Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

1-Propene, 3-chloro-2-methyl-

Evaluation statement

14 December 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

1-Propene, 3-chloro-2-methyl-

Chemical in this evaluation

Name	CAS registry number
1-Propene, 3-chloro-2-methyl-	563-47-3

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of industrial Chemicals (the Inventory). The evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Throughout this report, 1-propene, 3-chloro-2-methyl- is also referred to by its synonym methallyl chloride.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of methallyl chloride in Australia.

Based on international use information, this chemical is mainly used as an intermediate in the manufacture of other organic chemicals and plastics. It is also widely used in the manufacture of various pesticides and insecticides.

Human health

Summary of health hazards

Limited data are available for the chemical. Given their close structural similarities, data for the chemical allyl chloride (CAS No. 107-05-1), are used to support conclusions on acute toxicity endpoints for health hazard assessment. It is a chlorinated derivative of propylene and differs from methallyl chloride by a methyl group (similarity index 0.75) (MN-AM n.d.). They have similar molecular weights.

The chemical is readily absorbed via the gastrointestinal tract and excreted mostly through the urine. It has moderate acute toxicity via oral route (median lethal dose (LD50) 316–1000

mg kg/bw) and moderate acute inhalation toxicity (median lethal concentration (LC50) 1240 ppm).

The chemical is currently classified as corrosive to skin and eyes and as a skin sensitiser. Limited data are available to review these classifications. The chemical is reported as a corrosive. The structurally related chemical, allyl chloride (CAS No. 107-05-1) is irritating to the skin and eyes and has skin sensitising potential. The chemical has reported positive sensitisation data in humans and guinea pigs and is predicted to be a sensitiser.

Based on the available data, the chemical may cause adverse systemic health effects following repeated exposure. In 13 week oral studies, effects were observed in the liver (rats and mice) and kidney (mice). In longer term studies effects were also observed in the nasal cavity. Based on doses at which effects were observed in 13 week studies (≥ 300 mg/kg bw/day) classification is not warranted. In long term inhalation studies effects were observed in the nasal cavity. Data are not sufficient for classification.

Available data indicate that the chemical is carcinogenic in rodents. There is sufficient evidence for carcinogenicity in experimental animals. Increased incidence of tumours in the forestomach was observed in rats and mice following oral exposure and in mice following inhalation exposure. Other tumours observed that are potentially related to treatment include subcutaneous fibromas (female rats, oral exposure), adenoma of the Harderian gland (female mice, inhalation exposure) and follicular cell adenoma and follicular cell adenoma or adenocarcinoma (combined) of the thyroid gland (male rats, inhalation exposure). No human exposure data is available. Although the forestomach and Harderian gland have no equivalent tissue in humans, there is some evidence of carcinogenicity at other sites. The chemical has key characteristics of a carcinogen including being potentially genotoxic. Overall classification is warranted.

In vitro the chemical was found to induce gene mutation in bacterial and mammalian cells, chromosomal aberrations and sister-chromatid exchange in mammalian cells, and DNA damage in human (Hela) cells. Limited in vivo data are available in mammals. The chemical was negative in an in vivo mouse micronucleus test. Positive results were reported in in vivo studies in *Drosophila melanogaster*.

The chemical may cause adverse effects on fertility/sexual function following oral exposure. Additional information is required to confirm reproductive toxicity of the chemical.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity - oral	Acute Tox. 4	H302 (Harmful if swallowed)
Acute toxicity - inhalation	Acute Tox. 4	H332 (Harmful if inhaled)
Skin corrosion/irritation	Skin Corr. 1B	H314 (Causes severe skin burns and eye damage)
Skin sensitisation	Skin Sens. 1	H317 (May cause an allergic skin reaction)
Carcinogenicity	Carc. 2	H351 (Suspected of causing cancer)

Summary of health risk

Public

It is unlikely that the public will be exposed to these chemicals. Although the public could come into contact with plastic articles containing this chemical, the chemical will be fully reacted with other components and bound to the matrix of the articles and will not be bioavailable. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and manufacture, 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, cleaning and maintenance of 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 may vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local effects and systemic health effects following acute exposure, the chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation effects are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal, ocular and inhalation exposure to the chemical 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
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how this chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to this chemical, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

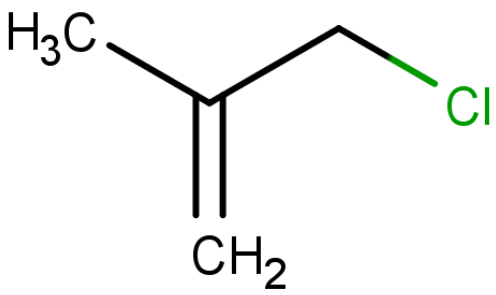
Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	1-propene, 3-chloro-2-methyl-
CAS No.	563-47-3
Synonyms	methallyl chloride
	2-methyl-3-chloropropene
	2-methallyl chloride
	isobutenyl chloride
Molecular formula	C4H7Cl
Molecular weight (g/mol)	90.55
SMILES	ClCC(=C)C
Chemical description	-



Structural formula

Relevant physical and chemical properties

Colourless to yellow liquid with a sharp penetrating odour. The substance may decompose when heated, explode when in contact with oxidising agents and can polymerise and react dangerously with acids.

