# 1-CHLORO-2-METHYLPROPENE

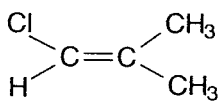
## 1. Exposure Data

### 1.1 Chemical and physical data

*1.1.1 Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 513-37-1
*Chem. Abstr. Name*: 1-Chloro-2-methyl-1-propene
*IUPAC Systematic Name*: 1-Chloro-2-methylpropene
*Synonyms*: α-Chloroisobutylene; 1-chloroisobutylene; dimethylvinyl chloride; 2,2-dimethylvinyl chloride; β,β-dimethylvinyl chloride; isocrotyl chloride; 2-methyl-1-chloropropene; 2-methyl-1-propenyl chloride

*1.1.2 Structural and molecular formulae and relative molecular mass*



$C_4H_7Cl$

Relative molecular mass: 90.55

*1.1.3 Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless to brown liquid (Budavari, 1989; Aldrich Chemical Co., 1994a)

(*b*) *Boiling-point*: 68 °C at 754 mm Hg [100 kPa] (Lide, 1993)

(*c*) *Freezing-point*: –1 °C (Aldrich Chemical Co., 1994b)

(*d*) *Density*: 0.9186 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [80595], grating [80595]) and nuclear magnetic resonance (proton [53505]) spectral data have been reported (Sadtler Research Laboratories, 1994).

(*f*) *Solubility*: Soluble in acetone, chloroform, diethyl ether and ethanol (Lide, 1993)

(*g*) *Conversion factor*: $mg/m^3 = 3.7 \times ppm$[1]

[1] Calculated from: $mg/m^3$ = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

### *1.1.4 Technical products and impurities*

1-Chloro-2-methylpropene is available commercially at a purity of at least 98% (Fluka Chemical Corp., 1993; Aldrich Chemical Co., 1994b). 3-Chloro-2-methylpropene (see monograph, this volume) has been reported as an impurity (US National Toxicology Program, 1986).

### *1.1.5 Analysis*

Capillary gas chromatography–mass spectrometry has been used for the analysis of emissions of organic vapours near sites for the disposal of industrial and chemical wastes. Samples of ambient air were collected with a sampler equipped with Tenax GC sorbent cartridges. For 1-chloro-2-methylpropene, the method has an estimated detection limit of 62 ng/m$^3$ (Krost *et al.*, 1982; Pellizzari, 1982).

## 1.2 Production and use

### *1.2.1 Production*

1-Chloro-2-methylpropene is a by-product of the production of 3-chloro-2-methylpropene (Hooper *et al.*, 1992). 1-Chloro-2-methylpropene is produced in research quantities by one company in Germany (Chemical Information Services Inc., 1994).

### *1.2.2 Use*

1-Chloro-2-methylpropene is not known to be used commercially other than for research purposes.

## 1.3 Occurrence

### *1.3.1 Natural occurrence*

1-Chloro-2-methylpropene is not known to occur as a natural product.

### *1.3.2 Occupational exposure*

No data were available to the Working Group.

### *1.3.3 Air*

1-Chloro-2-methylpropene was found among other organic compounds in the vapour phase of ambient air near industrial complexes and chemical waste disposal sites in the United States of America. Levels of 90–670 µg/m$^3$ were found in ambient air around four of five industrial complexes near Curtis Bay, MD (Pellizzari, 1982).

### *1.3.4 Water*

No data were available to the Working Group.

### 1.4 Regulations and guidelines

No occupational exposure limits have been reported for 1-chloro-2-methylpropene (ILO, 1991).

## 2. Studies of Cancer in Humans

No data were available to the Working Group.

