Acetic acid, ethenyl ester: 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.

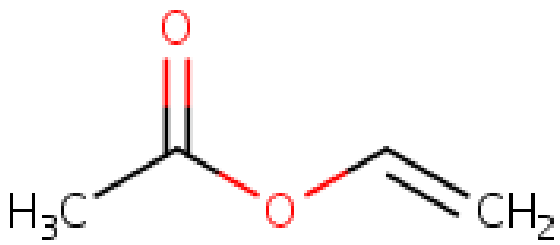
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	acetic acid, vinyl ester ethenyl acetate vinyl acetate 1-acetoxyethylene
Structural Formula	
Molecular Formula	C4H6O2
Molecular Weight (g/mol)	86.0894
Appearance and Odour (where available)	Clear, colourless liquid
SMILES	C(C)(=O)OC=C

Import, Manufacture and Use

Australian

The chemical has reported commercial or domestic uses in:

- automotive products;
- adhesives; and
- paints, lacquers and varnish.

The chemical is listed on the 2006 HVICL with industrial use at a reported volume of 1000–9999 tonnes (NICNAS, 2006).

The chemical is available for non-industrial use in Australia.

The chemical is not listed on the National Pollutant Inventory (NPI) in Australia.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Public Health Service Agency for Toxic Substances and Disease Registry (ATSDR, 1992); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); Patty's Toxicology (John Wiley & Sons, 2001); and the US Household Products Database.

The chemical has reported use in cosmetics and personal care products (ECHA, INCI, Galleria). However, cosmetic use in the European Union (EU) under Reg (EU) 944/2013 has been prohibited from January 1, 2015 (CosIng).

The chemical has reported domestic uses, including in:

- paints, lacquers and varnishes;
- cleaning agents (SPIN);
- adhesives;
- writing ink (SPIN); and
- sealants.

Although the chemical has reported domestic uses in the SPIN database, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical.

Domestic use identified overseas may include products containing a concentration of the chemical up to 67 % in a home maintenance paste (US Household Products Database). However, available data suggest that most products contain 1 % or less; glues/adhesives (0-1 %), foam sealants (0.1-2 %), or paints/varnish/primer (0.1-0.5 %) (US Household Products Database).

The chemical has reported commercial uses, including:

- in construction materials;
- in adhesives/glue;

- as an antifouling agent;
- in printing ink;
- in formulation of mixtures;
- engine oil;
- in repackaging; and
- in textile treatment and dyes (ECHA, SPIN, Galleria).

The chemical has reported site-limited uses, including:

- in the manufacture of safety glass; and
- as an intermediate in plastic production.

The chemical has reported non-industrial use as a modifier of food starch.

Restrictions

Australian

No known restrictions have been identified.

International

Using the chemical in the European Union (EU) is subject to the restriction described in EU Regulation No 944/2013, which prohibits the use of the chemical in cosmetics and personal care products from 1 January 2015 (CosIng).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is listed on the Safe Work Australia (SWA) Hazardous Substances Information System (HSIS) with the risk phrase 'Highly Flammable' (R11). No human health based risk phrases have been assigned to the chemical (HSIS).

Exposure Standards

Australian

The chemical has an exposure standard of 35 mg/m^3 (10 ppm) time weighted average (TWA) and 70 mg/m^3 (20 ppm) short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):

- 10 mg/m^3 TWA and 15 mg/m^3 STEL in China;
- US American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLV) of 10 ppm TWA and 15 ppm STEL;
- US National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs) of 15 mg/m^3 (4 ppm);
- a limit value (8 hours) of 17.6 mg/m^3 (5 ppm) and a short term limit value of 35.2 mg/m^3 (10 ppm) in the EU list of Indicative Occupational Exposure Limit Values (IOELVs);
- 35 mg/m^3 (10 ppm) TWA and 53 mg/m^3 (15 ppm) STEL in Abu Dhabi, and the United Arab Emirates;
- 10 ppm TWA and 15 ppm STEL in Canada and Uruguay;
- 30 mg/m^3 (10 ppm) TWA and 60 mg/m^3 (20 ppm) STEL in Argentina;
- 30 mg/m^3 (10 ppm) Occupational Exposure Limit (OEL) and 60 mg/m^3 (20 ppm) OEL-STEL in South Africa; and
- 35 mg/m^3 (10 ppm) TWA and 70 mg/m^3 (20 ppm) STEL in New Zealand.

