1-Propene, 3-chloro-: Human health tier II assessment

22 March 2013

CAS Number: 107-05-1

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.

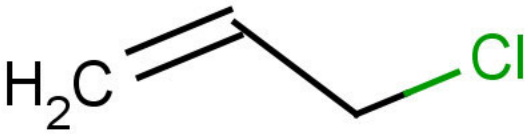
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3-Chloropropene a-Chloropropylene Allyl Chloride 2-Propenyl chloride Chlorallylene
Structural Formula	
Molecular Formula	C3H5Cl
Molecular Weight (g/mol)	76.53
Appearance and Odour (where available)	Colourless to pale yellow liquid with an unpleasant pungent odour.
SMILES	C(=C)CCl

Import, Manufacture and Use

Australian

No specific Australian use, import, manufacture information has been identified.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR) and the International Agency for Research on Cancer (IARC) report.

The chemical has reported site-limited use including:

- synthesis of epichlorohydrin and glycerine (predominant use);
- synthesis of acrylic polymers that may be used in cosmetics;
- used as a chemical intermediate for downstream allyl derivatives such as high-performance resins and polymers and in the synthesis of medical derivatives, agricultural chemicals, and allyl starches; and
- used as a thermosetting resin for varnishes, plastics, and adhesives.

Restrictions

Australian

No known restrictions have been identified.

International

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

EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products.

New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain.

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):

Carc.Cat.3; R40

Muta.Cat.3; R68

Xn; R20/21/22-48/20

Xi; R36/37/38

Exposure Standards

Australian

The chemical has an exposure standard of 3 mg/m³ (1 ppm) time weighted average (TWA) and 6 mg/m³ (2 ppm) short term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit TWA of 2-3 mg/m³ (0.7-1 ppm) and STEL of 4-9 mg/m³ (1.3-3 ppm) in different countries such as USA, Canada, China, Denmark and Sweden.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed in rats following oral or inhalation exposure (OECD, 2004). The chemical is thought to be first metabolised to allyl alcohol, and then to a variety of metabolites such as 3-hydroxypropylmercapturic acid and allyl mercapturic acid and its sulfoxide (which have been identified in rat urine) or allyl glutathione and S-allyl-L-cysteine (which have been detected in the bile of dosed rats) (IARC, 1999).

Acute Toxicity

Oral

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

The oral LD50 for rats ranged between 450 to 700 mg/kg bw, for mice it was from 425 to 500 mg/kg bw, and for rabbits it was 300 mg/kg bw (OECD, 2004). Major signs of toxicity included hind limb paralysis, tremor and occasional convulsions, with gastrointestinal, kidney, liver and lung changes (OECD, 2004).

Dermal

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

The chemical had a dermal LD50 of 2026 mg/kg b.w. in rabbits (OECD, 2004).

Although the information available does not support the current HSIS classification as NICNAS does not have access to all the information on the chemical and the classification cut-off is very close to the LD50 value, the removal of the current HSIS classification is not recommended.

Inhalation

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

The chemical has been investigated in a number of inhalation studies on rats, mice, cats, rabbits and guinea pigs with the LC_{50} (2-6h) ranging from 2.5-22.5 mg/L. Reported signs of toxicity include eye and nose irritation, hypoactivity, hypopnoea, paralysis of the hind limbs, drowsiness, dyspnoea, narcosis, tremors, convulsion, haemorrhage of the lungs and liver and kidney changes (OECD, 2004).

Observation in humans

The chemical has been reported to cause polyneuropathy, adverse effects on the central nervous system as well as reversible liver and kidney damage after occupational exposure (OECD, 2004).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (R37) in HSIS (Safe Work Australia).

Respiratory irritation was noted in acute inhalation studies with the chemical (OECD, 2004).

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (R38) in HSIS (Safe Work Australia). The data available support this classification.

The chemical was shown to be slightly irritating to the skin in rabbits (OECD, 2004).

Although the animal data do not meet the criteria for classification, irritation has been observed in human clinical studies (see below) and skin irritation has been observed in acute inhalation studies (OECD, 2004).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (R36) in HSIS (Safe Work Australia).

The chemical was shown to be slightly irritating to the eyes of rabbits (OECD, 2004). Although the animal data do not meet the criteria for classification, irritation has been observed in human clinical studies (see below).

Observation in humans

Exposure to vapours of the chemical has been reported to cause eye irritation, often with orbital pain along with nose, throat and respiratory irritation, and with eye and respiratory tract irritation reported to occur at concentrations as low as 75 mg/m^3. Prolonged skin contact with the chemical can result in erythema and oedema (OECD, 2004).

Sensitisation

Skin Sensitisation

No human or animal data are available. The chemical contains a structural alert for skin sensitisation (a-activated haloalkanes). These chemicals can potentially cause skin sensitisation effect as a result of protein conjugation via nucleophilic substitution at sp^3 Carbon atom (OECD Toolbox). The expected rapid evaporation of the chemical would limit intense and prolonged contact with the skin and

consequently potential for sensitisation. The lack of human case reports of sensitisation to the chemical is supportive of these conclusions.