## 3. Studies of Cancer in Experimental Animals

### Oral administration

*Mouse:* Groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, were administered 1-chloro-2-methylpropene (purity, 98%; the major impurity was 3-chloro-2-methylpropene) in corn oil by gavage at doses of 0, 100, or 200 mg/kg bw on five days per week for 102 weeks. Survival of treated male and female mice was significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were: 38 male controls, eight at the low dose and two at the high dose; and 41 female controls, six at the low dose and three at the high dose. Histopathological evaluation revealed dose-related increased incidences (by life-table tests) of forestomach neoplasms in both males and females and of preputial gland neoplasms in males. In males, the incidences of squamous-cell papillomas of the forestomach were 1/48 controls, 3/47 at the low dose ($p = 0.054$) and 8/44 at the high dose ($p = 0.011$); the incidences of squamous-cell carcinomas were 0/48 controls, 42/47 at the low dose ($p < 0.001$) and 35/44 at the high dose ($p < 0.001$); and the combined incidences of squamous-cell papillomas or carcinomas were 1/48 controls, 43/47 at the low dose ($p < 0.001$) and 41/44 at the high dose ($p < 0.001$). In females, the incidences of squamous-cell papillomas of the forestomach were not significantly increased in the treated groups in comparison with controls; the incidences of squamous-cell carcinomas were 0/50 controls, 40/47 at the low dose ($p < 0.001$) and 36/43 at the high dose ($p < 0.001$); and the combined incidences of squamous-cell papillomas or carcinomas were 0/50 controls, 40/47 at the low dose ($p < 0.001$) and 38/43 at the high dose ($p < 0.001$). The incidences of squamous-cell carcinomas of the preputial gland in male mice were 1/48 controls, 3/47 at the low dose and 16/44 at the high dose ($p < 0.001$) (United States National Toxicology Program, 1986).

*Rat*: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were administered 1-chloro-2-methylpropene (purity, 96–98%; the major impurities were 3-chloro-2-methylpropene, 1,2-dichloro-2-methylpropane, 2,2,4-trimethyl-3-hydroxypentanal and *tert*-butyl chloride) in corn oil by gavage at doses of 0, 100 or 200 mg/kg bw on five days per week for 103 weeks. Survival of treated male and female rats was significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were 38 control males,

nine at the low dose and none at the high dose; and 43 female controls, 11 at the low dose and none at the high dose. Histopathological evaluation revealed increased incidences (by life-table tests) of neoplasms of the nasal cavity, oral cavity, oesophagus and forestomach in males and females (Table 1). The incidences of epithelial hyperplasia of the forestomach were increased in treated males, occurring in 0/49 controls, 24/50 at the low dose and 19/50 at the high dose; and in treated females, occurring in 0/50 controls, 29/50 at the low dose and 24/49 at the high dose. The incidences of epithelial hyperplasia of the oesophagus were also increased in treated animals, occurring in 0/50 male controls, 6/50 at the low dose and 4/49 at the high dose and in 0/49 female controls, 7/50 at the low dose and 4/49 at the high dose (United States National Toxicology Program, 1986).

**Table 1. Incidences of neoplastic lesions in Fischer 344/N rats in two-year studies in which 1-chloro-2-methylpropene was administered by gavage**

| Site and tumour type | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Vehicle control | 100 mg/kg bw | 200 mg/kg bw | Vehicle control | 100 mg/kg bw | 200 mg/kg bw |
| Nasal cavity | | | | | | |
| Adenocarcinoma | 0/47 | 8/46<br>$p < 0.001$ | 4/32<br>$p < 0.001$ | 0/50 | 3/49<br>$p = 0.011$ | 6/41<br>$p < 0.001$ |
| Squamous-cell carcinoma | 0/47 | 3/46 | 0/32 | 0/50 | 2/49 | 2/41 |
| Carcinoma (not otherwise specified) | 0/47 | 12/46<br>$p < 0.001$ | 24/32<br>$p < 0.001$ | 0/50 | 11/49<br>$p < 0.001$ | 28/41<br>$p < 0.001$ |
| Oral cavity | | | | | | |
| Squamous-cell carcinoma | 0/50 | 5/50<br>$p = 0.007$ | 2/50<br>$p=0.030$ | 0/50 | 2/50 | 1/50 |
| Squamous-cell papilloma | 0/50 | 0/50 | 2/50 | 0/50 | 0/50 | 4/50<br>$p = 0.004$ |
| Papilloma or carcinoma | 0/50 | 5/50<br>$p = 0.007$ | 4/50<br>$p = 0.001$ | 0/50 | 2/50 | 5/50<br>$p < 0.001$ |
| Oesophagus | | | | | | |
| Squamous-cell carcinoma | 0/50 | 4/50<br>$p = 0.004$ | 1/49 | 0/49 | 3/50<br>$p = 0.024$ | 1/49 |
| Squamous-cell papilloma | 0/50 | 2/50<br>$p = 0.043$ | 3/49<br>$p = 0.011$ | 0/49 | 0/50 | 0/49 |
| Papilloma or carcinoma | 0/50 | 6/50<br>$p < 0.001$ | 4/49<br>$p = 0.004$ | | | |
| Forestomach | | | | | | |
| Squamous-cell carcinoma | 0/49 | 7/50<br>$p < 0.001$ | 0/50 | 0/50 | 5/50<br>$p = 0.004$ | 1/49 |
| Squamous-cell papilloma | 0/49 | 7/50<br>$p < 0.001$ | 0/50 | 1/50 | 4/50<br>$p = 0.027$ | 1/49 |
| Papilloma or carcinoma | 0/49 | 14/50<br>$p < 0.001$ | 0/50 | 1/50 | 9/50<br>$p < 0.001$ | 2/49 |