Health Hazard Information

Toxicokinetics

The chemical undergoes hydrolysis to form acetaldehyde and acetic acid. The available data indicate that this process can occur spontaneously in vitro, or can be completed by enzymes (as demonstrated by in vitro experiments using human plasma, isolated esterase enzymes, rat plasma, rat liver microsomes and rat lung microsomes) (Simon et al., 1985).

Results from a study in rats exposed to the chemical (as a vapour) for 1.4 hours or less indicated that either the uptake or metabolism of the chemical may be a saturable process (non linear kinetics). As the vapour levels of the chemical reduced, there was a transient increase in the amount of acetaldehyde, confirming acetaldehyde as a metabolite of the chemical. The total clearance of the chemical was estimated to be 30 000 mL/h/kg bw, which was similar to the maximum ventilation rate in rats of 32 000 mL/h/kg bw. Based on this similarity, it was reported that the metabolic rate is largely determined by the uptake of the chemical from the respiratory system (Simon et al., 1985).

Distribution of the chemical was investigated in rats following oral or inhalation exposure, using whole body autoradiograms. Results showed wide distribution of the chemical in tissues, with visible concentration in Harderian and salivary glands. The highest amount of radioactivity was excreted in expired air (as CO_2), with lesser amounts excreted in urine and faeces. During the first 12-24 hours, 75 % of the radioactivity was eliminated (ACGIH, 2001).

Acute Toxicity

Oral

The chemical has low acute oral toxicity based on results from studies conducted in rats.

The median lethal dose (LD50) values in rats ranged from 2500-3500 mg/kg bw. The LD50 in mice is reported as 1600 mg/kg bw (RTECS, REACH).

Symptoms of intoxication in rats at a high dose (8 mL/kg bw) included sluggish behaviour (REACH). Other sources report that the chemical can have a narcotic effect at high concentrations (John Wiley & Sons, 2001). In one rat study using tragacanth as a vehicle, symptoms of intoxication following oral dosing included dyspnoea, tremors, apathy and diarrhoea (REACH).

Dermal

The chemical has low acute dermal toxicity in rabbits.

In two studies in rabbits, the dermal LD50 values are reported to be 2335 or 7440 mg/kg bw (RTECS, REACH). One study reported symptoms of intoxication in rabbits with convulsions, vocalisation, and inwardly turned pupils. Skin observations included erythema, oedema and necrosis (REACH).

Inhalation

The chemical (as a vapour) has moderate acute inhalation toxicity in rats (based on the available data), warranting hazard classification.

The 4-hour median lethal concentration (LC50) in rats exposed (whole body) to the chemical vapour is reported to be 4490 ppm (approximately 15810 mg/m^3)(REACH).

The following 4-hour LC50 values are reported in animals (ATSDR, 1992; RTECS):

- 2500 - 2760 ppm in rabbits;
- 5210 - 6200 ppm in guinea pigs;
- 1460 - 1500 ppm in mice; and
- 4650 - 3680 ppm, and 11400 mg/m^3 in rats.

Symptoms of toxicity prior to death included laboured breathing and clonic convulsions (ATSDR, 1992). Study details are not available.

The chemical has a harmonised classification in the EU (Harmful if inhaled) (ECHA).

Corrosion / Irritation

Respiratory Irritation

Based on the available information, the chemical is considered to be a respiratory irritant, warranting hazard classification.

The chemical has a harmonised classification for respiratory irritation in the EU (REACH). There is some evidence of respiratory irritation in humans exposed to the chemical vapour (refer to **Observation in Humans** below).

Additional supporting information for respiratory irritation include the necropsy results from an acute inhalation study in rats that showed congested lungs at the mid dose of 4000 ppm and haemorrhagic lungs and white froth in the trachea at the high dose of 8000 ppm. Also, in a developmental study (via inhalational exposure) in rats, lung congestion in dams was reported (REACH).

In short-term inhalation studies conducted using the chemical, animals showed symptoms, such as laboured breathing or respiratory distress, that may be due to respiratory irritation (REACH). A summary of relevant findings is included below (see **Repeat Dose Toxicity** for additional details).

