2-Propenoic acid, ethyl ester: Human health tier II assessment

24 April 2015

CAS Number: 140-88-5

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.

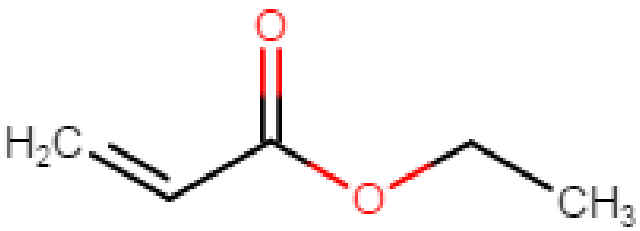
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	acrylic acid, ethyl ester ethyl acrylate ethyl-2-propenoate
Structural Formula	
Molecular Formula	C5H8O2
Molecular Weight (g/mol)	100.1162
Appearance and Odour (where available)	Colourless liquid with characteristic acrid odour.
SMILES	C(=O)(C=C)OCC

Import, Manufacture and Use

Australian

The following Australian industrial use was reported for the chemical under previous mandatory and/or voluntary calls for information.

The chemical has reported site-limited use as an intermediate for manufacturing other chemicals.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1000–9999 tonnes.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorization and Restrictions of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and the National Toxicology Program (NTP; 2014).

The chemical has reported domestic uses, including:

- as a fragrance adjuvant in consumer products;
- as an additive in floor polishes and sealants;
- in shoe polishes; and
- in caulking compounds and binders.

The chemical has reported commercial uses, including in:

- construction materials;
- corrosion inhibitors;
- cutting fluids and hydraulic fluids;
- reprographic agents;
- viscosity adjusters
- impregnation materials; and
- lubricants and additives

The chemical has reported site-limited uses, including:

- as a monomer in producing polymers and copolymers of acrylic resins, thermoplastics, latexes, adhesives, textile and paper coatings; and
- for plasticising synthetic polymers;

The chemical has reported non-industrial uses, including:

- in pharmaceuticals; and

- as a synthetic flavouring substance.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

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):

- Xn; R20/21/22 (acute toxicity)
- Xi; R36/37/38 (irritation)
- Xi; R43 (sensitisation)

Exposure Standards

Australian

The chemical has an exposure standard of 20 mg/m^3 (5 ppm) time weighted average (TWA).

International

The following exposure standards are identified for the chemical (Galleria Chemica).

TWA of:

- 20–42 mg/m^3 (5–10 ppm) in Canada (Alberta, British Columbia, Quebec, Saskatchewan), France, Germany, Iceland, Indonesia, Mexico, Norway, South Africa, the United Kingdom, and the United States of America (USA); and
- 100 mg/m^3 (25 ppm) in Canada (Yukon), Phillipines, and the USA (Vermont).

Short-term exposure limits (STEL) of:

- 40–100 mg/m^3 (10–25 ppm) in Canada, Estonia, Greece, Ireland, Mexico, Netherlands, Poland, South Africa, Sweden, and the USA.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed via oral, dermal and inhalation routes of exposure. Following absorption in rats, the highest concentrations of the chemical were detected in the liver and kidneys. Irreversible and dose-related binding to, and depletion of non-protein sulfhydryls (NPSH) in the forestomach and glandular stomach were observed. Following inhalation, most of the chemical vapours were absorbed in the upper respiratory tract (IARC, 1999; OECD, 2004; HSDB).

Acrylates are rapidly metabolised. This occurs via two pathways: one mediated by carboxylesterases to hydrolyse the ester linkage to form acrylic acid and alcohol; and the second is through conjugation with glutathione by a spontaneous Michael addition reaction or by glutathione-S-transferase (GSH) catalysis (OECD, 2004; HSDB).

In rats, the majority of orally administered chemical (60 %) was excreted as carbon dioxide within eight hours. The identified urinary metabolites were 3-hydroxypropanoic acid and two mercapturic acids (formed via glutathione conjugation). Urinary excretion of mercapturic acids decreased with increased dosing, consistent with glutathione depletion (IARC, 1999; HSDB).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification.

The median lethal dose (LD50) for the chemical was reported to be 760–1120 mg/kg bw in rats, 1800 mg/kg bw in mice and 280–420 mg/kg bw in rabbits. Reported sublethal signs of toxicity in rats included neurological effects (lethargy and passiveness) and respiratory depression (cyanosis and abdominal breathing). At necropsy, severe gastrointestinal irritation (enlarged stomachs accompanied by reddened stomach mucosa, intestines and thoracic cavity) was observed (OECD, 2004; HSDB).