From United States National Toxicology Program (1986)
$p$ values are given for incidences that are significantly greater than those of controls, on the basis of life-table tests.

# 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

## 4.1 Absorption, distribution, metabolism and excretion

### *4.1.1 Humans*

No data were available to the Working Group.

### *4.1.2 Experimental systems*

[2-$^{14}$C]1-Chloro-2-methylpropene (3.5 mCi/mmol; radiochemical purity, 96%) was administered by gavage to male Fischer 344 rats in single or up to four daily doses of 150 mg/kg bw in corn oil. The compound was extensively absorbed and rapidly excreted: 92% of the single dose was eliminated within 24 h after treatment. It was rapidly distributed to the tissues; liver and kidney contained higher concentrations of radiolabel than forestomach and glandular stomach, which had similar levels. The tissue concentrations increased monotonically after repeated doses but had declined significantly after four days of recovery following treatment. After a single dose, about 35% of the administered radiolabel was found in urine, 52% was exhaled and 5% was detected in the faeces. In the expired air, about 25% of the dose was $^{14}$C-carbon dioxide; 30% was volatile compounds, of which 96% was unchanged compound. The main urinary metabolite of 1-chloro-2-methylpropene was *trans*-2-amino-6-methyl-4-thia-5-heptene-1,7-dioic acid, indicating oxidation before glutathione conjugation. This metabolite constituted 23% of the total urinary radiolabel, and its corresponding N-acetyl derivative accounted for 9%. The profile of the urinary metabolites was quantitatively and qualitatively similar after one, two and four treatments (Ghanayem & Burka, 1987).

[2-$^{14}$C]1-Chloro-2-methylpropene (3.5 mCi/mmol; radiochemical purity, 96%) was administered by gavage to male B6C3F1 mice as a single dose of 150 mg/kg bw in corn oil. The compound was extensively absorbed and rapidly excreted; urine contained about 46% of the dose after 24 h, 25% was expired as carbon dioxide and 5% as the unchanged compound, whereas 9% of the dose was found in the faeces. The highest levels of radiolabel in tissues were detected in kidney, liver, forestomach and thymus 24 h after administration. As in rats, *trans*-2-amino-6-methyl-4-thia-5-heptene-1,7-dioic acid was the major urinary metabolite, constituting 35% of the total urinary radiolabel. Its N-acetyl derivative accounted for 12% (Ghanayem & Burka, 1987).

Incubation of 1-chloro-2-methylpropene with liver microsomes from phenobarbital-pretreated male Fischer 344 rats, untreated male rats or untreated female rats in the presence of NADPH resulted in the formation of (*E*)- and (*Z*)-3-chloro-2-methylpropen-1-ol in a ratio of 2:1. No alcohol was formed in the presence of microsomes from β-naphthoflavone-treated male rats. Synthetic (*E*)- and (*Z*)-3-chloro-2-methylpropenal reacted rapidly with *N*-acetylcysteine, the *E*-adduct being the sole product in both cases. In contrast, the corresponding acids reacted very slowly with sulfur nucleophiles. These results suggest that 1-chloro-2-methylpropene is oxidized to *E*- and *Z*-alcohols and subsequently to their respective electrophilic α,β-unsaturated chloro-

aldehydes, which then react instantaneously with glutathione to form the *E*-adduct (Srinivas & Burka, 1988).

## 4.2 Toxic effects

### *4.2.1 Humans*

No data were available to the Working Group.