In an inhalation exposure study, male Sprague Dawley (SD) rats were exposed to the chemical on either one, five or 20 occasions (for six hours per day, five days per week) at doses of 0, 50, 200, 600 or 1000 ppm as a vapour via whole body exposure. No clinical signs of toxicity were reported. No treatment-related findings were recorded at gross necropsy. There was a dose related increase in the severity of microscopic lesions in the olfactory epithelium of rats receiving doses of 600 ppm and above. Following a single exposure, degeneration, necrosis and exfoliation of olfactory epithelial cells were observed (REACH).

In three-month inhalation studies conducted in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress, hunched posture and ruffled fur. Increased lung weight observed in high dose animals (rats and mice) was attributed to lung congestion arising from respiratory irritation. Treatment-related lesions were observed in the lungs, trachea and nasal epithelium of high dose mice at necropsy (REACH).

In a four week repeat dose inhalation studies in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress (REACH).

Skin Irritation

The available data indicate that the chemical may cause slight skin irritation.

In a study conducted with three rabbits (OECD Test Guideline (TG) 404), the chemical (0.5 mL undiluted) caused slight irritation in two animals at the 24-hour observation. Signs of irritation persisted in one animal at the 48-hour observation, and no irritant effects were recorded at the 72-hour observation (individual mean scores were 0.67, 0.33 and 0 for erythema and zero for oedema in all animals) (REACH). The chemical may cause slight skin irritation.

Six rabbits exposed to the chemical (0.5 mL undiluted) for four hours (non-guideline study) showed stained skin which did not allow scoring for erythema. Each rabbit had two test sites, one intact site and one abraded site. Staining affected 4/6 rabbits at the 24-hour observation, with 1/6 rabbits still affected at the 72-hour observation. A subdural haemorrhage was observed in 1/6 rabbits at the 72-hour observation. The chemical was reported as not corrosive (REACH).

In another (non-guideline) study, five rabbits exposed to 0.01 mL of undiluted chemical on clipped intact skin for 24 hours showed no irritation effects (REACH).

Eye Irritation

The chemical may cause slight eye irritation. Although workers exposed to the chemical vapour were reported to show eye irritation (refer to **Observation in Humans** below), the information available is not sufficient to warrant hazard classification.

In a study conducted with three rabbits (OECD TG 405), slight irritation effects were observed at one and 24 hours after instillation of the chemical (0.1 mL undiluted). The mean individual score (24, 48 and 72 hours) for conjunctival redness for each animal was 0.33. There were no corneal or iridial effects observed. No irritation was observed at the 48-hour observation (REACH).

Following a single instillation of the chemical (0.5 mL undiluted) into the eye, corneal injury was assessed in five rabbits on a scale of 1-10. Corneal injury was present in four out of five rabbits (described as either trace or minor injury). Eye irritation was scored as two on the scale (1-10). The chemical was determined to be slightly irritating to the eyes (REACH).

Observation in humans

The chemical can cause irritation to the nose and throat following exposure via the inhalation route (ATSDR, 1992). Respiratory irritation was reported in volunteers exposed to the chemical at 19.4-71 ppm for 0.5-4 hours (ACGIH, 2001).

In workers exposed to the chemical at average levels of 5-10 ppm (with possible acute exposures of 300 ppm), irritation of the throat and eyes was reported at levels of 21 ppm, but eye irritation was not reported under 10 ppm (ACGIH, 2001).

Sensitisation

Respiratory Sensitisation

No data were available.

Skin Sensitisation

Based on the negative results observed for the chemical in a well conducted (OECD TG 429 compliant) local lymph node assay (LLNA), the chemical is not considered a skin sensitiser.

In an OECD TG 429 compliant LLNA using CBA/CaOlaHsd mice, the chemical was determined not to be a skin sensitiser. The stimulation index (SI) values for the chemical at the tested concentrations were 2 (5 % concentration), 2.4 (10 %), 1.9 (25 %), 1.7 (50 %), and 1.3 (100 %). Signs of skin irritation were not observed during the irritation screen; however, slight to moderate ear swelling was observed during the main test which may indicate increased potential for skin irritation caused by the chemical with repeated dosing (REACH).

