratory epithelium and olfactory epithelium up to 1.7 ppm, excessive macrophage accumulation at 3 ppm, and lung lesions at an unknown concentration (US EPA, 2003).

In 90-day studies in monkeys, inflammatory changes in sections of liver, lung, kidneys and heart, and occasional emphysema were observed at 0.22–0.70 ppm (0.5–1.6 mg/m^3). Eye irritation including ocular discharge, excessive salivation, squamous cell metaplasia and basal cell hyperplasia of the trachea were reported at 1.8 ppm (4.1 mg/m^3). Mortalities which involved pulmonary hepatic, splenic, liver lesions and lung haemorrhage were observed at the highest tested dose at 3.7 ppm (8.5 mg/m^3) (CLH, 2011).

Genotoxicity

Based on the weight of evidence, classification for mutagenicity is not warranted.

The chemical is an alkylating agent and therefore a direct-acting mutagen for bacteria. Induction of gene mutations and sister chromatid exchanges were observed, but negative results in chromosome aberrations test in mammalian cells in vitro were obtained. Positive results were generally observed in a narrow, near lethal, dose range. In vivo tests were negative.

In vitro

The following results were reported in in vitro assays:

- positive in bacterial gene mutation assays with certain strains of *Salmonella typhimurium* (TA100, TA104 and TA98), mainly in assays without metabolic activation (EURAR, 2001);
- when tested under 2 different protocols, the preincubation protocol gave weakly positive results in strain TA100, with metabolic activation, and equivocal results in TA100 and TA1535, with metabolic activation. Negative results were obtained with strains TA98 and TA1537, with or without metabolic activation. The vapour protocol gave negative results for all strains and activation conditions (NTP, 2006);
- no chromosome aberrations in four standard mammalian gene mutation tests with Chinese hamster ovary (CHO) cells, mouse embryo fibroblasts and normal human fibroblasts. Chromosome tangling was observed at cytotoxic concentrations (≥40 µM) with no chromosome breakage (EURAR, 2001; CLH, 2011);
- weakly positive in three sister chromatid exchanges (SCE) studies with CHO cells and human lymphocytes only at highest concentrations tested, without metabolic activation. Negative in another SCE study with CHO cells up to 0.75 µg/mL;
- an increase in gene mutations in a non-standard cell line, DNA repair deficient human fibroblasts (Xeroderma pigmentosum cells), but not in normal repair proficient human fibroblasts (EURAR, 2001; CLH, 2011);
- negative for petite mutations in the yeast *Saccharomyces cerevisiae* strains S211 and S138 (EURAR, 2001).

The chemical is highly toxic in bacterial and mammalian cells and; therefore, the experimental dose range is restricted. The genotoxic doses are close to or overlap cytotoxic doses (EURAR, 2001). The positive findings in in vitro bacterial systems may be due to the lack of an endogenous glutathione detoxification pathway. Glutathione reacts readily with the chemical (see **Toxicokinetics** section), thus protecting sensitive intracellular systems from damage (CLH, 2011).

In vivo

The chemical was negative in a bone marrow cytogenetics test (OECD TG 475) in male SD rats administered the chemical by gavage up to 8.2 mg/kg bw (a lethal dose). Negative results were obtained in two dominant lethal studies in mice (CLH, 2011).

The chemical appeared genotoxic in the 'somatic mutation and recombination' (SMART) test in *Drosophila melanogaster*, but did not exhibit genotoxic activity in the 'sex chromosome loss test' (SCLT), while equivocal results were obtained in the 'sex-

linked recessive lethal test' (SLRLT) (EURAR, 2001; NTP, 2006).

Carcinogenicity

Based on available animal data and the results for genotoxicity indicating lack of systemic mutagenic potential (see **Genotoxicity** section), the chemical is not considered to be carcinogenic. However, the available data are not sufficient to examine the long term potential to produce point of contact respiratory tumours as seen for formaldehyde (NICNAS, 2006).

The available oral gavage studies in rats and mice did not indicate carcinogenic potential. Available inhalation studies in rats and hamsters are inadequate for determining carcinogenicity due to study limitations.

In lifetime gavage carcinogenicity studies (OECD TG 453), SD rats (n = 70–75/sex/dose) were administered the chemical at 0, 0.05, 0.5 or 2.5 mg/kg bw/day, and CD-1 mice (n = 70–75/sex/dose) were administered the chemical at 0, 0.5, 2 or 4.5 mg/kg bw/day. No treatment-related increases in tumour incidence were observed up to the highest dose tested in either species. A statistically significant reduction in survival was observed in rats and in male mice at the highest dose. However, this was due to dosing error (EURAR, 2001; CLH, 2011).

Two long-term inhalation studies are available, 1 in rats and the other in hamsters. Both studies have limitations in reporting and of their methodology. No treatment-related tumours or metaplasia were observed in the lungs of rats exposed to the vapour of the chemical at 18.3 mg/m^3 (8 ppm) for 10 or 18 months. Syrian golden hamsters were exposed to the vapour of the chemical at 9.3 mg/m^3 (4 ppm) for 52 weeks. Nasal inflammatory changes and olfactory epithelium metaplasia were observed but were reversible after a 29-week withdrawal period. No treatment-related respiratory tract, nasal tumours or tumours at other sites were observed. Additionally, the chemical was not determined to have an enhancing (co-carcinogenic) effect with benzo[a]pyrene or *N*-nitroso-diethylamine on respiratory tract tumours. However, the experimental duration is relatively short and is not a lifetime study for hamsters (EURAR, 2001; CICAD, 2002).