Physical form	Liquid
Melting point	-80.0°C
Boiling point	72.2°C
Vapour pressure	13.5 kPa at 20°C
Water solubility	1.40 mg/mL at 25°C
log K_{ow}	2.48

Introduction and use

Australia

No specific information is available for the introduction, use and end use of this chemical in Australia.

International

The chemical has reported site limited use as an intermediate. It is used in the manufacture of plastics and organic chemicals, including 2-methylepichlorohydrin (NTP, 2021, IARC 2018, US CDR 2016, US CDR 2020).

In non-industrial uses, it is an important intermediate in the production of various pesticides, including fumigant for seeds (HSDB, 2014).

The chemical is listed in the Organisation for Economic Cooperation and Development (OECD) High Production Volume (HPV) Chemicals list (OECD n.d.).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is listed in the Hazardous Chemical Information System HCIS (Safe Work Australia, SWA) with the following hazard categories and statements for human health:

Health hazards	Hazard category	Hazard statement
Acute toxicity - inhalation	Acute Tox. 4	H332 (Harmful if inhaled)
Acute toxicity - oral	Acute Tox. 4	H302 (Harmful if swallowed)
Skin corrosion	Skin Corr. 1B	H314 (Causes severe skin burns and eye damage)
Skin sensitisation	Skin Sens. 1	H317 (May cause an allergic skin reaction)

There are no specific exposure standards available in Australia (Safe Work Australia).

International regulatory status

Exposure standards

The following exposure standards were identified for the chemical:

- The following temporary emergency exposure limits (TEELs) have been recommended by the United States Department of Energy (Galleria Chemica):
  - 45 ppm (TEEL-3)
  - 13 ppm (TEEL-2)
  - 1.2 ppm (TEEL-1)

- The Russian maximum allowed concentration (PDK), and the Belarus maximum permissible concentration (MPC) for the chemical is 0.3 mg/m^3 (Galleria Chemica).

Health hazard information

Toxicokinetics

Based on the chemical's molecular weight and log K_{ow} the chemical is expected to be absorbed following all routes of exposure. In a toxicokinetic study (Ghanayem 1987) in male Fischer 344 (F344) rats, the chemical was rapidly absorbed through the gastrointestinal tract following a single dose or up to four daily doses of 150 mg/kg bw in corn oil by oral gavage.

Distribution in the tissues was rapid and the highest concentrations were found in the forestomach, liver and kidney. The tissue concentrations were approximately doubled after two doses, but a slight additional increase was observed after four doses. The concentrations decreased after cessation of treatment. The compound was rapidly excreted: 82% of the single dose was eliminated within 24 h after treatment. Excretion was primarily

via the urine, but large amounts (10%) were also exhaled as carbon dioxide and 7% as volatile compounds. The major metabolite detected in rat urine was characterised as N-acetyl-S-(2-methylpropenyl) cysteine, which constituted 45% of the total urinary radiolabel (IARC 1995). This metabolite is presumed to arise from direct conjugation of glutathione with the allylic carbon of the chemical, followed by catabolism (enzymatic degradation) to the mercapturate (Ghanayem 1987).

Acute toxicity

Oral

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Acute Toxicity (Oral)- Category 4'. Data is consistent with this classification.

In a GLP compliant acute oral toxicity study, similar to OECD TG425, F344/N rats (5/sex/dose) were administered a single dose of the chemical in corn oil by oral gavage at 100, 316, 1000, 3160 or 10000 mg/kg bw. All rats administered the chemical at 1000 mg/kg bw and above died after 2 days. No compound related effects were observed in animals dosed at 100 or 316 mg/kg bw. The LD50 in this study was established to be in the range 316−1000 mg/kg bw (NTP 1986).

In a second acute oral toxicity study similar to OECD TG425, B6C3F1 mice (5/sex/dose) were administered a single dose of the chemical in corn oil by gavage at 31.6, 100, 316, 1000 or 3160 mg/kg bw. Mice administered the chemical at 3160 mg/kg bw died before the end of the 14 day observation period. No compound related effects were observed in animals dosed at 31.6, 100, 316 or 1000 mg/kg bw (NTP 1986).

Dermal

No data are available for the chemical.

Inhalation

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Acute Toxicity (Inhalation) - Category 4'. The limited available data support this classification.

Limited data are available on acute inhalation toxicity. The Japanese National Institute of Technology and Evaluation (NITE) has reported two LC50s in rats for 4 hours exposure: >1,350 ppm and 1,240 ppm. Based on the lower LC50 value (1,240 ppm), NITE has classified the chemical as 'Acute Toxicity (Inhalation) - Category 4' (NITE n.d.).

According to Deichmann and Gerarde (1969) a single 10-minute exposure to 22000 ppm methallyl chloride is fatal.