Some skin sensitisation potential was reported in a study using methodology similar to OECD TG 406 (Buehler assay method; except with nine induction doses using the undiluted chemical), where the chemical tested positive (minimum positive response of 15 %; only 3/20 animals showed a sustained response over 48h at challenge) for skin sensitisation in Hartley guinea pigs following challenge with the chemical at a concentration of 25 % in acetone (REACH).

The methodology used in this study (i.e. nine inductions) would likely maximise any potential for sensitisation of the chemical compared with the Buehler protocol but only resulted in the minimum positive response level for the Buehler protocol. The LLNA result is considered to be the more reliable indicator of the skin sensitisation potential of the chemical.

Repeated Dose Toxicity

Oral

The chemical is not considered to cause severe effects following repeated oral exposure.

In a 92-day study, groups of male BDF1 mice and male Fischer 344 (F344) rats (n = 20/species/dose) were administered the chemical at doses of 0, 1000, 5000, 10000 or 24000 ppm in drinking water (approximately 0, 81, 350, 660 or 1400 mg/kg bw/day in rats and 0, 250, 1200 2300 or 5300 mg/kg bw/day in mice). There were no deaths during the study and no clinical signs of toxicity were observed in rats or mice. Statistically significant reductions in body weight and body weight gains were observed in rats at 5000 ppm and above, but not in mice. There were no treatment-related gross or microscopic lesions in the oral cavity, oesophagus or forestomach of high dose rats or mice, and no observations of cytotoxicity, hyperplasia or hypertrophy were reported (Valentine et al., 2002).

In a three-month study (OECD TG 408), CD rats (n = 40/sex/dose) were administered the chemical at doses of 0, 200, 1000 or 5000 ppm in drinking water (approximately 0, 31/36, 163/193 or 684/810 mg/kg bw/day in males/females). Excretion of darker urine (more concentrated) was observed in high dose females. The no observed adverse effect level (NOAEL) of 5000 ppm (approximately 684/810 mg/kg bw/day in males/females) was reported due to the absence of adverse toxic effects at the highest dose tested (REACH).

In another three-month study (OECD TG 408), CD-1 mice (n = 40/sex/dose) were administered the chemical at doses of 0, 200, 1000 or 5000 ppm (approximately 0, 11.4/11.2, 57/56, or 285/281 mg/kg bw/day) in drinking water. The NOAEL in the study was 5000 ppm (approximately 285/281 mg/kg bw/day in males/females) due to the absence of adverse toxic effects at the highest dose tested (REACH).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is not considered to cause severe systemic effects following repeated inhalation exposure, apart from causing histopathological changes in the olfactory epithelium and respiratory system, which are considered possible evidence of precursor events to tumour formation (see **Carcinogenicity)**.

Repeated inhalation exposure to the chemical can result in symptoms consistent with respiratory irritation and inflammation (REACH).

In a three-month study, SD rats (n = 10/sex/dose) were exposed (whole body) to the chemical vapour at concentrations of 0, 50, 200 or 1000 ppm for six hours per day, five days per week. There were no treatment related deaths during the study. Clinical signs of toxicity were confined to the high dose group and consisted of intermittent symptoms of respiratory distress, hunched posture and ruffled fur. Increased lung weight observed in high dose animals was attributed to lung congestion arising from respiratory irritation. The no observed effect concentration (NOEC) was determined to be 200 ppm (approximately 704 mg/m^3), based on observed effects at the highest tested dose (REACH).

In another three-month study, CD-1 mice (n = 10/sex/dose) were exposed (whole body) to the chemical vapour at concentrations of 0, 50, 200 or 1000 ppm for six hours per day, five days per week. Clinical signs of toxicity included hunched posture (200 ppm and above) and intermittent respiratory symptoms (200 ppm group up to study day nine), respiratory distress (high dose) and ruffled fur (high dose only). Increased lung weight observed in high dose animals was attributed to lung congestion arising from respiratory irritation. Treatment-related lesions were observed in the lungs, trachea and nasal epithelium of high dose mice. The no observed adverse effect concentration (NOAEC) was determined to be 200 ppm (approximately 704 mg/m^3), based on no pathological changes despite initial symptoms of respiratory irritation at this dose level (REACH).