The acute toxicity of acrylates decreases with increasing chain length of the alcohol (Greim et. al., 1995).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The LD50 value in rabbits supports this classification.

The reported dermal LD50s were 1800 to >5000 mg/kg bw in rats, and 1200–1800 mg/kg bw in rabbits. All animals exhibited skin irritation (erythema, oedema and necrosis). Sublethal signs of toxicity in rats included neurological effects (passiveness and ataxia), salivation, yellow-stained anogenital areas and red-stained eyes and muzzles (OECD, 2004).

Rabbits were reported to be more sensitive to the chemical, with observed effects including congestion and haemorrhage of the lungs and kidneys, increased accumulation of blood in the intestinal blood vessels, and mottling on the liver. Furthermore, varying severity of inflammation, intense oedema and several incidences of haemorrhage were observed, due to the irritant properties of the chemical (OECD, 2004; REACH).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification.

The median lethal concentration (LC50) in rats was 1500–2180 ppm (6.1–8.9 mg/L), following four hours of exposure to the chemical vapour. Reported signs of toxicity included eye, nose and respiratory tract irritation, breathing difficulties, salivation, hypothermia, ruffled fur, and neurotoxicity (piloerection, hunched posture, uncoordinated and convulsive movements, hyperexcitability and tremor). Mortalities were attributed to generalised cardiopulmonary collapse (OECD, 2004; REACH).

Observation in humans

Acute oral exposure to the chemical has been reported to cause abdominal pain, nausea, vomiting and diarrhoea in humans (HSDB).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical has been reported to be a respiratory irritant in humans and animals following inhalation exposure. Acute inhalation studies in rats, guinea pigs and monkeys have reported irritation in the lungs and upper respiratory tract at concentrations >300 ppm (1.23 mg/L) (HSDB).

Animal studies have shown that the target within the respiratory tract is the olfactory epithelium that lines the dorsal meatus (see **Repeat dose toxicity: Inhalation**). Irritation effects were localised and were observed at concentrations >5 ppm (0.02 mg/L) (OECD; 2004).

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.

In a skin irritation study conducted according to the OECD Test Guideline (TG) 404, undiluted chemical (0.5 mL) was applied (semi-occlusively) on the skin of New Zealand White rabbits for one hour (n = 1) or four hours (n = 2), with observation up to 14 days. A one-hour exposure caused slight to moderate erythema, with average scores (24–72 hours) of 2.0 and 0.0 for erythema and oedema, respectively. Exposure to the chemical for four hours caused slight to marked erythema, with average scores (24–72 hours) of 2.2 and 0.0 for erythema and oedema, respectively. The observed effects were reversed within 14 days (OECD, 2004; REACH).

The potential to cause dermal corrosion was tested using the EpiDerm skin corrosivity method (OECD TG 431) by applying the chemical (50 µL) on reconstructed human epidermis tissue samples. The tissue destruction was measured using a colourimetric test. The viability of the treated tissues was reported to be 88 % and 7 % using an MTT assay, for exposure periods of three minutes and one hour, respectively. The study concluded that the chemical 'showed corrosive potential' under the test conditions used (OECD, 2004; REACH).

In several other skin irritation studies in rabbits (OECD TG 404 or non-guideline), severe erythema and oedema were observed following application of the undiluted chemical for durations of one minute to 24 hours. Exposures for longer periods (≥20 hours) caused necrosis. Other reported skin irritation effects included whitened patches, eschar or concave eschar with peripheral healing by fibrosis, and scaling (OECD, 2004).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia). The available data overall support this classification.

In an eye irritation study, the undiluted chemical (0.1 mL) was instilled into one eye of each rabbit (n = 6), and observed for up to 72 hours. At 24 hours post application, mild to severe conjunctival inflammation, some corneal opacity, and iritis were observed. The study was terminated in one animal due to the severity of eye lesions. Conjunctival redness and chemosis were not fully reversible for the other animals within 72 hours. The mean scores for all timepoints post application (24, 48 and 72 hours) were 0.07 for corneal opacity, 0.07 for iritis, 2.0 for conjunctival redness and 1.0 for chemosis. The authors concluded that the chemical was an eye irritant (OECD, 2004; REACH).

