Ethene, 1,1-dichloro-: 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.

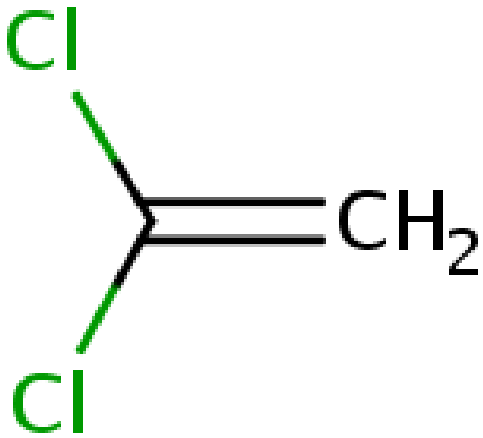
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,1-dichloroethene 1,1-DCE vinylidene chloride
Structural Formula	
Molecular Formula	C2H2Cl2
Molecular Weight (g/mol)	96.9
Appearance and Odour (where available)	colourless liquid or gas with mild, sweet, chloroform-like odour
SMILES	C(=C)(Cl)Cl

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the OECD High Production Volume chemical program (OECD HPV);
- the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR);
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB);
- National Toxicology Program (NTP, 2015) report;
- World Health Organisation (WHO, 2003) Concise International Chemical Assessment Document 51 (CICAD);
- the USA Environmental Protection Agency (EPA, 2002) Toxicological Review;
- Environment and Health Canada (Health Canada, 2013) report; and
- the Agency for Toxic Substances & Disease Registry (ATSDR, 1994) report.

The chemical has reported commercial uses, including:

- as a solvent in paint and varnish remover;
- as a refrigerant; and
- as an industrial cleaning agent.

The chemical has reported site-limited uses in:

- organic synthesis;
- manufacturing piping and coatings for steel pipes; and
- production of flame retardant coatings for fibre and carpet backings.

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;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- 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 (acute toxicity); and
- R40 Carc. Cat 3 (carcinogenicity).

Exposure Standards

Australian

The chemical has an exposure standard of 20 mg/m^3 (5 ppm) time weighted average (TWA) and 79 mg/m^3 (20 ppm) short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 4–40 mg/m^3 TWA and 4–80 mg/m^3 (1-20 ppm) STEL/occupational exposure limit (OEL) in different countries such as the USA (Alaska, Hawaii), Canada (Ontario), Norway and Switzerland.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 20 mg/m^3 (5 ppm) TWA.

Health Hazard Information

Toxicokinetics

The chemical, 1,1-dichloroethene (1,1-DCE) is rapidly absorbed when administered via oral and inhalation routes. It is distributed throughout the body tissues within one hour of exposure. The primary target organs are the liver, kidneys and lungs

(Clara cells), where most of the free chemical and its metabolites are detected. Excretion of the unchanged chemical is mainly through the lungs and excretion of metabolites is mainly through urine (EHC, 1990; ATSDR, 1994; IARC, 1999; EPA, 2002; WHO, 2003; Health Canada, 2013; REACH).

In a toxicokinetics study in rats, 1,1-DCE in corn oil was administered at oral doses of $\leq$ 350 μg/kg bodyweight (bw). The chemical was completely absorbed from the gastrointestinal tract. It was easily distributed across the alveolar membrane, and equilibrium in the blood was reached in approximately 45 mins. The chemical is metabolised rapidly to non-volatile compounds including dithioglycolic acid and covalently bound derivatives (ATSDR, 1994; EPA, 2002; WHO, 2003).

In mice, 125 mg/kg bw of radiolabelled (^{14}C) 1,1-DCE administered by intraperitoneal (i.p.) injection showed covalent binding at high concentrations in the kidney, lung and liver. This covalent binding was correlated with the high concentration of CYP2E1 (an enzyme involved in metabolism of xenobiotics) in the kidney, lung and liver. It is reported that 1,1-DCE is metabolised more extensively in mice than in rats (ATSDR, 1994; EPA, 2002; WHO, 2003).

Acute Toxicity

Oral

The chemical, 1,1-DCE has moderate to high acute toxicity in mice and rats, with median lethal dose (LD50) values in the range of 194-1800 mg/kg bw. The toxicity of the chemicals in mice is higher than that in rats. The available data indicate that the chemical warrants hazard classification.