Rats and mice exposed to the chemical vapour up to 1500 ppm for four weeks showed intermittent symptoms of respiratory distress and hunched posture. Some animals had significantly reduced spleen weights compared with controls (REACH). Male SD rats (n = 5/dose) exposed to the chemical vapour on either one, five or 20 occasions (six hours per day, five days per week) at concentrations of 0, 50, 200, 600 or 1000 ppm showed a dose-related increase in the severity of microscopic lesions in the olfactory epithelium at 600 and 1000 ppm. With repeated doses, there was evidence of post necrotic repair and adaptation; regenerative hyperplasia of the epithelium; and attenuation and/or disorganisation of the mucosa. Degeneration and atrophy of the nerve bundles in the olfactory lamina propria were observed after 20 exposures. High dose animals receiving five or 20 doses showed areas of squamous metaplasia in the olfactory epithelium. A NOAEC was determined as 200 ppm (approximately 704 mg/m^3) based on histopathological changes to the olfactory epithelium at the next highest dose (REACH).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical may have genotoxic potential, warranting hazard classification.

Although in vitro assays utilising bacterial cells have shown negative results for mutagenicity, positive results have been obtained using mammalian cells (in vitro and in vivo), particularly for chromosome effects (ACGIH, 2001; IARC, 1995; Norppa et al., 1985; REACH). It has been hypothesised that the genotoxicity of the chemical may be attributable to the formation of acetaldehyde, although the lowering of cell pH that occurs when large doses of the chemical are metabolised to acetic acid may also be a contributing factor (Albertini, 2013).

The chemical vapour tested negative for mutagenicity in *Salmonella typhimurium* strains TA 98, 100, 1535 and 1537, in the presence or absence of metabolic activation. The chemical also tested negative when used as a liquid in *S. typhimurium* strains TA98, 100, 1535, 1537 and 1538, with or without metabolic activation (ACGIH, 2001).

All other in vitro assays showed positive results with the chemical:

- a dose-dependent and statistically significant increase in sister chromatid exchange (SCE) was observed in human lymphocytes (whole blood culture) following 48 hours' exposure to concentrations of 0.1 mM of the chemical and above. A dose-dependent increase in chromosome aberrations was also observed; an increased number of aberrant cells (gaps included or excluded), number of cells carrying chromatid-type aberrations or chromatid-type exchanges was statistically significant at 0.5 mM (Norppa et al., 1985);

- a dose-dependent increase in SCE was observed in Chinese hamster ovary (CHO) cells following 24 hours' exposure to the chemical at doses of 0.125-1 mM or four hours' exposure to the chemical at doses of 0.3-5 mM (Norppa et al., 1985);

- induced DNA cross links in isolated human lymphocytes and rat nasal epithelial cells at 860 µg/mL (IARC, 1995);
- produced increased numbers of micronuclei in human lymphoblastoid cells (TK6) following a 4-hour exposure to concentrations of 0.25, 0.5, 1 or 2 mM in a micronucleus assay (a similar protocol to OECD TG 487). Acetaldehyde, a metabolite of the chemical, was also found to be positive in this same assay at concentrations of 0.25, 0.5 and 1 mM acetaldehyde (REACH);
- induced an increase in chromosome aberrations in human whole blood and isolated human lymphocytes following 24 hours' exposure (similar to OECD TG 473) to concentrations of 0.25, 0.5, 1 or 2 mM, without metabolic activation (REACH); and

Four in vivo genotoxicity studies are available for the chemical, three showing positive results (REACH):

- Germ cells were analysed in C57B1 mice which received a single intraperitoneal (i.p.) injection of the chemical at 0, 250, 500, 750 or 1000 mg/kg bw or acetaldehyde at 0, 125, 250 or 375 mg/kg bw, 13 days after the treatment (non-guideline study). Both compounds did not induce meiotic micronuclei;
- A dose-dependent increase in micronuclei was observed in C57BL mice that received an i.p. injection of the chemical at 0, 250, 500, 1000 or 2000 mg/kg bw (similar to OECD TG 474). Increases were statistically significant at the two high doses, which caused increased mortality;
- There was an increased frequency of chromosomal aberrations in cultured lymphocytes of humans following occupational exposure (IARC, 1995). No additional details were available; and
- Male mice that received the chemical for five days at 0, 125, 250, 500 or 750 mg/kg bw/day via i.p. injection showed effects on testicular weight (reduced at 125 and 500 mg/kg bw/day), sperm count (decreased with increased dosing) and morphology (five weeks after treatment 3/7 had sperm abnormalities at 500 mg/kg bw/day). One mouse (1/5) survived at the highest dose, and showed an increased level of abnormal sperm.