In another eye irritation study, two rabbits had the undiluted chemical instilled (one drop each) and had observations recorded at 10 minutes and one, three and 24 hours. The chemical caused strong conjunctival redness in both animals. Corneal opacity was observed in one rabbit within 24 hours (REACH). No scores are available.

Results from another irritation study in rabbits indicated that exposure to 0.5 mL of the chemical produced severe necrosis of the cornea, and moderate necrosis was seen with a dose of 0.1 mL within 24 hours of application (REACH). No scores are available.

Observation in humans

Workers exposed to the chemical dust (from ethyl acrylate polymerisation) reported itching of the skin in the facial creases, ears and nose. The vapour of the chemical was reported as 'can be very irritating' at moderate concentrations of 4–5 ppm (16.4–20.5 mg/m^3) (HSDB).

In one case report, a worker exposed to the chemical dust (concentration and duration not reported) was hospitalised for respiratory effects, cough, and itching of facial skin and ears (HSDB).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the (HSIS) (Safe Work Australia). The available data indicate the chemical to be a weak skin sensitiser, supporting this classification.

A local lymph node assay (LLNA) (OECD TG 429) was conducted using four acrylates (including ethyl acrylate) at concentrations of 2.5, 5.0, 10, 25 or 50 % on CBA mice, for three consecutive days. A stimulation index (SI) above the threshold (SI >3) was obtained for ethyl acrylate at the highest tested concentration (SI = 4). The chemical was shown to be a potential skin sensitiser with an estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 36.8 % (HSDB; REACH).

In a three-day hypersensitivity test in female mice, the chemical was tested, together with two other acrylates, using an LLNA and a mouse ear swelling test (MEST). The chemical showed negative results in both assays up to the highest concentration tested, which was 30 % (HSDB).

The chemical was sensitising in 7/8 guinea pigs in a Freund’s complete adjuvant test (FCAT), but gave negative results in a guinea pig maximisation test. The guinea pigs, already sensitised to the chemical, exhibited cross-sensitisation to challenges with several other acrylates (OECD, 2004; HSDB).

An OECD report (2004) stated that ‘ethyl acrylate is considered likely to be a sensitiser and exposure to ethyl acrylate may result in cross-sensitisation with other acrylates and methacrylates’.

Observation in humans

A human maximisation test was conducted in 24 volunteers using the chemical in 4 % petrolatum. Sensitisation reactions were observed in 10/24 volunteers (HSDB). In a course of predictive patch testing, several male volunteers developed allergic contact dermatitis to the acrylic-based adhesive used to hold the test materials in place. The subjects were further tested with four acrylate components of the tape, which included this chemical, but did not react to ethyl acrylate. The study indicated cross-sensitisation with other acrylates (REACH).

A dental technician was reported to have developed eyelid and hand dermatitis. She was previously patch-tested with a sample of acrylic material from a nail salon that gave positive reactions only after one month. She was subjected to repeated testing with ethyl acrylate and methyl methacrylate, which produced no reaction up to 96 hours, but were positive five weeks later. The authors concluded that this delayed reaction was an allergic manifestation and not a case of active sensitisation (HSDB).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause serious damage to health from repeated oral exposure. Rats that received the chemical through repeated oral doses showed irritation effects in the forestomach.

In a repeated dose toxicity study (OECD TG 408), Fischer 344 (F344) rats (n = 10/sex/dose) were administered the chemical by oral gavage at doses of 0, 7, 14, 28, 55 or 110 mg/kg bw/day, five days a week for 13 weeks. At the highest dose, reddening of the duodenal mucosa was observed in 1/10 males and increased markings on the cardiac region of the stomach in 2/10 males. No chemical-related clinical toxicity symptoms or treatment-related findings were reported. The reproductive tissues were examined and no effects were reported. A no observed adverse effect level (NOAEL) of 55 mg/kg bw/day was established, based on the effects observed in the duodenal mucosa and cardiac region of the stomach at 110 mg/kg bw/day (OECD, 2004; REACH)

In another repeated dose oral toxicity study (OECD TG 408), F344 rats (n = 20/sex/dose for low and mid doses and n = 30/sex/dose for the highest dose) were administered the chemical in corn oil at doses of 0, 20, 100 or 200 mg/kg bw/day for four or 13 weeks. This study was conducted to specifically evaluate stomach lesions. Ten animals in the highest dose group were treated with 200 mg/kg bw/day for four weeks and observed for nine weeks (recovery group). At the highest dose, decreased body weight gain (~7 %) was observed. Dose-related increases in stomach weights were observed after four weeks of exposure ≥100 mg/kg bw/day. All treated animals showed changes in the forestomach, which included thickening, discoloured foci or areas, irregular surfaces, raised plaques and nodules, hyperplasia of the squamous epithelium, hyperkeratosis, submucosal inflammation, focal submucosal oedema, focal eschar, focal epithelial haemorrhage and focal ulcers of the limiting ridge. Changes in stomach weight and the forestomach were no longer evident after the recovery period. Based on stomach effects observed at all doses, no NOAEL could be established (OECD, 2004; REACH).