In a study in Fischer 344 (F344/N) rats and B6CF1 mice, 1,1-DCE was administered by gavage in corn oil at doses of 0, 10, 50, 100, 500 or 1000 mg/kg bw to five animals/sex/group for each species. All mice in the 1000 mg/kg bw group died after treatment, while for rats, 2/5 males died at this dose. At 500 mg/kg bw, mortalities were reported in 1/5 female rats, while in mice, mortalities were reported in 3/5 females and 5/5 males at this dose. The effects observed in the liver included an increase in liver enzymes, severe histopathological damage (disruption of bile canaliculi, cytoplasmic vacuolisation and haemorrhagic necrosis), an increase in covalent binding of the chemical and a decrease in the glutathione (GSH) levels. Histopathological changes in the kidneys included tubular dilation and necrosis of the proximal tubules, while depletion of GSH levels and covalent binding of the chemical were reported in the Clara cells of the lung. The range of LD50 values was reported to be 1500-1800 mg/kg bw for rats and 194-217 mg/kg bw for mice were reported (ATSDR, 1994; IARC, 1999; EPA, 2002; WHO, 2003; Health Canada, 2013; NTP, 2015; REACH).

Sublethal effects observed in two other studies in Sprague Dawley (SD) rats included dilatation and disruption of bile canaliculi, invagination of plasma membrane and loss of microvilli, cytoplasmic vacuolisation and loss of density in the mitochondrial matrices. A significant increase (approximately 75-fold) in aspartate aminotransferase, approximately 70-fold increase in alanine aminotransferase, 110-fold increase in lactate dehydrogenase and approximately 320-fold increase in sorbitol dehydrogenase were reported four to eight hours after exposure (EPA, 2002).

Dermal

No data are available.

Inhalation

The chemical, 1,1-DCE is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data (median lethal concentration—LC50—1.63 mg/L/4 hours in male rats) support this classification (ATSDR, 1994; DOW, 2002; EPA, 2002; WHO, 2003).

In an acute inhalation study conducted similarly to OECD Test Guideline (TG) 403, SD rats (10 animals/sex) were exposed to 1,1-DCE at concentrations ranging from 416—47,600 mg/m^3 as a whole body inhalation exposure for a 4 hour exposure duration. The animals were observed for 14 days after exposure. Observed sublethal signs included colourless eyes, reddish

nasal secretions, dyspnoea, apathy, crouched position, scrubby fur and anaesthesia. Clinical effects observed were acute ventricular contraction in the heart, pulmonary emphysema with bloody oedema, browned and widened periphery in the liver lobules and mild ascites in the kidney. The LC50 values were reported to be 1.63 and 26 mg/L for males and females respectively (EPA, 2002; WHO, 2003; REACH).

In a study conducted similarly to OECD TG 403, NMRI mice (10 or 20 animals/sex/dose) were exposed to 1,1-DCE vapours at concentrations in the range of 0.04—0.6 mg/L by whole body inhalational exposure for four hours. Clinical signs observed included apathy, dyspnoea, narcosis, shock, crouched position and closed eyelids. Gross pathological examination showed acute hyperaemia with acute dilation in the heart, acute emphysema with blood, isolated brightening in the kidneys and peripheral lobular pattern in the liver. Mortality was reported in all males administered doses ≥ 0.3 mg/L and in all females administered 0.5 mg/L and 0.6 mg/L. Fasting mice showed high sensitivity to the chemical. The LC50 value was reported to be 0.2 mg/L for males; and although an LC50 value of 0.5 mg/L for female mice was reported in this study, all females died at this dose (EHC, 1990; REACH).

In another inhalation study, male SD rats were exposed to 1,1-DCE at 0, 20, 250, 300, 375 or 400 ppm for 4 hours. Mortalities were reported in increasing order in all treated groups. Significant increases in kidney-to-body weight ratios, serum urea nitrogen and creatinine were reported at doses ≥ 250 ppm. Severe tubular necrosis with calcium deposits was seen at doses ≥ 300 ppm (EPA, 2002). No LC50 value was reported.

Corrosion / Irritation

Skin Irritation

Based on the available information, while the chemical is not expected to be corrosive to the skin, exposure may cause skin irritation. However, there is insufficient evidence to warrant hazard classification.