Repeated Dose Toxicity

Oral

In mice, a 17 week gavage study showed effects down to 300 mg/kg bw/day which was the lowest dose tested. In a 10 day gavage study in rats a LOAEL of 45 mg/kg bw/day was set. Effects seen in the studies include neuropathy and focal kidney damage (OECD, 2004).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Danger of serious damage to health by prolonged exposure (inhalation)' (Xn; R48/20) in HSIS (Safe Work Australia). The data available support this classification.

There are at least 19 repeat dose inhalation toxicity studies on the chemical, with exposure periods up to 34 weeks (OECD, 2004). In a subchronic inhalation study in rodents, neurological effects (reversible effects on the central nervous system), along with effects on male reproductive parameters (see **reproductive and developmental toxicity** below), were observed at doses of 1.1 mg/m³, with the NOAEC being 0.29 mg/m³, and developmental toxicity and effects on the liver and kidneys were observed in rats exposed to a slightly higher concentration (3.1 mg/m³) (Environment and Health Canada, 2009). Degenerative changes in kidney and liver were observed in rats, guinea-pigs and rabbits inhaling 8 ppm (25 mg/m³) of the chemical for five weeks, although, at the lower concentration of 3 ppm (9 mg/m³) for six months under the same conditions, no adverse effects were observed (IARC, 1999). Changes to the liver and kidney were only observed at much higher concentrations in other studies.

Observation in humans

After occupational exposure to the chemical polyneuropathy, adverse effects on the central nervous system as well as reversible liver and kidney damage have been reported in workers (OECD, 2004).

Genotoxicity

The chemical is classified as hazardous as a Category 3 mutagenic substance with the risk phrase 'possible risk of irreversible effect' (R68) in HSIS (Safe Work Australia).

The chemical has been tested in a wide range of *in vitro* and *in vivo* assays. The chemical was positive for mutagenicity in *in vitro* gene mutation tests with *Salmonella typhimurium*, *Escherichia coli* and *Streptomyces coelicolor* both with and without metabolic activation. No signs of mutagenicity were seen however in an *in vitro* gene mutation test with *Aspergillus nidulans*.

The chemical induced gene conversions in *Saccharomyces cerevisiae* and somatic segregation in *Aspergillus nidulans* and induced unscheduled DNA synthesis in human HeLa S3 cells, but not in human embryonic intestinal cells and no significant chromosome damage was observed in RL1 cells.

Although in *in vivo* tests no sign of mutagenicity was recorded, it has been noted that the tests did not meet current guidelines with low doses and no evidence that the chemical reached the target cells. The mutagenicity in bacterial systems is supported by the direct alkylation of DNA and NBP [4-(p-nitrobenzyl)pyridine] by the chemical (OECD, 2004). Therefore the data available are considered to be supportive of the current classification.

Carcinogenicity

The chemical is currently classified with the risk phrase 'Limited evidence of a carcinogenic effect (R40)' in Australia (Safe Work Australia, 2012). The data available support this classification.

The chemical is classified by the International Agency on Cancer (IARC) as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999) based on inadequate evidence in humans and experimental animals.

The chemical has been tested for carcinogenicity by gavage in mice and rats, by skin application in mice, both by repeated application and in a two-stage assay, and by intraperitoneal injection in mice. The chemical induced tumours in the forestomach and lung in mice, exposed via oral gavage or intraperitoneal injection respectively. The chemical also exhibited tumour initiating potential when applied dermally, but did not induce tumours in the absence of a promoter.

By gavage in mice a nonsignificant increase in the incidence of squamous cell papillomas and carcinomas of the forestomach was observed. In rats, the experiment was inadequate for evaluation due to poor survival rates.

No skin tumours were observed in mice as a result of repeated skin applications in the absence of a promoter. However, a single application followed by treatment with the promoter (12-O-tetradecanoylphorbol 13-acetate (TPA)) increased the incidence of tumour-bearing mice from 6/90 in the TPA controls to 7/30 in treated mice ($p<0.025$) and reduced the time to first papilloma from 449 days to 197 days.

Following intraperitoneal injection in mice, there was a marginal increase in the multiplicity of lung adenomas (IARC, 1999).

The was no evidence from limited epidemiological studies for an increased cancer incidence in workers exposed to the chemical.

Reproductive and Developmental Toxicity

The chemical produced adverse effects in sperm after inhalation by rats at concentrations of 1.1 mg/m³, with a subcutaneous study confirming the effects by the chemical. Although the chemical was shown to produce developmental effects following inhalation by rats at concentrations down to 3.1 mg/m³, the effects were not replicated in a second inhalation study which tested at doses up to 300 ppm.

A decrease in sperm motility time and the average number of normal spermatogonia was seen in rats exposed via inhalation, for 4 months with a LOEC of 1.1 mg/m³ and a NOAEC of 0.29 mg/m³. At higher concentrations reduced testicular weights and reduced spermatogenic index were seen (Environment and Health Canada, 2009). In a second reproductive study where the chemical was administered in a single subcutaneous dose of 124 mg/kg, the number of homogenisation-resistant testicular spermatids and the number of epididymal sperm began to decrease on days 4 and 14 respectively (ACGIH, 2011). Based on the time taken from the administration of the chemical to the changes in the sperm compared to the time it takes sperm to pass through the epididymis, it appears that the chemical damages sperm when it is present in the epididymis. The data available support classification for reproductive toxicity (refer to **recommendation section**).