Many short-term repeated dose oral toxicity studies (5–14 days) were conducted in rats. Increased stomach weights were observed at doses ≥20 mg/kg bw/day. Irritation of the forestomach (gastritis, submucosal oedema, and ulcer or eschar formation) at ≥50 mg/kg bw/day, decreased body weight gain, thickened stomach walls and abdominal adhesions at ≥100 mg/kg bw/day, ulcerative and non-ulcerative inflammation of the forestomach at ≥400 mg/kg bw/day, and neurological symptoms (reduced activity and ruffled fur) at ≥450 mg/kg bw/day were reported (OECD, 2004; REACH).

In mice, no overt toxic effects were observed in 13-week studies at doses up to 100 mg/kg bw/day. Fourteen-day studies showed thickening of forestomach walls in males at ≥100 mg/kg bw/day, and in females at ≥200 mg/kg bw/day (OECD, 2004).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is not considered to cause serious damage to health from repeated inhalation exposure.

Studies in rats and mice showed that the primary target following repeated inhalation exposure was the olfactory epithelium that lines the dorsal meatus. No other toxicity effects were reported at concentrations less than 75 ppm (0.31 mg/L).

In a combined chronic toxicity/carcinogenicity study (OECD TG 453), groups of rats (n = 115/sex/dose) and mice (n = 105/sex/dose) were exposed to the chemical vapour at 0, 25, 75 or 225 ppm (0, 0.10, 0.31 or 0.92 mg/L) for three, six, 12, 18 or 27 months. At the highest dose, the animals showed aggression at the start of exposure and lethargy at the end. This group exhibited significant body weight loss and exposure had to be terminated at six months. All animals displayed dose-dependent lesions (metaplasia, atrophy and hyperplasia of basal cells and Bowman's glands) in the olfactory portion of the nasal mucosa. The regions lined by the respiratory epithelium were relatively unaffected. Reduced body weights (statistically significant) were observed at ≥75 ppm. No other treatment-related findings were reported. The reproductive tissues were examined and no effects were reported. A follow-up study conducted by the same authors reported no treatment-related changes in the nasal mucosa at a concentration of 5 ppm (0.02 mg/L), following a 24-month exposure. Based on these studies, no observed adverse effect concentrations (NOAECs) of 25 ppm (0.10 mg/L) and 5 ppm (0.02 mg/L) were established for systemic toxicity (based on reduced body weight at the higher doses) and nasal irritation, respectively (OECD, 2004; HSDB; REACH).

In several repeated dose inhalation toxicity studies (13–30 days), rats and mice were exposed to the chemical vapour at concentrations up to 540 ppm (2.2 mg/L). Clinical symptoms reported were localised irritation in the nasal mucosa at ≥25 ppm (0.10 mg/L), reduced body weight gain at ≥75 ppm (0.31 mg/L), salivation, eye and respiratory irritation at ≥272 ppm (1.1 mg/L), and lethargy at ≥300 ppm (1.2 mg/L). Exposure concentrations >500 ppm (2.0 mg/L) caused mortality and changes in the kidneys, liver, lungs and spleen (OECD, 2004; REACH). No deaths or clinical symptoms were observed in rats exposed to concentrations of 25–75 ppm for 72–199 days (US EPA, 2007).

Genotoxicity

Based on the available data, the chemical is not considered genotoxic.

The chemical is clastogenic to mammalian cells in vitro, but not in vivo. An OECD report (2004) stated that 'positive mutagenic activity in some in vitro assays occurred only at concentrations resulting in significant cell death'. It was reported as unclear whether the mutations were derived from chromosomal damage or point mutations as the colony sizes were not evaluated (OECD, 2004).