The structurally related chemical, allyl chloride (CAS No. 107-05-1), was investigated in a number of inhalation studies on rats, mice, cats, rabbits and guinea pigs with the LC50 (2−6 hours exposure) 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).

Corrosion/Irritation

Skin Corrosion

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Skin Corrosion 1B; H314 (Causes severe skin burns and eye damage). Although, limited data are available to evaluate this classification an amendment to this classification is not warranted.

Information on skin irritation effect of the chemical is not available. It is reported to be corrosive to rabbit skin and irritating to the human skin (NITE n.d). No further details are available. The structurally related chemical, allyl chloride (CAS No. 107-05-1) was shown to be slightly irritating to the skin in rabbits, and irritation has also been observed in human clinical studies (see **Observation in humans**) (OECD 2004).

Eye irritation

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Skin Corrosion 1B; H314 (Causes severe skin burns and eye damage). Information on eye irritation effect of the chemical is not available.

Given the corrosiveness of the chemical to rabbit skin (NITE n.d.), it is reasonable to assume that the chemical would be irritating to eyes. The structurally related chemical, allyl chloride (CAS No. 107-05-1) was shown to be slightly irritating to the eyes in rabbits, and irritation has also been observed in human clinical studies (see **Observation in humans**) (OECD 2004).

Observation in humans

Exposure to vapours of the structurally related chemical, allyl chloride (CAS No. 107-05-1) 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

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Skin sensitisation- Category 1; H317 (May cause an allergic skin reaction)'. The limited available data are consistent to warrant this classification.

Information on skin sensitisation of the chemical is not available. NITE reported that a sensitisation test using guinea pigs was positive, and skin sensitisation was also reported in humans (NITE n.d.). The chemical has structural alerts for protein binding based on the mechanistic profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Application Toolbox (OECD QSAR Toolbox v4.2).

QSAR modelling using OASIS TIMES (optimized approach based on structural indices set tissue metabolism simulator) predicted that the chemical is a skin sensitiser, with alerts for alpha-activated haloalkenes (OASIS LMC). The expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Lhasa Limited n.d.),

presented skin sensitisation alerts (alkyl halide) and predicted an LLNA EC3 of 4.6%, indicating that the chemical may be a moderate skin sensitiser.

Repeat dose toxicity

Oral

Based on the available data, the chemical may cause adverse systemic health effects following repeated oral exposure. In 13 week studies effects were observed in the liver (rats and mice) and kidney (mice). In longer term studies effects were also observed in the nasal cavity. Based on doses at which effects were observed in 13 week studies classification is not warranted.

The National Toxicology Program (NTP) of the United States of America Department of Health and Human Services conducted repeat oral dose toxicology and carcinogenesis studies with the chemical (NTP 1986). Three dosing periods were selected for these studies: 14 days, 13 weeks and 103 weeks. The studies were conducted at Litton Bionetics, Inc. Guidelines used for these studies have not been specified. Following is a summary of the repeat dose effects of the chemical in rats and mice for the three exposure periods.

14 day study (rats and mice)

In the 14 day repeat dose toxicity study in rats, F344/N rats (5/sex/dose) were administered the chemical in corn oil by gavage at 0, 89, 158, 281, 500 or 750 mg/kg bw/day daily for 14 days. Rats administered the chemical at 500 or 750 mg/kg bw/day died before the end of the observation period. Animal autopsies indicated yellow intestines, dark stomach, darkened and pale areas on the liver, and dark fluid in the urine. Male rats that received 281 mg/kg bw/day had lower mean body weights compared to vehicle controls. No further details were provided.

In the 14 day study in mice, B6C3F1 mice (5/sex/dose) were administered the chemical in corn oil by gavage at 0, 125, 250, 500, 750, 1250, 1750 or 2500 mg/kg bw/day for 14 days. Mice administered the chemical at 740 mg/kg bw/day and above died on day 1. Mice that died during the studies had bright red or orange lungs, pale liver or soft intestines. No gross lesions were observed at necropsy at the end of the study.

13 week study (rats and mice)

In the 13 week repeat dose toxicity study in rats, F344/N rats (10/sex/dose) were administered the chemical in corn oil by gavage at 0, 50, 100, 200, 300 or 400 mg/kg bw/day daily for 13 weeks. All rats that received the chemical at 400 mg/kg bw/day and 5/10 males and 2/10 females that received 300 mg/kg bw/day died before the end of the 13 week observation period. Rough coats were observed in higher dose male and female rats. Acute and chronic inflammation was observed in the livers of both male and female rats that received 300 or 400 mg/kg bw/day. Areas of necrosis were observed and distributed throughout the liver for the rats that received 300 or 400 mg/kg bw/day of the chemical, with more acute legions of necrosis surrounded by congestion or neutrophils.