In an in vitro human skin model test (EST-1000), the corrosive potential of 1,1-DCE was tested at 50 µL volume per tissue for exposure durations of 3 minutes and 1 hour. Cell viability was reported to have decreased to 79 % after 3 minutes' exposure and to 53 % after 1 hours' exposure. These values did not reach the threshold of corrosivity of 50 % (3 minutes) and 15 % (1 hour). The chemical was not reported to be corrosive (REACH).

In a non-guideline study, 2 mL of undiluted chemical was applied to shaved skin on the back and on the ears of Vienna white rabbits (two animals/group) for one, five and 15 minutes' and 20 hours by occlusive patch. Slight redness, slight oedema, necrosis, superficial crust formation, weeping ears and desquamation were observed with one minutes' exposure on the back and following 15 minutes' exposure on the ears. These effects were not reversible within eight days (REACH).

Another in vitro study was conducted using reconstructed human epidermis (RhE) to assess the irritation potential of 1,1-DCE. A volume of 15 µL of the chemical was applied to each of the three tissues of the human skin model EpiSkin ^{TM} for 15 minutes' exposure. The cell viabilities of 96.6 % was reported after the treatment, hence the chemical was not reported to be a skin irritant (REACH).

Eye Irritation

The chemical is reported to be a moderate eye irritant in animal studies. The effects are sufficient to warrant hazard classification.

In an eye irritation study in freshly isolated bovine cornea (OECD TG 437), 0.75 mL of 1,1-DCE was placed on the surface of the cornea which was incubated at 32 ± 2 °C in a water bath for ten minutes. The chemical caused a slight increase in the opacity values with an in vitro score of 43.9 and was reported to be moderate eye irritant (REACH).

In other non guideline study, 50 µL of 1,1-DCE was instilled in one eye of two Vienna white rabbits with observation at 1 hour, 24 hours and 8 days. Slight irritation of the eyes (signs of redness and oedema) was observed at 1h, 24h and 7 days after exposue. After eight days, effects were fully reversed (REACH).

Sensitisation

Skin Sensitisation

Based on the available information, the chemical was not found to induce dermal sensitisation.

In a mouse local lymph node assay (LLNA), conducted similarly to OECD TG 429, female CBA mice (four animals/concentration) were exposed to 25µL doses of 1,1-DCE at 0, 10, 25 or 50 % for three exposures daily, for three consecutive days. The stimulation index (SI) values were calculated as 1, 0.84, 0.75 and 0.91 for the concentrations tested, respectively. No increases in the SI above three suggests that the chemical is not a dermal sensitiser (WHO, 2003; REACH).

Repeated Dose Toxicity

Oral

On repeated oral exposure to the chemical in rats and mice, the liver was the main target organ for toxicity. A lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day was reported. Based on the available data, hazard classification for repeated oral toxicity is not warranted.

In a study, male and female F344/N rats (five animals/sex/dose) were administered 1,1-DCE in corn oil at doses of 0, 10, 50, 100, 500 or 1000 mg/kg bw/day for 14 days. Mortality was reported as 3/10 and 7/10 in the 500 and 1000 mg/kg bw/day dose groups, respectively. Significant depression in the mean body weights of animals was reported at doses ≥ 500 mg/kg bw/day. Histopathological examination of the dead animals showed haemorrhagic necrosis in the liver (EPA, 2002; WHO, 2003; NTP, 2015; REACH).

In another study conducted according to OECD TG 408, groups of F344/N rats (10 animals/sex/dose) were administered 1,1-DCE in corn oil by gavage at doses of 0, 5, 15, 40, 100 or 250 mg/kg bw/day five times/week for 13 weeks (90 days). Mortality in three female rats in the 250 mg/kg bw/day dose group in the first week of treatment was reported and 20 % depression of weight gain was seen in males at this dose. Histopathological examination of the dead female rats showed severe centrilobular necrosis of the liver. Surviving rats in the 250 mg/kg bw/day group, sacrificed at the end of the study, showed minimal to moderate hepatocytomegaly. Other clinical effects observed in animals in this group included portal and subcapsular fibrosis, bile duct hyperplasia, pigmented macrophages and hepatocellular atrophy. Mild hepatocytomegaly was observed in 6/10 males and 3/10 females in the 100 mg/kg bw group. All treated showed varying degrees of fatty metamorphosis and/or cytoplasmic vacuolisation. The NOAEL of 40 mg/kg bw/day and a LOAEL of 100 mg/kg bw/day were reported (EPA, 2002; REACH).