The US EPA determined that the ‘data are inadequate for an assessment of human carcinogenic potential by either the inhalation or oral routes of exposure’. The highly reactive nature of the chemical and the lack of systemic toxicity suggest that the chemical is not likely to reach potential target sites at a concentration sufficient to initiate a carcinogenic process in mammalian species (US EPA, 2003).

In a case-control study of employeees of chemical manufacturing companies, slightly higher than expected incidences of non-Hodgkin's lymphoma with an odds ratio (probability of being affecting in the exposed group to that being affected in the control group) of 2.6 were reported in workers exposed to acrolein. However, these results were not statistically significant and there were co-exposures to other chemicals besides acrolein (CICAD, 2002; AEP, 2011).

Reproductive and Developmental Toxicity

Based on available data, the chemical is not likely to be a reproductive or developmental toxicant. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a 2-generation reproductive toxicity studies (OECD TG 416), SD rats were administered the chemical (gavage) up to doses of 7.2 mg/kg bw/day (115 days) or 6 mg/kg bw/day (10 weeks). Statistically significant decreased body weight gains in the parental (F0) at 6–7.2 mg/kg bw/day were observed in both studies. Other reported parental toxicity effects (mortality, gastric lesions, histopathological stomach changes) were observed at ≥3 mg/kg bw/day. Dams developed respiratory irritation at ≥4 mg/kg bw/day and wheezing, dyspnoea and stomach lesions at 7.2 mg/kg bw/day. Reproductive parameters including male and female fertility were not affected up to the highest tested doses. In 1 study, reduced pup weights of the F1 generation pups at 6 mg/kg bw/day were observed. The NOAELs for parental toxicity were established as 1 mg/kg bw/day (stomach lesions) or 4 mg/kg bw/day. The NOAELs for developmental toxicity were established as 3 mg/kg bw/day (reduced F1 pup bodyweights during lactation) or 7.2 mg/kg bw/day (EURAR, 2001).

Developmental toxicity

In an oral teratology study, SD rats were exposed (gavage) to the chemical at doses of 0, 3.6, 6 or 10 mg/kg bw/day at gestation days (GD) 7–19. At the highest dose, increased mortality was observed in the dams. Decreases in total litter size (24 %) and mean foetal weight (18 %), increased incidences of delayed ossification (36 %) and skeletal anomalies were also observed at

the highest dose compared to the controls. Clinical toxicity (wheezing and dyspnoea) and statistically significantly reduced body weight gain for the dams were observed from 6 mg/kg bw/day. The effects occurred at doses that caused significant maternal toxicity. The NOAELs for maternal and developmental toxicity were 3.6 mg/kg bw/day and 10 mg/kg bw/day, respectively (EURAR, 2001; CLH, 2011).

In developmental toxicity study, NZW rabbits were administered (gavage) the chemical at 0, 0.1, 0.75 or 2 mg/kg bw/day at GD 7–19. At the highest dose, dams showed a transient decrease in body weight gain accompanied by decreased food consumption. An increase in mean foetal body weights was observed but not considered to be an adverse effect. No effect on pregnancy indices, implantation sites, number of live foetuses, or skeletal anomalies were observed. The NOAELs for maternal and developmental toxicity were 0.75 mg/kg bw/day and ≥2 mg/kg bw/day, respectively (EURAR, 2001; CLH, 2011).

In a poorly reported developmental toxicity study, CD-I mice were treated at doses up to 10 mg/kg bw/day, from GD 7–17. Maternal toxicity was observed at the highest dose, including lethargy, squinted eyes, dyspnoea and hunched posture. In the foetuses, an increased incidence of cleft palate was observed but occurred in mice with a high background incidence. Delayed ossification was observed only at a dose that caused maternal toxicity. An increased incidence of subcutaneous oedema was observed in foetuses and was suggestive of a dose-related response. However, the severity of this effect was not stated and it is not known if it is a localised or generalised oedema. A developmental NOEL was established at less than 4.0 mg/kg bw/day (resorptions at 10 mg/kg bw/day and generalised delayed ossification) and a maternal NOEL was established at 6.3 mg/kg bw/day (decreased body weight gain) (CLH, 2011; CDPR, 2015).

In vitro tests

A number of in vitro toxicity tests were conducted using rat embryo cultures, mouse limb bud culture and chicken eggs. Embryolethality, abnormal development and growth retardation effects were reported. These results indicate that the chemical is toxic when administered directly to the embryos or foetuses but not when administered orally in vivo. Therefore, it is proposed that the reactivity of the chemical may limit its ability to reach critical sites in the developing embryo (EURAR, 2001; EPA, 2003).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

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

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

Sensory irritation in humans following acute exposure is reported at airborne concentrations of 0.34 mg/m^3 and above, which is below the current exposure standard of 0.69 mg/m^3 STEL. Therefore, a review of the current exposure standard may be beneficial to mitigate the risk of adverse effects. Airborne concentrations of the chemical should be kept as low as reasonably practicable to minimise risk.

NICNAS Recommendation

It is recommended that Safe Work Australia consider whether current controls adequately minimise the risk to workers. A Tier III assessment might be necessary to provide further information about whether the current exposure controls offer adequate protection to workers.

All other risks are considered to have been sufficiently assessed at the Tier II level, provided that all 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	Fatal if swallowed - Cat. 2 (H300)* Toxic in contact with skin - Cat. 3 (H311)* Fatal if inhaled - Cat. 1 (H330)*
Irritation / Corrosivity	Not Applicable	Corrosive to the respiratory tract (AUH071)* Causes severe skin burns and eye damage - Cat. 1 (H314)*

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, 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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