In the 13 week study in mice, B6C3F1 mice (10/sex/dose) were administered the chemical in corn oil by gavage at 0, 125, 250, 500, 750 or 1250 mg/kg bw/day daily for 13 weeks. All mice in the 750 and 1250 mg/kg bw/day group, and 9/10 males and 5/10 females in the 500 mg/kg bw/day group died before the end of the 13 week observation period. Compound related degenerative lesions were observed in the kidney and liver**.** The majority of lesions

were observed in animals treated at 500 mg/kg bw/day and above although some histopathological changes were reported at lower doses. The kidney lesions consisted of degeneration and necrosis of cortical tubules, with accumulations of cellular debris in damaged tubules. Kidney lesions varied in severity within affected dose groups. The incidence and severity were greater in males than in females. Liver lesions consisted of coagulative necrosis and/or cytoplasmic vacuolisation of hepatocytes. Liver and kidney lesions often occurred in the same mice; more severe liver lesions were often associated with the more severe kidney lesions. Nephrosis was observed in males and females treated at 500 mg/kg bw/day and above.

103 week study (rats and mice)

In a 2 year carcinogenicity study (see **Carcinogenicity** section), F344/N rats (50/sex/dose) were administered 0, 75, or 150 mg/kg bw/day the chemical- in corn oil by gavage, 5 days per week for 103 weeks. B6C3F1 mice (50/sex/dose) were administered 0, 100, or 200 mg/kg bw/day on the same schedule.

In rats, the mean body weight of high dose male rats was consistently 10−15% lower than that of the vehicle control group, with a non-significant reduction in survival of high dose male rats.

Incidences of basal cell hyperplasia in the forestomach (treated male and females) and nephropathy (treated males and high-dose females) were increased Hepatocellular necrosis was observed in dosed male rats but not in dosed females. Suppurative inflammation, acute/chronic inflammation, or chronic inflammation of the nasal cavity occurred at increased incidences in high dose male and female rats.

In mice, dose related incidences of forestomach inflammation were increased in male and female mice (0/49, 9/49, 7/49 in males and 2/50, 3/48 and 9/44 in females at 0, 100 and 200 mg/kg bw/day, respectively). Acute inflammation of the nasal cavity was observed in high dose male and female mice, incidences of thyroid follicular cysts in low dose and high dose female mice were greater than that in the vehicle controls, whereas incidence of nephrosis was increased in high dose male mice.

Dermal

No data are available.

Inhalation

Based on the available data, the chemical may cause serious systemic health effects following repeated inhalation exposure. In long term studies effects were observed in the nasal cavity. Data are not sufficient for classification.

The effect of long term inhalation exposure to the chemical was studied in a chronic inhalation toxicity and carcinogenicity study in mice (Katagiri et al 2000). BDF1 mice (50/sex/dose) were exposed to 0, 50, 100 or 200 ppm (v/v in clean air) 6 hours per day, 5 days a week for
104 weeks. At the end of the exposure period, incidence of non-neoplastic and neoplastic lesions was examined.

Male and female mice in the exposed groups had decreased body weight but no noticeable clinical signs when compared with the control group. An increased incidence of mucosal polypoid lesions in the forestomach was observed in both male and female mice in the

100 ppm and 200 ppm groups. In males, a decrease in absolute organ weight was observed in the spleen and liver in all experimental groups, in the heart and kidneys in the 100 ppm and 200 ppm groups, and in the brain in the 200 ppm group. In females, a decrease in absolute weight was observed in heart, kidneys and brain at 100 ppm, and brain in the 100 ppm and 200 ppm groups. The decrease in the body and organ weight ratio were reported not to be correlated to the exposed concentration of chemical.

Non-neoplastic lesions of the nasal cavity (eosinophilic exudate, atrophy of olfactory epithelia, respiratory metaplasia of olfactory epithelia and gland, Intracytoplasmic eosinophilic globules) and the stomach (mucosal hyperplasia of forestomach) were observed and were mostly dose related.

A brief summary of a second 2 year inhalation toxicity and carcinogenicity study is provided by the Japan Bioassay Research Center, Japan (JISHA 1998). In this study, conducted according to OECD 451 Test Guidelines, F344/DuCrj rats (50/sex/dose) were exposed to whole body inhalation of the chemical at target concentrations of 0, 50, 100 or 200 ppm (v/v in clean air), 5 days a week for 104 weeks. In exposed males, survival rates were decreased compared with the male control males. Growth rates of 100 and 200 ppm exposed males and 200 ppm exposed females were slightly suppressed as compared with the respective controls. The incidence and severity of eosinophilic change in the olfactory epithelium in the nasal cavity were increased in an exposure concentration related manner in all the chemical exposed groups of both sexes. Since the eosinophilic change in the olfactory epithelium is known to be age related, this nasal lesion was considered to be enhanced by the exposure to the chemical. No other non-neoplastic changes were observed.

Genotoxicity

Based on the available data, the chemical is considered to be potentially genotoxic. Data are not sufficient to warrant classification. In vitro the chemical was found to induce gene mutation in bacterial and mammalian cells, chromosomal aberrations and sister-chromatid exchange in mammalian cells, and DNA damage in human (Hela) cells. Limited in vivo data are available in mammals. The chemical was negative in an in vivo mouse micronucleus test. Positive results were reported in in vivo studies in *Drosophila melanogaster*.