In a 90-day study conducted similarly to OECD TG 408 in male and female B6C3F1 mice, a 10 mL/kg of 1,1-DCE in corn oil was administered (10 animals/sex/dose) by gavage at doses of 0, 5, 15, 40, 100 or 250 mg/kg bw/day, five times per week for 13-weeks (90 days). Mortality was reported in all male mice and in 9/10 female mice in the 250 mg/kg bw/day groups within 48 hours of study commencement. Two of ten males and 3/10 females in the 100 mg/kg bw/day also died before the end of the study. All treated males showed a dose-dependent decrease in mean body weight gains. Histopathological examination showed centrilobular necrosis, haemorrhage and congestion of the liver in the 250 mg/kg bw/day dose groups. Seven of ten males and 6/10 females in the 100 mg/kg bw/day dose group showed cellular atypia of the liver. The severity of hepatic lesions in all other dose-groups was dose-dependent and males showed higher susceptibility compared with females. Fatty metamorphosis and patchy foci with smaller cells and sparse cytoplasm were other effects observed. The NOAEL of 40 mg/kg bw/day and the LOAEL of 100 mg/kg bw/day were reported (EPA, 2002; REACH).

The chemical 1,1-DCE in peanut oil administered in beagle dogs by gavage at doses of 0, 6.25, 12.5 or 25 mg/kg bw/day for 97 days, did not result in significant effects on mortality, body weight, food consumption, haematology, urinalysis, organ weights and histology. No treatment-related effects were observed in the liver or kidneys. The NOAEL of 25 mg/kg bw/day was reported (EHC, 1990; EPA, 2002).

In a 2-year study, SD rats (48 animals/sex/dose) were administered the chemical in drinking water at doses of 7, 10 or 20 mg/kg bw for males and 9, 14 or 30 mg/kg bw for females. The effects observed in females at all doses included slightly increased cytoplasmic vacuolation of hepatocytes and hepatocellular fatty change. These effects were only observed in males at 20 mg/kg

bw/day dose. A NOAEL of 10 mg/kg bw/day for males and 9 mg/kg bw/day for female rats were reported. A LOAEL of 20 mg/kg bw/day for for males and 14 mg/kg bw/day for female rats were reported (EHC, 1990; REACH).

Dermal

No data are available.

Inhalation

On repeated inhalation exposure to the chemical in rats and mice studies, liver and kidneys were the main target organs for toxicity. Based on the available data, hazard classification for repeated inhalation toxicity is recommended.

In a 90-day study in Long Evans rats (15 animals/dose), SD rats (15 animals/dose), 1,1-DCE was administered at 0, 20, 61, 101, 189 or 395 mg/m^3 for eight hours per day, five days per week. No significant changes in mortality or haematological effects were observed. Significant increases in the serum alanine aminotransferase and liver alkaline phosphatase activities were reported in rats at 395 mg/m^3. Histopathological effects observed were liver damage including fatty metamorphosis, focal necrosis, haemosiderosis, lymphocytic infiltration, bile duct proliferation and fibrosis at 189 mg/m^3. Nuclear hypertrophy of the tubular epithelium was observed in the kidneys of all treated rats. A no observed adversed effect concentration (NOAEC) of 101 mg/m^3 was reported and a lowest observed adversed effect concentration (LOAEC) of 189 mg/m^3 was reported (EPA, 2002; WHO, 2003; Health Canada, 2013; REACH).

In a study, Charles River (CD-1) male mice were exposed to 1,1-DCE at 0, 15, 30 or 60 ppm for 22-23 hours/day for 1-5 days by inhalation. Significant increases in serum enzymes such as alanine aminotransferase and aspartate aminotransferase and tubular nephrosis were observed in male mice at doses ≥ 15 ppm and hepatocellular degeneration was observed in 1/5 mice after the first exposure (EPA, 2002).

In another study, CD male rats were exposed to 1,1-DCE at 0 or 60 ppm for 22-23 hours/day for 1-3 days by inhalation. Mild centrilobular degeneration and necrosis were observed in 2/5 male rats at 60 ppm. After the second exposure, significant increases in the serum enzymes were reported (EPA, 2002).