The chemical gave mixed results in several in vitro assays: (OECD, 2004; REACH)

- generally negative results in bacterial reverse mutation assays with strains of *Salmonella typhimurium*, with or without metabolic activation; but weakly positive in a *S. typhimurium* strain TA100 with metabolic activation;
- negative results in yeast cytogenetic assays using *Saccharomyces cerevisiae*, without metabolic activation;
- positive results in mouse lymphoma L5178Y tk mutagenicity assays, with or without metabolic activation; and
- it induced chromosome aberrations in Chinese hamster lung (CHL) cells, with or without metabolic activation; and it gave mixed results in Chinese hamster ovary (CHO) cells, depending on the incubation method.

The chemical was negative in several in vivo assays in mice. It did not induce DNA damage in the forestomach and liver of rats orally administered the chemical once, up to 400 mg/kg bw, and failed to induce sister chromatid exchange (SCE) or chromosomal aberrations in mouse splenocytes at doses up to 1000 mg/kg bw in vivo (IARC, 1999; OECD, 2004; US EPA, 2007; REACH).

In an in vivo micronucleus study (OECD TG 474), BALB/c mice were intraperitoneally (i.p.) administered the chemical at 0, 461 or 738 mg/kg bw (corresponding to 80 % of a previously determined mean lethal dose). The bone marrow cells were collected at 24, 48 and 72 hours post application. No significant increase in the incidence of micronucleated polychromatic erythrocytes (MPE) was observed in the treated animals. Statistically significant depression in erythropoiesis occurred in high dose males (at all time points) and in females (after 48 hours) (OECD, 2004).

The chemical gave negative results in a sex-linked recessive lethal test in *Drosophila melanogaster* at a concentration of 40000 ppm (164 mg/L) (REACH).

Carcinogenicity

Based on the available data, the chemical may have some potential for carcinogenicity following oral exposure. However, the available information is not sufficiently conclusive to warrant hazard classification. Forestomach tumours in animals were only reported following long-term oral exposure to high concentrations of the chemical (e.g. at 200 mg/kg bw/day for 12 months). These effects were reported as due to marked localised irritation and cellular proliferation (NTP, 2014).

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on no epidemiological data relevant to carcinogenicity in humans, but sufficient evidence for carcinogenicity in animals (IARC, 1999). The chemical was reported to be scheduled for re-evaluation by IARC (OECD, 2004), and final conclusions have yet to be reached.

In a combined chronic toxicity/carcinogenicity study (OECD TG 453), F344 rats and B6C3F1 mice were exposed to the chemical vapour at 0, 25, 75 or 225 ppm (0, 0.10, 0.31 and 0.92 mg/L) for six months (highest dose) or 27 months for the other two doses. Exposure at the highest dose was terminated at six months due to a significant decrease in body weight gain. All animals were examined for gross lesions. No increase in tumour incidences was observed. Histopathological lesions in the olfactory epithelium with hyperplasia and metaplasia were observed in all animals after six months. Increased incidence of thyroid adenomas was observed in the highest-dosed male mice but it was within the historical control range and, therefore, reported as non-treatment related (OECD, 2004; HSDB).

In a two-year carcinogenicity study, F344/N rats and B6C3F1 mice (n = 50/sex/dose) were administered the chemical in corn oil by gavage at doses of 0, 100, or 200 mg/kg, five days/week. Both dose levels induced squamous cell papillomas and squamous cell carcinomas of the forestomach at the exposure site. No systemic toxicity was observed. The observed effects were attributed to the amount of the chemical delivered to the target tissue, rather than to systemic effects in the whole animal (NTP, 1986).

In an oral carcinogenicity study, rats were treated with the chemical in corn oil at a dose of 200 mg/kg bw/day, five days/week for six or 12 months. Histopathological evaluation was limited to the forestomach. No treatment-related neoplastic lesions were observed in the forestomach of rats administered the chemical for six months. After 12 months, hyperplastic lesions were observed in all rats and after a nine-month recovery period, squamous cell carcinomas (3/13) and papillomas (1/13) of the forestomach were observed at the site of application (IARC, 1999; OECD, 2004; REACH). Several other two-year animal gavage studies of the chemical in corn oil showed forestomach carcinogenicity as the only treatment-related neoplastic effect (OECD, 2004; HSDB).

A re-evaluation of the histological preparations of the forestomach of rats confirmed that ethyl acrylate was carcinogenic for the forestomach when administered via a tube as a 4 % solution in corn oil. No significant increase in squamous cell carcinomas was reported in other dose groups of rats (OECD, 2004).