In vitro

- In a bacterial reverse mutation test the chemical was tested on *Salmonella typhimurium* strain TA 100, TA1535, TA1537 and TA98 both in the presence and absence of metabolic activation at concentrations up to 3850 mg/mL. The chemical was reported to be mutagenic in *S. typhimurium* TA100 both in the presence and absence of metabolic activation (Eder 1982; IARC 2018) and *S. typhimurium* TA1537 (385 mg/mL) in the presence of metabolic activation (IARC 2018; Haworth 1983).
- The chemical induced both chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells both in the presence and absence of metabolic activation (IARC 2018; Gulati 1989).
- In a gene mutation test on mouse lymphoma L5178Y cells, an increased frequency of both large and small colonies was observed without exogenous metabolic activation (IARC 2018, Myhr 1991).
- The chemical induced unscheduled DNA synthesis at 10^{-3} mol/L in HeLa cells (Schiffmann 1983; Eder 1982).
- In a wing spot test on *Drosophila melanogaster* positive results were observed when the chemical was administered by inhalation at the LC50 value of 2.75 µg/L (Chroust 2007; IARC 2018).

In vivo

- In a micronucleus induction test on B6C3F1 mice bone marrow cells, micronuclei were not induced in bone marrow cells of male treated intraperitoneally with the chemical at doses up to 250 mg/kg bw (Shelby 1993).
- In a recombination test on *Drosophila melanogaster* a positive result was reported for the induction of sex linked recessive lethal mutations at 4500 ppm in post meiotic and meiotic germ cells of adult males fed the chemical. The same test sample was reported to have negative results for the induction of reciprocal translocations at 5000 ppm (Foureman 1994).

In silico

- A quantitative structure activity relationship multivariate analysis of a series of structurally similar halogenated aliphatic compounds, including the chemical, indicated that nucleophilic superdelocalisability of the halogen atom (calculated by quantum mechanics) was a good structural parameter to predict the toxicity and genotoxicity of these compounds, this was consistent with the direct reactivity or bioactivation at the halogenated carbon (Chroust 2007).
- Modelling using OASIS TIMES predicted that the chemical and metabolites induce micronucleus formation in vitro. There were alerts for in vitro mutagenicity (Ames test). In vivo predictions were negative (OASIS LMC). The predictions were within the applicability domain of the genotoxicity models and based on alerts for alpha, beta-unsaturated carboxylic acids and esters and haloalkane derivatives with labile halogen.

Carcinogenicity

Based on the weight of evidence, the chemical is considered to be carcinogenic warranting classification.

Available data indicate that the chemical is carcinogenic in rodents. There is sufficient evidence for carcinogenicity in experimental animals. Increased incidences of tumours in the forestomach were observed in rats and mice following oral exposure and in mice following inhalation exposure. Other tumours observed that are potentially related to treatment include:

- subcutaneous fibromas (female rats, oral exposure)
- adenoma of the Harderian gland (female mice, inhalation exposure)
- follicular cell adenoma
- follicular cell adenoma or adenocarcinoma (combined) of the thyroid gland (male rats, inhalation exposure).

No human exposure data is available. Although the forestomach and Harderian gland have no equivalent tissue in humans, there is some evidence of carcinogenicity at other sites and the chemical has key characteristics of a carcinogen including being potentially genotoxic in vitro.

Oral

The National Toxicology Program (NTP) of the USA Department of Health and Human Services conducted toxicology and carcinogenesis Studies of the chemical (NTP 1986). The studies were conducted at Litton Bionetics, Inc. The guidelines used for these studies have not been specified.

In the 2 year carcinogenicity study, groups of 50 F344/N rats of each sex were administered 0, 75, or 150 mg/kg bw/day the chemical in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 B6C3F1 mice of each sex were administered 0, 100, or 200 mg/kg bw/day on the same schedule.

Rats

In rats, the mean body weight of high dose male rats was consistently 10− 15% lower than that of the vehicle control group, with a non-significant reduction in survival of high dose male rats. Mean body weights and survival in low dose male rats and in both dosed groups of female rats were comparable to those of their vehicle control groups. Tumours were observed at several different tissue sites (Table 1 and Table 2). The chemical induced forestomach squamous cell papillomas and squamous cell carcinomas. Papillomas were observed at significantly increased incidences in high dose male and female rats. Squamous cell carcinomas were observed only in high dose male rats. Increased incidence of forestomach basal cell hyperplasia was observed in male and female rats.

Subcutaneous fibromas in female rats occurred with a significant positive trend. The observed incidence was greater than historical incidence of subcutaneous fibroma in control female rats at the study laboratory and in NTP studies. The IARC Working Group concluded that these subcutaneous tumours may have been related to treatment (IARC 2018).