In a multi-species 90-day study in New Zealand White rabbits (three animals/sex/dose), Hartley guinea pigs (15 animals/dose), Beagle dogs (two animals/dose) and squirrel monkeys (three animals/dose), 1,1-DCE was administered at 0, 20, 61, 101, 189 or 395 mg/m^3 for eight hours/day, five days/week. No significant changes in the mortality and haematological effects were observed in dogs and rabbits. However, observed mortality in guinea pigs and monkeys was reported to be dose-dependent. Significant increases in the serum alanine aminotransferase and liver alkaline phosphatase activities were reported in guinea pigs at 189 or 395 mg/m^3. At 189 mg/m^3, liver damage including fatty metamorphosis, focal necrosis, haemosiderosis, lymphocytic infiltration, bile duct proliferation and fibrosis was reported in dogs and monkeys. A NOAEC of 101 mg/m^3 was reported as there were no adverse effects on liver and kidneys in any treated groups at ≥ 101 mg/m^3 and a LOAEC of 189 mg/m^3 were reported for all species (EPA, 2002; WHO, 2003; Health Canada, 2013; REACH).

In a 18-month study, SD rats (86 animals/sex/dose) were exposed to 1,1-DCE at doses of 0, 100 or 300 mg/m^3 by inhalation exposure for 1, 6, 12 and 18 months for six hours per day, five days per week. No treatment-related changes in mortality, body weight, appearance, clinical chemistry examination, urinalysis and haematological examinations were observed. All animals had hepatocellular fatty changes in the hepatic lobules after 6 to 12 months' exposure at both dose levels. The midzonal hepatocellular fatty changes were only reported in female rats, after an 18 month exposure. A NOAEL of 300 mg/m^3 for male rats and 100 mg/m^3 for female rats was reported (EHC, 1990; REACH).

Genotoxicity

Based on the available in vitro and in vivo genotoxicity studies, the chemical is not considered to have genotoxic potential (EHC, 1990; ATSDR, 1994; IARC, 1999; EPA, 2002; WHO, 2003; Health Canada, 2013; NTP, 2015; REACH).

In vitro

In an Ames test conducted according to OECD TG 471, *Salmonella typhimurium* strains TA 100 and TA 1530 were exposed to 1,1-DCE at concentrations up to $3.3x10^{-2}$ M. The chemical gave positive results in both strains in the presence of metabolic activation (EPA, 2002; WHO, 2003; Health Canada, 2013; NTP, 2015; REACH).

In a gene mutation assay, 1,1-DCE at concentration of 2.5 mM tested in *Escherichia coli (E.coli*) caused positive results in the presence of an external metabolic activation system (WHO, 2003; REACH).

In a DNA damage and/or repair test, conducted according to OECD TG 481, the chemical caused small increases in the number of revertants in *Saccharomyces cerevisiae* strains D7 and D61.N at concentrations up to 100 mM, both in presence and absence of metabolic activation (EHC, 1990; WHO, 2003; REACH).

In a mammalian gene mutation assay conducted according to OECD TG 476, 1,1-DCE gave negative results in Chinese hamster lung fibroblasts (V79) at concentrations up to 20 % (EHC, 1990; WHO, 2003; REACH).

The chemical caused positive results in a gene mutation study in mouse lymphoma L5178Y cells, both in presence and absence of metabolic activation (EPA, 2002).

The chemical, 1,1-DCE at concentrations of up to 2.0 mg/mL caused positive mutagenic activity with metabolic activation in a chromosome aberration test in Chinese hamster lung fibroblast (CHL) cells. A significant increase in the number of chromosomal aberrations in the presence of S9 was observed (EPA, 2002; WHO, 2003; Health Canada, 2013; REACH).

In vivo

In a micronucleus assay, 1,1-DCE in olive oil was administered once in pregnant female ICR mice (six animals /dose) by intraperitoneal injection at doses of 25, 50 or 100 mg/kg bw. The chemical was negative for genotoxicity (EPA, 2002; WHO, 2003; REACH).

In a dominant lethal assay conducted according to OECD TG 478, 1,1-DCE was tested in CD-1 mice (20 animals/sex/dose) at concentrations of 0, 10, 30 or 50 ppm. The chemical did not cause dominant lethal mutations in male CD-1 mice (EPA, 2002; WHO, 2003; REACH).

