3-CHLORO-2-METHYLPROPENE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

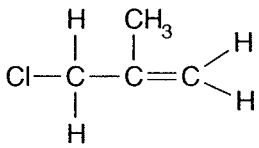
Chem. Abstr. Serv. Reg. No.: 563-47-3

Chem. Abstr. Name: 3-Chloro-2-methyl-1-propene

IUPAC Systematic Name: 3-Chloro-2-methylpropene

Synonyms: 3-Chloroisobutene; γ-chloroisobutylene; 3-chloroisobutylene; 2-(chloromethyl)-1-propene; isobutenyl chloride; MAC; methallylchloride; β-methylallylchloride; methallyl chloride; β-methallyl chloride; 2-methallyl chloride; methylallyl chloride; 2-methylallyl chloride; 2-methyl-3-chloropropene; 2-methyl-2-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 pale-yellow liquid with sharp irritating odour (Verschueren, 1983; FMC Corp., 1990; Aldrich Chemical Co., 1994a)

(*b*) *Boiling-point*: 71–72 °C (Lide, 1993)

(*c*) *Freezing-point*: –12 °C (Aldrich Chemical Co., 1994b)

(*d*) *Density*: 0.9165 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [4689]; grating [29193]), nuclear magnetic resonance (proton [9682, 9369]; C-13 [2018]) and mass [174] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Insoluble in water; soluble in acetone, chloroform, diethyl ether and ethanol (FMC Corp., 1990; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 102 mm Hg [13.6 kPa] at 20 °C; relative vapour density (air = 1), 3.12 (FMC Corp., 1990)

(*h*) *Stability*: Lower inflammable limit (air), 3.2%; polymerizes at room temperature and in the presence of sunlight (FMC Corp., 1990)

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

1.1.4 Technical products and impurities

3-Chloro-2-methylpropene is available commercially at purities ranging from 95% (technical grade) to 98%, with isocrotyl chloride (1-chloro-2-methylpropene; see monograph, this volume) as an impurity (Crescent Chemical Co., 1990; FMC Corp., 1990; Aldrich Chemical Co., 1994b).

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 3-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

3-Chloro-2-methylpropene is produced by substitutive chlorination of isobutylene. Production of this compound in the United States of America in 1984 was 5.4–11 thousand tonnes (United States National Toxicology Program, 1986). It is produced by two companies in the United States and one each in China, Germany and Japan (Chemical Information Services Inc., 1994).

1.2.2 Use

3-Chloro-2-methylpropene is used as an insecticide and fumigant and as an intermediate in the production of plastics, pharmaceuticals and other organic chemicals (Hooper *et al.*, 1992). Its use as a fumigant in individual sacks of grain in order to control the maize weevil in developing countries was promoted in the 1970s (Taylor, 1975); this use has been claimed to have been successful (Braby, 1992). It has been used in the Russian Federation to fumigate bulk grains (Taylor, 1975) and pulses that are not for human consumption (Braby, 1992).

1.3 Occurrence

1.3.1 Natural occurrence

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

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

1.3.2 Occupational exposure

No data were available to the Working Group.

1.3.3 Air

3-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. Levels of 110–400 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 (ILO, 1991). When the status of 3-chloro-2-methylpropene was reviewed in Germany in 1991, no MAK value was established, and it was placed in carcinogen category IIIB (justifiably suspected of having carcinogenic potential) (Deutsche Forschungsgemeinschaft, 1993).

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 3-chloro-2-methylpropene (technical-grade, containing 5% dimethylvinyl chloride [1-chloro-2-methylpropene; see monograph, p. 315]) in corn oil by gavage at doses of 0, 100 or 200 mg/kg bw on five days per week for 103 weeks. Survival in the treated groups was not significantly lower than that in vehicle controls; the numbers of survivors at the end of the experiment were: 26 male controls, 37 at the low dose and 32 at the high dose; and 37 female controls, 43 at the low dose and 27 at the high dose. Histopathological evaluation revealed dose-related increased incidences (by the incidental tumour test) of forestomach neoplasms in males and females. In males, the incidences of squamous-cell papillomas were 3/49 controls, 19/49 ($p < 0.001$) at the low dose and 30/49 ($p < 0.001$) at the high dose; the incidences of squamous-cell carcinomas were 0/49 controls, 5/49 ($p = 0.031$) at the low dose and 7/49 ($p = 0.016$) at the high dose; and the combined incidences of squamous-cell papillomas or carcinomas were 3/49