Low incidences of renal tubular cell adenocarcinomas, renal transitional cell carcinomas, and transitional cell papillomas of the urinary bladder were observed in male rats dosed with 150 mg/kg bw/day -the chemical. No such effects were seen at lower doses, or in females at any dose level. Renal tubular cell adenomas (1/50) were also seen in male rats dosed at 75 mg/kg bw/day. In the testes, interstitial cell tumours occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls. Observed numbers were within the range of historical controls. There is uncertainty whether these tumours were related to treatment (IARC 2018).

Table 1. Incidences of neoplastic lesions in male rats

Tumour type	**0 mg/kg**	75 mg/kg	150 mg/kg	Historical incidences
Forestomach: squamous cell carcinoma	0/50 (0%)	0/50 (0%)	2/48 (4%)	5/1062 (0.5%)
Forestomach: squamous cell papilloma	1/50 (2%)	5/50 (10%)	30/48 (63%)	5/1062 (0.5%)
Renal tubular cell adenoma	0/50 (0%)	1/50	0/49 (0%)	-
Renal tubal cell adenocarcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	-
Renal transitional cell carcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	-
Transitional cell papilloma	0/48 (0%)	0/49 (0%)	1/46	-
Interstitial cell tumours	36/50 (72%)	43/50 (86%)	43/48 (90%)	(90.4%)

Table 2. Incidences of neoplastic lesions in female rats

Tumour type	0 mg/kg	75 mg/kg	150 mg/kg	Historical incidences
Forestomach: squamous cell carcinoma	0/50 (0%)	0/50 (0%)	2/48 (4%)	5/1062 (0.5%)
Forestomach: squamous cell papilloma	1/50 (2%)	1/50 (2%)	10/50 (20%)	5/1062 (0.5%)
Subcutaneous Fibroma, Sarcoma or Fibrosarcoma	1/50 (2%)	3/50 (6%)	5/50 (10%)	2/150 (3.6-5%)

Mice

In mice, the mean body weights of high dose males and of both higher dosed groups of female mice were 5−9% lower than those of the controls, whereas survival in both male and female mice was not affected by the chemical administration.

Squamous cell papillomas in male and female mice, squamous cell carcinomas in male mice, and squamous cell papillomas or carcinomas (combined) in both sexes occurred with positive trends and were significantly greater than those in the vehicle controls (Table 3 and Table 4). Dose related increases in the incidence of forestomach inflammation and epithelial hyperplasia were observed in male and female mice. The microscopic characteristics of squamous cell neoplasms of mice were similar to those described in rats. Evidence of metastasis or invasion of other organs was observed in 2 low dose and 3 high dose males and in one high dose female (IARC 2018).

Negative trends were observed in the incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice and of hemangiomas or hemangiosarcomas (combined) in dosed female mice.

Table 3. Incidences of neoplastic lesions in male mice

Tumour type	0 mg/kg	100 mg/kg	200 mg/kg	Historical incidences
Forestomach: squamous cell carcinoma	0/49 (0%)	5/49 (0%)	7/49 (4%)	7/1005 (0.7%)
Forestomach: squamous cell papilloma	3/50 (6%)	19/50 (39%)	30/49 (61%)	7/1005 (0.7%)

Table 4. Incidences of neoplastic lesions in female mice

Tumour type	0 mg/kg	100 mg/kg	200 mg/kg	Historical incidences
Forestomach: squamous cell carcinoma	0/50 (0%)	1/48 (2%)	2/44 (5%)	4/1005 (0.4%)
Forestomach: squamous cell papilloma	0/50 (6%)	16/48 (33%)	31/44 (70%)	4/1005 (0.4%)

Inhalation studies

In the chronic inhalation toxicity and carcinogenicity study described above (JISHA 1998), F344/DuCrj rats (50/sex/dose) were exposed, by whole body inhalation, to 0, 50, 100 or 200 ppm the chemical, 6-hours a day, 5 days per week for 104 weeks. Similarly, BDF1 mice (50/sex/dose) were exposed to 0, 50, 100 or 200 ppm, 6 hours a day, 5 days per week for 104 weeks. The incidence of neoplastic lesions was statistically analysed by Fisher's exact test (Katagiri 2000).

In rats, slight but significantly increased incidences of thyroid follicular cell adenoma and of thyroid follicular cell adenoma or follicular adenocarcinoma (combined) were observed in males, (follicular cell adenoma: 2/50, 0/50, 2/50 and 6/50 and thyroid follicular cell adenoma or follicular adenocarcinoma (combined): 4/50, 4/50, 3/50 and 10/50 at 0, 50, 100 and 200 ppm, respectively. The range of historical control is 0–4%. No significant increase in the incidence of tumours was observed in treated female F344/ DuCrj rats.

In mice, a significant positive trend in the incidence of forestomach squamous cell papilloma was observed (1/50, 0/49, 3/50 and 4/50 in males; and 1/50, 0/48, 5/50, and 4/49 in females at 0, 50, 100 and 200 ppm respectively) (IARC 2018). One incidence of squamous cell carcinoma was observed in one male exposed to 100 ppm the chemical. The incidence of forestomach epithelial hyperplasia was also significantly increased in males and females at 200 ppm.