In another dominant lethal assay, 1,1-DCE produced negative results when tested in CD rats at 55 ppm by inhalation exposure for 11 weeks at six hours per day, five days per week (ATSDR, 1994; EPA, 2002; WHO, 2003; NTP, 2015).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ Xn; R40 in the HSIS (Safe Work Australia). The available data support this classification.

In a combined repeat dose inhalation and carcinogenicity study in mice, inhalation exposure to 220 mg/m^3 of 1,1-DCE for 12 months caused small nodules of bronchio-alveolar adenoma in six mice, and hepatic haemangiosarcoma and hepatoma were observed in three mice. One or two mice showed each of hepatic cell carcinoma renal adenoma or skin keratoacanthoma (low-grade skin cancer). The NOAEL of 220 mg/m^3 was reported (EPA, 2002; REACH).

In a 12-month inhalation and carcinogenicity study, CD-1 mice (36 animals/sex) were exposed to 1,1-DCE vapours by inhalation exposure at 220 mg/m^3 for six hours/day and 5 days/week. Enlarged and basophilic hepatocytes with enlarged nuclei, mitotic figures, microfoci of mononuclear cells, focal degeneration and necrosis were observed in the liver of all treated mice. Two of 28 mice were reported with haemangiosarcoma in the liver. Based on the effects observed in the liver, a LOAEC of 220 mg/m^3 was reported (EHC, 1990; EPA, 2002; REACH).

B6C3F1 mice (50 animals/sex/dose) were exposed to vapours of 1,1-DCE at concentrations of 0, 6.25, 12.5 or 25 ppm (corresponding to 0.0267, 0.0534 or 0.107 mg/L or 26.7, 53.4 and 107 mg/m^3), 6 hours and 10 minutes per day, 5 days per week for 105 weeks. Significant reductions in the survival rates of males at 25 ppm and females at 6.25 and 25 ppm were observed. Reductions in the mean body weights in males at 12.5 and 25 ppm after weeks 17 and 13 respectively, and in females at 25 ppm in week 21 were observed. All treated females and males at 25 ppm showed thinness and abnormal breathing. All male groups showed incidences of renal tubule adenomas, renal tubule carcinomas and renal tubule hyperplasia. Significant increase in the incidences of haemangioma of all organs (all females), hepatocellular adenoma (females at 12.5 ppm), hepatocellular carcinoma (25 ppm females), alveolar/bronchiolar carcinomas (12.5 ppm females) and hepatocellular adenoma/carcinoma (in 12.5 and 25 ppm females) were reported in all treated females. The majority of treated males and females showed dose-dependent turbinate atrophy, hyperostosis and olfactory epithelium respiratory metaplasia in the nose. Males in the 12.5 and 25 ppm and females in the 25 ppm were reported to have increased incidences of olfactory epithelium hyaline droplet accumulation and females at 25 ppm were reported to have significantly increased incidences of respiratory epithelium hyperplasia (ATSDR, 1994; EPA, 2002; WHO, 2003; NTP, 2015; REACH).

In a 105-week study, F344/N rats (50 animals/sex/dose) were exposed to 1,1-DCE at concentrations of 0, 25, 50 or 100 ppm for six hours and 10 minutes, five days per week. A positive trend in the incidence of malignant mesothelioma was observed in all male rats and one female at 25 ppm and one female at 50 ppm. Significant increases in the incidence of C-cell adenomas (females at 100 ppm) and C-cell carcinomas (females at 25 ppm) of the thyroid gland were observed. Females in 100 ppm groups also showed significantly increase incidences of mononuclear cell leukaemia and several treated males were reported with renal tubule carcinomas. Other effects reported in all treated male and female groups included increased incidences of turbinate atrophy, hyperostosis, olfactory epithelium respiratory metaplasia, respiratory epithelium hyperplasia and chronic active inflammation. An increased incidence in alveolar epithelium hyperplasia in the lung was observed in male rats of all dose groups. All groups showed an increased incidence of chronic inflammation, diffuse fatty change and cystic degeneration and necrosis was reported in females (ATSDR, 1994; EPA, 2002; WHO, 2003; NTP, 2015; REACH).