The report by the National Toxicology Program (2014) recommended that ethyl acrylate be delisted from the 'Report on Carcinogens' (which contains substances 'either *known* or *reasonably anticipated to be human carcinogens'*) because the ‘relevant data are not sufficient to meet the current criteria to list this chemical *as reasonably anticipated to be a human carcinogen*’. The NTP concluded that the forestomach tumours in animal studies following oral exposure appeared to be attributed to marked localised irritation and cellular proliferation, and occurred only when the chemical was administered at high concentrations. Significant human oral exposure to high concentrations of the chemical (as a monomer) is unlikely. Inhalation studies in animals did not result in treatment-related neoplastic lesions (NTP, 2014).

Reproductive and Developmental Toxicity

Based on the limited data available, the chemical is not considered to have reproductive or developmental toxicity.

No reproductive toxicity studies are available. The reproductive organs were examined in repeated dose oral and inhalation studies in rats and mice, and no effects were observed (see **Repeat dose toxicity**).

Two developmental toxicity studies are available in rats. In an inhalation study, Sprague Dawley (SD) rats (n = 17–19/dose) were exposed to the chemical vapour at concentrations of 0, 25, 50, 100 or 200 ppm (0, 0.10, 0.21, 0.41 or 0.82 mg/L) on gestation days (GD) 6–20. No maternal deaths occurred. At the highest concentration, there was a significant decrease in maternal and foetal body weights. The numbers of implantation sites, live foetuses, non-live implants and resorptions, and the

foetal sex ratio were not affected. No treatment-related increases in embryo/foetal lethality or foetal malformations (external, visceral or skeletal) were observed. The NOAEL for maternal and foetal toxicity was established as 100 ppm (0.41 mg/L), and the NOAEL for developmental toxicity was >200 ppm (0.82 mg/L) (OECD, 2004; US EPA, 2007).

In an oral exposure study, Wistar rats (n = 10–23/dose) were administered the chemical by oral gavage, at doses of 25, 50, 100, 200, or 400 mg/kg bw/day on GD 7–16. The NOAEL was 50 mg/kg bw/day based on a significant increase in resorptions at ≥100 mg/kg bw/day. There were no significant decreases in the number of live foetuses. A non-dose related delay in ossification was observed in all dose groups. It was reported that 'A final evaluation of a possible embryotoxic effect cannot be assumed from the observed maternal toxicity' as maternal weight loss and food consumption were not recorded (OECD IUCLID, 2005; HSDB).

Other Health Effects

Neurotoxicity

A few acute and repeated dose toxicological studies in animals indicate neurotoxic effects such as lethargy, passiveness and ataxia at acute lethal oral and dermal doses in rats. Piloerection, tremor and hunched posture in rats following acute inhalation exposure at ≥6.1–8.9 mg/L were reported. In repeated dose studies in rats, reduced activity at ≥450 mg/kg bw/day (oral) and lethargy at ≥225 ppm (0.92 mg/L) (inhalation) were reported (OECD, 2004; HSDB; REACH).

In humans, repeated inhalation exposure to the chemical at concentrations of 50–75 ppm (0.2–0.3 mg/L) was reported to cause drowsiness, headache and nausea (US EPA, 2007).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (skin sensitisation; eye, skin and respiratory irritation); and
- systemic acute effects through oral, dermal and inhalation exposure.

The chemical could have some potential for carcinogenicity through oral exposure to high doses.

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemical was reported to be used overseas in floor and shoe polishes, sealants, binders and as a fragrance adjuvant in consumer products (concentrations not specified). Given the low concentrations at which respiratory irritation occurs, it is considered that high concentrations of the chemical would render the products unmarketable; therefore, long-term or high-level inhalation exposure is not expected.

The public could come into contact with articles/coated surfaces containing the chemical. It is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore, the chemical is not considered to pose an unreasonable risk to public health from its use in articles/coated surfaces.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. 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 health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals 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.

Considering a concentration of 4 ppm has been identified for respiratory irritation in humans, the current Australian exposure standard (5 ppm) might not be adequate to mitigate the risk of adverse effects and could require reconsideration.

NICNAS Recommendation

It is recommended that Safe Work Australia consider whether current controls adequately minimise the risk to workers. A Tier III assessment may be necessary to provide further information about whether the current exposure controls offer adequate protection to workers. All other human health risks are considered to have been sufficiently assessed at the Tier II level.

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	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	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)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from 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 chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, 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 chemicals.

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 this chemical has not been undertaken as part of this assessment.

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Last update 24 April 2015

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