Reductions in the number of live embryos per litter and significant increases in pre-implantation loss and resorption sites were seen in developmental studies with rats with a LOEC of 3.1 mg/m³ (Environment and Health Canada, 2009). In another inhalation study rats and rabbits were exposed to the chemical during pregnancy at concentrations of 0, 30 or 300 ppm (ACGIH, 2011). At 30 ppm, the only sign of developmental toxicity was a slight delay in skeletal toxicity, while at 300 ppm there was significant maternal toxicity. In further intraperitoneal and gavage studies on rats and mice respectively foetal toxicity was seen at 80 mg/kg (rats) or 5 mL/kg (mice) although there was significant maternal toxicity at these doses (ACGIH, 2011).

Other Health Effects

Neurotoxicity

The neurotoxic effects of the chemical have been studied extensively in mice, rats, rabbits and cats. The chemical is a neurotoxic agent, which especially damages the peripheral nervous system resulting in a dying-back pattern of axonal degeneration. In the most reliable study a NOAEL for neurotoxicity of 31 mg/m³ (duration adjusted: 7.38 mg/m³) has been established (OECD, 2004).

No neurological effects were seen in rats when dosed with the chemical at 0.015 mg/kg for 6 month in drinking water or in rabbits in an 8 month gavage study at the same dose.

Risk Characterisation

Critical Health Effects

The critical effects for risk characterisation are systemic long-term effects (carcinogenicity, mutagenicity, repeat dose toxicity and reproductive toxicity). The chemical also has acute oral and inhalation toxicity and potential sensitisation and irritant properties.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that public will be exposed to this chemical.

Acrylic polymers that are synthesised using the chemical are known to be used in cosmetic products in Canada with the residual chemical present in the products at concentrations up to 0.01 % (Environment and Health Canada, 2009). Modelled worst case estimates of air concentrations of the chemical during use of consumer products was 0.9 mg/m³ for hair dye or 0.2 mg/m³ for more frequently used products, such as shampoo (Environment and Health Canada, 2009). The results of the indoor air survey of homes in California in which the substance was not detected, suggest that consumer exposure is likely to be to much less than 1 µg/m³. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During formulation of products, dermal, ocular and inhalation exposure of workers to the chemical may occur particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur during use of formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Dermal exposure will be limited given the expected rapid evaporation of the chemical.

Given the critical systemic longterm effects of the chemical, the chemical may pose an unreasonable risk to workers if adequate control measures to minimise inhalation exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) e.g. employer at a workplace has adequate information to determine appropriate controls.

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

Based on the male reproductive effects observed at doses of 1.1 mg/m³ the current exposure standard may not be adequate to mitigate the risk of adverse effects. Airborne concentrations of the chemical should be kept as low as reasonably practicable to minimise risk.

NICNAS Recommendation

The chemical is recommended for Tier III assessment to examine the adequacy of the current exposure standard. All other aspects have been sufficiently assessed at the Tier II level provided that the recommendation is adopted for the amendment of the classification and labelling of the chemical and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the approved criteria and adopted GHS as below:

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) Harmful if inhaled - Cat. 4 (H332)
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)
Repeat Dose Toxicity	Danger of serious damage to health by prolonged exposure (Xn; R48)*	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
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)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)	Suspected of damaging fertility - Cat. 2 (H361f)

[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 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 storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of closed systems or isolation of operations;
- use of 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;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of personal protective equipment can be obtained from Australia, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting 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 hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

References

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of the Threshold Limit Values for Chemical Substances, ACGIH Signature Publications, 7th Edition. Allyl chloride 2011.

ECHA (2012). REACH Dossier for 1-propene,3-chloro (107-51-5). http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c421c-82e7-3558-e044-00144f67d249/AGGR-319e1e22-6c24-4657-8ca1-507f09fc7f73_DISS-9d8c421c-82e7-3558-e044-00144f67d249.html#section_3_5. Accessed October 2012.

Environment and Health Canada (2009). Screening Assessment for the Challenge 1-Propene, 3-chloro- (3-Chloropropene) (107-05-1). Accessed February 2013. http://www.ec.gc.ca/ese-ees/1D14AC0D-4E1B-43C4-9A73-2836599B52AC/batch6_107-05-1_en.pdf

IARC (1999). Volume 71- Re-evaluation of some organic chemicals, hydrazine, and hydrogen peroxide. http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-27.pdf. Accessed October 2012.

NTC (National Transport Commission) 2007 Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), 7th Edition, Commonwealth of Australia.

OECD (2004), SIAR 1-propene,3-chloro (107-51-5).http://webnet.oecd.org/hpv/UI/handler.axd?id=87d12c5b-089b-4ef9-94d2-

277815dce452. Accessed October 2012.

OECD QSAR Toolbox version 3.0 http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm
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