In a 2-year study conducted according to OECD TG 451, SD rats (48 animals/sex/dose) were administered the chemical at 0, 50, 100 or 200 mg/L in drinking water. No treatment-related effects were seen on mean body weight, food and water consumption, haematology, urinalysis or clinical chemistry. Female rats from all dose groups and males in the 200 mg/L dose group showed small amounts of hepatocellular fatty changes and swelling. Female rats in the 50 mg/L groups had a significant increase in the incidence of mammary gland fibroadenomas or adenofibromas. The author concluded that the incidences of mammary gland neoplasms were not treatment-related (EPA, 2002; REACH).

The International Agency for Research on Cancer (IARC) classified 1,1-DCE in 1999 as 'not classifiable as to its carcinogenicity to humans' based on limited evidence in experimental animals and inadequate evidence in humans (IARC, 1999). The US EPA and the EU have reported suggestive evidence for carcinogenicity and that the chemical is suspected of causing cancer (Health Canada, 2013).

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. While in most studies, reproductive and developmental effects were only observed secondary to maternal toxicity, one study in mice reported non-significant foetal effects at a sub-maternally toxic dose. However, only limited data are available and results from this study are insufficient to warrant hazard classification

In a three-generation study, SD rats (10 males and 20 females per group) were administered 1,1-DCE in drinking water at 0, 50, 100 or 200 mg/L. The parental generation rats (F0) were mated after 100 days of exposure to produce F1a (first generation) litters. The F0 were mated again 10 days after weaning the F1a to produce F1b litters. The F1a and F1b animals were randomly mated at 110 days of age to produce the F2 and F2a (second generation) litters, respectively. The F2 rats were mated again 10 days after weaning to produce F3a and F3b litters, respectively. Females rats in the F2 generation receiving 200 mg/L 1,1-DCE had elevated relative liver weights and an increase in the serum alanine aminotransaminase. Rats in the F1 and F2 generations in the 100 and 200 mg/L dose groups showed signs of slight hepatocellular fatty change in the livers and male rats at 200 mg/L had greater incidence of chronic renal disease. The treatment had no effect on fertility. A NOAEL of 200 mg/L (about 30 mg/kg bw/day) was reported (EHC, 1990; EPA, 2002).

In a developmental toxicity study, pregnant SD rats (27 animals/dose) were administered 1,1-DCE in drinking water on gestation days 6 to 15 at 200 ppm (40 mg/kg bw/day). No evidence of toxicity in the dams or their offspring and no teratogenic effects in the embryos were observed. A NOAEL for developmental toxicity of 200 ppm (40 mg/kg bw/day) was reported (EPA, 2002).

In another developmental toxicity study, pregnant CD-1 mice (20 animals/dose) were administered the chemical by inhalation at 0, 15, 30, 57, 144 or 300 ppm for 22-23 hours/day on gestation days 6-16 and sacrificed on gestation day 17. Significant maternal weight loss at all doses ≥ 30 ppm and mortality at doses ≥ 144 ppm were observed. Severe foetal toxicity with complete early resorption of the litters was observed at concentrations $\geq$ 30 ppm. Non-significant increases in the mean number of foetuses/litter with hydrocephalus, occluded nasal passages, microphthalmia, cleft palate, small liver, hydronephrosis and a significant increase in foetuses with unossified incus and incompletely ossified sternebrae were reported at 15 ppm. There was some evidence of non-significant developmental toxicity at 15 ppm without any significant maternal toxicity. A LOAEL for developmental toxicity of 15 ppm (60 mg/m^3) was reported (EPA, 2002).

In a 105-week combined carcinogenicity and reproductive toxicity study, F344/N rats (50 animals/sex/dose) were exposed to 1,1-DCE vapours at concentrations of 0, 25, 50 or 100 ppm for six hours and 10 minutes, five days per week. No treatment-related effects were seen on reproductive organs (REACH).

Other reproductive toxicity studies in rats and rabbits gave negative results at 1,1-DCE concentrations up to 640 mg/m^3 (160 ppm) for seven hours/day by inhalation exposure (EHC, 1990).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects of carcinogenicity and systemic acute effects of acute toxicity from oral and inhalation exposure. The chemical can also cause skin and eye irritation.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Due to the volatility of the chemical, it will not remain in the articles where it was used in the manufacturing process.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, systemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

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

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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 by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure through inhalation (Xn; R48/20)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
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 oral 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 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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