Carcinogenicity

The available animal data indicate that the chemical has carcinogenic potential, warranting hazard classification. The available human evidence is not sufficient to warrant a higher hazard classification.

The chemical was classified as 'possibly carcinogenic to humans (Group 2B)' by the International Agency for Research on Cancer (IARC) in 1995. The IARC classification was based on limited evidence in experimental animals, although the evidence in humans was considered to be insufficient to establish carcinogenicity (IARC, 1995). The chemical has a harmonised GHS classification in the EU as a Category 2 carcinogen (suspected of causing cancer).

Groups of mice (Swiss derived strain) and SD rats (n = 60/sex/dose) exposed (via inhalation) to the chemical at 0, 50, 200 or 600 ppm, six hours per day, five days per week, for 104 weeks showed evidence of carcinogenicity. One lung squamous cell carcinoma was reported in a high dose male mice. Several non-neoplastic lesions in mice were reported in the respiratory tract (olfactory epithelium atrophy, respiratory metaplasia, squamous metaplasia of respiratory epithelium in nasal cavity, tracheal epithelial hyperplasia). There was an increased incidence of squamous cell carcinoma in the nasal cavity in high dose female rats (4/59) compared with controls. There was a statistically significant increase in the total number of nasal tumours (benign and malignant) in high dose male rats. Non-neoplastic observations in rats included thinning of the olfactory epithelium of the nasal cavity, accompanied by basal cell hyperplasia (IARC, 1995).

Repeated dose inhalation studies in rats showed microscopic findings that may be precursors of carcinogenicity (see **Repeat Dose Toxicity - Inhalation)**.

Groups of F344 rats (n = 20/sex/dose) that received the chemical at doses of 0, 1000 or 2500 mg/L in drinking water for 100 weeks showed treatment-related increases in the incidence of liver neoplastic nodules (both sexes), uterine adenocarcinomas (females) and thyroid C-cell adenomas (females) (IARC, 1995).

Other carcinogenicity studies have been published after the IARC evaluation of the chemical. Groups of Crj:BDF1 mice and F344/DuCrj rats (n = 50/sex/group) administered the chemical at doses of 0, 400, 2000 or 10000 ppm in drinking water (approximately 0, 42/63, 202/301 or 989/1418 mg/kg bw/day for male/female mice and 0, 21/31, 98/146 or 442/575 mg/kg bw/day for male/female rats) for 104 weeks showed statistically increased incidences of squamous cell carcinoma at the high dose (in the oral cavity of mice, and oesophagus and forestomach of male rats) (Umeda et al., 2004). The chemical

administered to Wistar rats (for 104 weeks) and Swiss mice (for 78 weeks) at concentrations of 0, 1000 or 5000 ppm in drinking water showed statistically significant increases in the percentage of animals with malignant tumours at the high dose (cancers in the oral cavity, tongue, oesophagus and forestomach, and upper gastrointestinal tract). High dose female mice also showed tumours in the uterus (Soffritti et al., 2008).

In a cohort study of 4806 men employed at a chemical manufacturing plant in the US between 1942-1973, the cohort had an excess risk of cancer (as compared to national rates) in the respiratory system. One subgroup, with undifferentiated large-cell lung cancer, had higher exposure to vinyl acetate (IARC, 1995).

A nested case-control study of a cohort of 29 139 people employed at a chemical manufacturing plant or a research centre in the US investigated individuals who had died between 1940-1978 from certain cancers (non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukaemia or non-lymphocytic leukaemia). Exposure to 21 chemicals including vinyl acetate was assessed. Potential exposure to vinyl acetate was reported for 7/52 deaths associated with non-Hodgkin's lymphoma, 3/20 deaths associated with multiple myeloma, 2/18 deaths associated with lymphocytic leukaemia and 2/39 deaths associated with non-lymphocytic leukaemia. The agency determined that the available data for carcinogenicity in humans was 'too limited to form the basis for an evaluation of the carcinogenicity of vinyl acetate to humans' (IARC, 1995).