The incidence of Harderian gland adenoma was 3/50, 7/49, 9/50, 5/50 in males and 0/50, 4/48, 7/50, 8/49 in females at 0, 50, 100 and 200 ppm respectively. The incidence of Harderian gland adenoma in female mice was significantly higher in the groups exposed to 100 and 200 ppm compared to historical control data.

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to the chemical.

Summary and Conclusion

Technical grade methallyl chloride was tested for carcinogenicity by oral administration (gavage) and by whole-body inhalation in rats and mice. In rats, the chemical caused a significantly increased incidence (with a significant positive trend) of forestomach squamous cell papilloma and forestomach squamous cell papilloma or carcinoma (combined) in males and that of forestomach squamous cell papilloma in females. Treated female rats also developed subcutaneous fibromas that may have been related to treatment.

In mice, there were significantly increased incidences of forestomach squamous cell papilloma, forestomach squamous cell carcinoma, and forestomach squamous cell papilloma or carcinoma (combined) in males and that of forestomach squamous cell papilloma and forestomach squamous cell papilloma or carcinoma (combined) in females.

Inhalation exposure to the chemical resulted in a significant positive trend in the incidence of thyroid follicular cell adenoma and follicular cell adenoma or adenocarcinoma (combined) of the in male rats. No significant increase in the incidence of tumours was observed in female rats. In mice a significantly increased positive trend in the incidence of forestomach squamous cell papilloma in males and females was observed. It also caused a significantly increased incidence of adenoma of the Harderian gland in females.

The IARC (IARC 2018) reviewed the carcinogenicity studies and concluded that there is sufficient evidence in experimental animals for the carcinogenicity of the chemical. It exhibits

characteristics of a carcinogen. It is genotoxic; induced gene mutation in bacterial and mammalian cells, chromosomal aberrations and sister-chromatid exchange in mammalian cells, and genetic crossing over (or recombination) and sex linked recessive lethal mutation in post meiotic and meiotic germ cells in *Drosophila melanogaster*. There is also moderate evidence that the chemical induces chronic inflammation. The chemical induced inflammation in the liver and nasal cavity in rats and mice, and inflammation in the forestomach in male and female mice. There is weak evidence that the chemical alters cell proliferation. Proliferation of the epithelial cells of the forestomach was increased in rats exposed to the chemical. There were minimal data were available on the other key characteristics of carcinogens (alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, is immunosuppressive, modulates receptor mediated effects or causes immortalisation) (IARC 2018).

The United States National Toxicology Program (NTP) report on carcinogens concluded that the chemical "is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals" (NTP 2021).

The structurally related chemical, allyl chloride (CAS No. 107-05-1), also produced tumours in the forestomach in mice following oral exposure. The chemical induced tumours in the lung in mice, exposed via intraperitoneal injection. The chemical also exhibited tumour initiating potential when applied dermally, but did not induce tumours in the absence of a promoter (NICNAS 2013)

Reproductive and development toxicity

Very limited information is available on reproductive toxicity of the chemical. In, a briefly described 14 day reproductive study, 10 male rats (albino Wistar, 10 weeks old) were dosed with the chemical in arachis oil by oral gavage at doses of 0, 40 or 160 mg/kg bw/day (Cassidy 1979). Minor testicular changes were observed in the rats exposed to the chemical, with 2 rats showing widespread bilateral testicular atrophy. These changes were believed to be a secondary effect due to nutritional deficiencies consequential to gastric lesions observed in those rats. No significant differences were observed between treated and control animals in the following: maternal mortality; clinical observations; mean testes weights; morphology; epididymides; efferent ducts and sperm ducts.

The authors concluded that due to the small number of. animals affected, the frequent lack of a dose response effect and the possibility of competing toxicity, these changes could not unequivocally be attributed to exposure to the chemical.

The NITE reported a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test using rats dosed by gavage (doses not specified). A decrease in the number of live pups at birth was observed at 180 mg/kg bw/day where effects on total bilirubin and liver enzymes (in females, details unspecified), an increase in post implantation embryo loss, and forestomach epithelial hyperplasia were observed in the parental animals. In summary, an increase in embryo death and a decrease in the number of live pups at birth were seen at the dose where general toxicity in parental animals was manifested (NITE n.d).

References

Cassidy SL, Linnett SL and Dix K N (1979). 'Toxicity of Fine Chemicals: Preliminary studies for the detection of testicular changes in rats', *Shell Toxicology Lab*. Unpublished.

Chemwatch (n.d.) *Galleria Chemica*, Chemwatch website, accessed 7 August 2023.

Chroust K, Pavlová M, Prokop Z, Mendel J, Bozková K and Kubát Z (2007). Quantitative structure-activity relationships for toxicity and genotoxicity of halogenated aliphatic compounds: wing spot test of Drosophila melanogaster. *Chemosphere*, 67(1):152–9, doi 10.1016/j.chemosphere.2006.09.020.

Deichmann WB and Gerarde HW (1969). Toxicology of Drugs and Chemicals. Academic Press. New York and London.