### *4.2.2 Experimental animals*

Groups of 10 male and 10 female Fischer 344/N rats and B6C3F1 mice were administered 0, 63, 125, 250, 500 or 750 mg/kg bw 1-chloro-2-methylpropene (purity, 96%) in corn oil by gavage, on five days per week for 13 weeks. Rats developed necrosis of the crypts of the small intestine at doses of 250 mg/kg bw and higher; similar changes, but at a lower incidence, occurred in the colonic mucosa. In addition, bone-marrow hypoplasia was noted at the two highest doses. In mice, necrosis of lymphopoietic cells, leading to atrophy of the thymus, lymph nodes and spleen, was observed at doses of 125 mg/kg bw and higher. Compound-related necrotic and/or degenerative changes also occurred in the pancreatic islet cells, liver, ovary and testis at the highest doses (United States National Toxicology Program, 1986).

In a study of cell proliferation in the forestomach, 1-chloro-2-methylpropene (purity, 98%) in corn oil was administered by gavage to groups of eight male Fischer 344/N rats at doses of 0, 100 or 200 mg/kg bw on five days per week for two weeks. Multifocal epithelial cell proliferation of the forestomach occurred in two animals at the low dose and in eight at the high dose, and hyperkeratosis of the forestomach developed in eight animals at the high dose (Ghanayem *et al.*, 1986).

## 4.3 Reproductive and prenatal effects

No data were available to the Working Group.

## 4.4 Genetic and related effects

### *4.4.1 Humans*

No data were available to the Working Group

### *4.4.2 Experimental systems* (see also Table 2 and Appendices 1 and 2)

1-Chloro-2-methylpropene was mutagenic to *Salmonella typhimurium* strain TA100 in the presence of exogenous metabolic activation in a single study, in which bacterial cells were exposed in chambers specially devised for testing volatile compounds. No clearly positive responses were obtained in a preincubation test.

## Table 2. Genetic and related effects of 1-chloro-2-methylpropene

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 0.00 | Neudecker *et al.* (1986) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 3850 | Zeiger *et al.* (1987) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 3850 | Zeiger (1990) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | + | 100[c] | Zeiger (1990) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 3850 | Zeiger *et al.* (1987) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 3850 | Zeiger *et al.* (1987) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 3850 | Zeiger (1990) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 3850 | Zeiger *et al.* (1987) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 3850 | Zeiger (1990) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 200[c] | Zeiger (1990) |
| DMX, *Drosophila melanogaster,* sex-linked recessive lethal mutation | + | | 12 750 feed | US National Toxicology Program (1986) |
| DMH, *Drosophila melanogaster,* heritable translocation | + | | 12 750 feed | US National Toxicology Program (1986) |
| G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro* | + | 0 | 0.4 | US National Toxicology Program (1986) |
| SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro* | + | + | 100 | Anderson *et al.* (1990) |
| CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro* | – | – | 1600 | Anderson *et al.* (1990) |

[a]+, considered to be positive; –, considered to be negative; 0, not tested

[b]LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, mg/ml; in-vivo tests, mg/kg bw; 0.00, dose not reported

[c]Exposure in a desiccator: atmospheric concentration (μg/ml)

1-Chloro-2-methylpropene induced a significant increase in the frequency of both sex-linked recessive lethal mutations and heritable reciprocal translocations in the germ cells of *Drosophila melanogaster* after adult males were fed for three days at a dose of 12 750 ppm [μg/g] in 5% sucrose.

1-Chloro-2-methylpropene induced gene mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in the absence of metabolic activation.

Sister chromatid exchange, but not chromosomal aberration, was induced in Chinese hamster ovary cells in both the presence and absence of metabolic activation.

# 5. Summary and Evaluation

## 5.1 Exposure data

1-Chloro-2-methylpropene occurs as an impurity in the production of 3-chloro-2-methylpropene. It has no known commercial application.

## 5.2 Human carcinogenicity data

No data were available to the Working Group.

## 5.3 Animal carcinogenicity data

1-Chloro-2-methylpropene was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. It produced squamous-cell carcinomas of the preputial gland in male mice and squamous-cell carcinomas of the forestomach in animals of each sex. In rats, it produced carcinomas of the nasal cavity and papillomas and carcinomas of the oral cavity, oesophagus and forestomach in animals of each sex.