Reproductive and Developmental Toxicity

The chemical is not considered to cause reproductive or developmental toxicity. Developmental effects in rats were only observed at maternally toxic doses.

In a two-generation reproduction study (similar to OECD TG 416), rats were administered doses of the chemical at 0, 200, 1000 or 5000 ppm in drinking water (approximately 0, 28, 140 or 700 mg/kg bw/day). There were no statistically significant effects on mating, fertility or gestation indices in the parents (F_0 generation). A decreased fertility index was observed in the 5000 ppm group of the first generation offspring (F_1 generation) (not statistically significant compared with controls). Mating and gestation indices for the F_1 generation were not affected by treatment. A cross mating trial (between control males and high dose females, and vice versa) was performed; fewer pregnancies occurred when treated males were mated with control females, although the fertility index was not affected. A NOAEL of 1000 ppm was established for reproductive toxicity (approximately 100 mg/kg bw/day) (REACH).

In an OECD TG 414 compliant developmental toxicity study, CD rat dams (n = 24/dose) were exposed (whole body) to the chemical (vapour) at concentrations of 0, 50, 200 or 1000 ppm for six hours per day on gestation days (GD) 6-15. High dose dams had a higher incidence of lung congestion compared with controls. No significant effects on embryotoxicity parameters were observed. Mean litter weight, foetal weight and foetal crown/rump length were significantly lower in the high dose group. A significantly increased incidence of skeletal variations (reduced ossification) was observed in the high dose group, and was consistent with delayed development as a result of observed maternal toxicity at the same concentration. The NOAEC for developmental and maternal toxicity was reported as 200 ppm (approximately 205 mg/kg bw/day) (REACH).

In another OECD TG 414 compliant developmental toxicity study, CD rat dams (n = 24/dose) received the chemical at doses of 0, 200, 1000 or 5000 ppm via drinking water (approximately 0, 28, 124 or 477 mg/kg bw/day) on GD 6-15. No dams died during the study. No significant embryotoxicity was seen. There were no treatment related effects on foetal parameters. The NOAELs were established as 1000 ppm (approximately 124 mg/kg bw/day) for maternal toxicity and 5000 ppm (approximately 477 mg/kg bw/day) for foetal toxicity (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (respiratory irritation);
- systemic acute effects from inhalation; and

- systemic long-term effects (carcinogenicity and mutagenicity).

Public Risk Characterisation

The chemical has domestic uses identified in Australia in automotive products, adhesives, paints, lacquers and varnish. No use concentrations of the chemical in these products are available. Domestic use identified overseas may include products containing a concentration of the chemical up to 67 % in a home maintenance paste (US Household Products Database). However, available data suggest that most products contain 1 % or less; glues/adhesives (0-1 %), foam sealants (0.1-2 %), or paints/varnish/primer (0.1-0.5 %) (US Household Products Database).

Whilst use in cosmetics and personal care products overseas has been identified, potential use in cosmetics and personal care products in Australia is unknown. Recently, the chemical was prohibited for use in cosmetics in the EU (CosIng).

The chemical may also be present in consumer articles manufactured from plastics, but the chemical is not expected to be released from these items and is therefore not considered to pose an unreasonable health risk to the general public.

There are no restrictions in Australia on using this chemical in cosmetics or domestic products. In the absence of regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

Given the critical local effects, systemic acute and long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 hazard classification of the chemical (refer to **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to the Poisons Standard, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and Poisons Standard legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in domestic and cosmetic products. Due to the toxicity profile, the chemical is recommended for scheduling in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) to restrict or prohibit its use in domestic and cosmetic products.

Matters to be taken into consideration include:

- the known domestic uses of the chemical in Australia (in automotive products; adhesives, paints, lacquers and varnish);
- the chemical was used in cosmetics overseas and has been prohibited from January 2015 (CosIng) (see **International restrictions**).

- the chemical is a respiratory irritant and may have potential to cause genotoxicity and carcinogenicity.

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 by inhalation (Xn; R20)	Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to respiratory system (Xi; R37)	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

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

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

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

Advice for 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 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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