Eder E, Neudecker T, Lutz D, Henschler D (1982), 'Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation'. *Chemico-Biological Interactions*, 38(3):303–15, doi 10.1016/0009-2797(82)90060-6.

Foureman P, Mason JM, Valencia R, Zimmering S (1994). Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environmental and Molecular Mutagenesis*, 23(3):208–27, doi 10.1002/em.2850230310.

Ghanayem BL, Maronpot RR and Matthew HB. (1986) 'Association of chemically induced forestomach cell proliferation and carcinogenesis', *Cancer Letters*., 32, 27 1-278, doi 10.1016/0304-3835(86)90179-5.

Gulati DK, Witt K, Anderson B, Zeiger E and Shelby MD (1989) 'Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. II: Results with 27 chemicals', *Environmental and Molecular Mutagenesis*, 13, 133- 1 93, doi 10.1002/em.2850130208.

Haworth S, Lawlor T, Mortelmans K, Speck W and Zeiger E (1983) 'Salmonella mutagenicity test results for 250 chemicals', *Environmental and Molecular Mutagenesis*, Suppl. 1,3-142, doi 10.1002/e,.2860050703.

Hazardous Substances Data Bank (HSDB) (2014),*3-Chloro-2-methyl-1-propene. Report. CASRN: 563-47-3. Hazardous Substances Data Bank [online database]*. United States National Library of Medicine, accessed 25 August 2023.

International Agency for Research on Cancer (IARC) (1995). *Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC Monographs evaluation of carcinogenic risks to humans*, International Agency for Research on Cancer, 63:1-551, accessed 25 August 2023.

International Agency for Research on Cancer (IARC) (2018). *Working Group on the Evaluation of Carcinogenic Risks to Humans. Some Industrial Chemicals: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. International Agency for Research on Cancer. https://publications.iarc.fr/563, accessed 25 August 2023.

JISHA (1998). Japan Industrial Safety and Health Association. *Summary of Inhalation Carcinogenicity Study of 2-Methallyl Chloride in F344 Rats*. Japan Bioassay Research Center, accessed 9 August 2023.

Katagiri T, Takeuchi T, Mine T, Noguchi T, Nishizawa T, Yamamoto S, Okudaira M and Matsushima T (2000). Chronic inhalation toxicity and carcinogenicity studies of 3-chloro-2-methylpropene in BDF1 mice. *Industrial Health*, 38(3):309–18, doi 10.2486/indhealth.38.309.

Lhasa Limited Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (Version 6.0.1), [Computer software], Lhasa Limited, accessed August 2023.

Molecular Networks GmbH and Altamira, LLC (MN-AM), ChemTunes.ToxGPS (Version 4.0) [Computer software], accessed 20 September 2023.

Myhr BE and Caspary WJ. (1991) Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results from 31 coded compounds in the National Toxicology Program. *Environmental and Molecular Mutagenesis*, 18, 51-83, doi 10.1002/em.2850180109.

NITE (National Institute of Technology and Evaluation (n.d.) *GHS Classification Results*, accessed 7 August 2023.

NTP (National Toxicology Program (1986)). Toxicology and carcinogenesis studies of 3-chloro-2-methylpropene, NTP, accessed 20 September 2023.

NTP (National Toxicology Program) (2021) *3-Chloro-2-methylpropene*. CAS No. 563-47-3. Report on carcinogens, 15th Ed. National Toxicology Program, accessed 20 August 2023.

OASIS LMC (Laboratory of Mathematical Chemistry) Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator (OASIS–TIMES) (Version 2.28.1.6), [Computer software], LMC, accessed 20 August 2023.

OECD (Organisation for economic cooperation and development), Quantitative Structure-Activity Relationship (QSAR) Toolbox (Version 4.4) [Computer software], OECD, accessed 9 August 2023.

OECD (n.d.) *The 2004 OECD List of High Production Volume Chemicals*, accessed 20 August 2023.

OECD (2004), SIAR *1-propene,3-chloro* (107-51-5), accessed 20 August 2023.

Safe Work Australia (SWA) *Hazardous Chemical Information System* (HCIS). Exposure Standards, accessed 25 August 2023.

Sax N. (1979) Dangerous Properties of Industrial Materials, 5th edn, Van Nostrand Reinhold Corp, New York.

Schiffmann D, Eder E, Neudecker T, Henschler D (1983). Induction of unscheduled DNA synthesis in HeLa cells by allylic compounds. *Cancer Letters*, 20(3):263–9, doi 10.1016/0304-3835(83)90023-X.

Shelby, M.D., Erexson, G.L., Hook, G.J. & Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. *Environmental and Molecular Mutagenesis*, 21,160-179, doi 10.1002/em.2850210210.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)* Seventh Revised Edition, UNECE, accessed 01 August 2023, accessed 20 August 2023.

US CDR (2016) United States Environmental Protection Agency. *Chemical Data Reporting*. 2016 CDR Database, accessed 11 September 2023.

US CDR (2020) United States Environmental Protection Agency. *Chemical Data Reporting*. 2020 CDR Database, accessed 11 September 2023.