## 5.4 Other relevant data

No data were available on the toxicokinetics or toxic effects of 1-chloro-2-methylpropene in humans. It is rapidly absorbed and excreted after oral administration to rats and mice. In rats, more of the dose was excreted via the lungs than in the urine, whereas in mice similar proportions were excreted by the two routes. Both the unchanged compound and carbon dioxide were exhaled. The major urinary metabolite in rats and mice was formed after oxidation and glutathione conjugation.

Repeated oral administration of 1-chloro-2-methylpropene to rats resulted in tissue necrosis in a number of organs, including the small and large intestine, thymus and spleen. Repeated administration of the compound to rats by gavage induced proliferation of forestomach cells.

Gene mutation and sister chromatid exchange, but not chromosomal aberrations, were induced in cultured rodent cells in single studies. 1-Chloro-2-methylpropene induced gene and chromosomal mutation in insects (in a single study). It was mutagenic to bacteria.

### 5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 1-chloro-2-methylpropene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-chloro-2-methylpropene.

**Overall evaluation**

1-Chloro-2-methylpropene *is possibly carcinogenic to humans (Group 2B).*

## 6. References


Aldrich Chemical Co. (1994a) *Specification Sheet:1-Chloro-2-methylpropene*, Milwaukee, WI

Aldrich Chemical Co. (1994b) *Aldrich Catalog/Handbook of Fine Chemicals 1994–1995*, Milwaukee, WI, p. 338

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L. & Loveday, K.S. (1990) Chromosome aberration and sister chromatid exchange test results with 42 chemicals. *Environ. mol. Mutag.*, **16** (Suppl. 18), 55–137

Budavari, S., ed. (1989) *The Merck Index*, 11th Ed., Rahway, NJ, Merck & Co., p. 331

Chemical Information Services, Inc. (1994) *Directory of World Chemical Producers 1995/96 Standard Edition*, Dallas, TX, p. 179

Fluka Chemical Corp. (1993) *Fluka Chemika-BioChemika*, Buchs, p. 321

Ghanayem, B.I. & Burka, L.T. (1987) Comparative metabolism and disposition of 1-chloro- and 3-chloro-2-methylpropene in rats and mice. *Drug Metab. Disposition*, **15**, 91–96

Ghanayem, B.I., Maronpot, R.R. & Matthews, H.B. (1986) Association of chemically induced forestomach cell proliferation and carcinogenesis. *Cancer Lett.*, **32**, 271–278

Hooper, K., LaDou, J., Rosenbaum, J.S. & Book, S.A. (1992) Regulation of priority carcinogens and reproductive or developmental toxicants. *Am. J. ind. Med.*, **22**, 793–808

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva

Krost, K.J., Pellizzari, E.D., Walburn, S.G. & Hubbard, S.A. (1982) Collection and analysis of hazardous organic emissions. *Anal. Chem.*, **54**, 810–817

Lide, D.R., ed. (1993) *CRC Handbook of Chemistry and Physics*, 74th Ed., Boca Raton, FL, CRC Press, p. 3-146

Neudecker, T., Dekant, W., Jorns, M., Eder, E. & Henschler, D. (1986) Mutagenicity of chloroolefins in the *Salmonella*/mammalian microsome test. II. Structural requirements for the metabolic activation of non-allylic chloroprenes and methylated derivatives via epoxide formation. *Biochem. Pharmacol.*, **35**, 195–200


[1] For definition of the italicized terms, see Preamble, pp. 22–26.

Pellizzari, E.D. (1982) Analysis of organic vapour emissions near industrial and chemical waste disposal sites. *Environ. Sci. Technol.*, **16**, 781–785

Sadtler Research Laboratories (1994) *Sadtler Standard Spectra, 1981–1994, Supplementary Index*, Philadelphia, PA

Srinivas, P. & Burka, L.T. (1988) Metabolism of 1-chloro-2-methylpropene. Evidence for reactive chloroaldehyde intermediates. *Drug Metab. Disposition*, **16**, 449–454

United States National Toxicology Program (1986) *Toxicology and Carcinogenesis Studies of Dimethylvinyl Chloride (1-Chloro-2-methylpropene) (CAS No. 513-37-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies)* (NTP Tech. Rep. No. 316; NIH Publ. No. 86-2572), Research Triangle Park, NC

Zeiger, E. (1990) Mutagenicity of 42 chemicals in *Salmonella*. *Environ. mol. Mutag.*, **16** (Suppl. 18), 32–54

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. mol. Mutag.*, **9** (Suppl. 9), 1–110