controls, 24/49 ($p < 0.001$) at the low dose and 36/49 ($p < 0.001$) at the high dose. In females, the incidences of squamous-cell papillomas were 0/50 controls, 15/48 ($p < 0.001$) at the low dose and 29/44 ($p < 0.001$) at the high dose; the incidences of squamous-cell carcinomas were: 0/50 controls, 1/48 at the low dose and 2/44 at the high dose; and the combined incidences of squamous-cell papillomas or carcinomas were 0/50 controls, 16/48 ($p < 0.001$) at the low dose and 31/44 ($p < 0.001$) at the high dose. The incidences of epithelial hyperplasia were also increased in treated animals: males – 0/49 controls, 14/49 at the low dose and 15/49 at the high dose; females – 4/50 controls, 6/48 at the low dose and 13/44 at the high dose (Chan *et al.*, 1986; United States National Toxicology Program, 1986).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were administered 3-chloro-2-methylpropene (technical grade, containing 5% dimethylvinyl chloride) in corn oil by gavage at doses of 0, 75 or 150 mg/kg bw on five days per week for 103 weeks. Survival was marginally reduced among male rats receiving the high dose; the numbers of survivors at the end of the experiment were 30 male controls, 25 at the low dose and 17 at the high dose; and 31 female controls, 32 at the low dose and 26 at the high dose. Histopathological examination revealed increased incidences (by the incidental tumour test) of squamous-cell papillomas of the forestomach in animals of each sex receiving the high dose: 1/50 male controls, 5/50 at the low dose and 30/48 ($p < 0.001$) at the high dose; 1/50 female controls, 1/50 at the low dose and 10/50 ($p = 0.006$) at the high dose. The incidences of basal-cell or epithelial hyperplasia of the forestomach were also increased in treated animals: 19/50 male controls, 41/50 at the low dose and 44/48 at the high dose; 24/50 female controls, 42/50 at the low dose and 45/50 at the high dose (Chan *et al.*, 1986; United States National Toxicology Program, 1986).

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]3-Chloro-2-methylpropene (specific activity, 2.5 mCi/mmol; radiochemical purity, 93%; 5% 1-chloro-2-methylpropene) was administered by gavage to male Fischer 344 rats as single or up to four daily doses of 150 mg/kg bw in corn oil. The compound was extensively absorbed and rapidly excreted: 82% of the single dose was eliminated within 24 h after treatment. It was rapidly distributed to tissues, and the highest concentrations were found in forestomach, liver and kidney; the concentration of radiolabel was considerably lower in glandular stomach than in forestomach. The tissue concentrations were approximately doubled after two doses, but little additional increase was observed after four doses. The concentrations

decreased after cessation of treatment. After a single dose, about 58% of the administered radiolabel was found in the urine, 22% was exhaled and 2% was detected in the faeces. In the expired air, about 12% of the dose was ^{14}C-carbon dioxide and 7% was volatile compounds. The main urinary metabolite was *N*-acetyl-*S*-(2-methylpropenyl)cysteine, which constituted 45% of the total urinary radiolabel. This metabolite is presumed to arise from direct conjugation of glutathione with 3-chloro-2-methylpropene (Ghanayem & Burka, 1987).

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 were administered 0, 50, 100, 200, 300 or 400 mg/kg bw 3-chloro-2-methylpropene (purity, 93%; containing 5% 1-chloro-2-methylpropene) in corn oil by gavage on five days per week for 13 weeks. Groups of 10 male and 10 female B6C3F1 mice received 0, 125, 250, 500, 750 or 1250 mg/kg bw by the same schedule. Focal areas of necrosis with inflammation were noted in the livers of rats given 300 and 400 mg/kg bw. In mice, degeneration and necrosis of the cortical tubules of the kidneys were observed at doses of 500 mg/kg bw and higher, and the incidence and severity of these lesions were greater in males than in females. Coagulative necrosis in the liver was also observed in mice at doses of 500 mg/kg bw and higher (United States National Toxicology Program, 1986).

In a study of cell proliferation in the forestomach, 3-chloro-2-methylpropene (purity, 90%; most of the remainder was 1-chloro-2-methylpropene) was administered by gavage to groups of eight male Fischer 344/N rats at doses of 0, 75 or 160 mg/kg bw on five days per week for two weeks. All treated animals had generalized epithelial cell proliferation and hyperkeratosis of the forestomach (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 1 and Appendices 1 and 2)

3-Chloro-2-methylpropene (purity, 90.7%) was mutagenic to *Salmonella typhimurium* strain TA100 both in the presence and absence of metabolic activation and when the cells were treated in a modified liquid suspension test or, as reported in an abstract, in chambers specially devised for volatile compounds. A 100% pure preparation was also mutagenic to this strain

Table 1. Genetic and related effects of 3-chloro-2-methylpropene

Test system	Result[a]		Dose[b] (LED/HID)	Purity	Reference
	Without exogenous metabolic system	With exogenous metabolic system			
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.00	100	Eder *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	1280	90.7	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation (Tedlar bag technique)	+	+	0.00	–	Warner *et al.* (1988) (Abstract)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1280	90.7	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	+	385	90.7	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	3850	90.7	Haworth *et al.* (1983)
DMG, *Drosophila melanogaster,* genetic crossing-over or recombination	+		1000 inh.	–	Vogel & Nivard (1993)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	23.0	90.7	Myhr & Caspary (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	16	90.7	Gulati *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	?	120	90.7	Gulati *et al.* (1989)
MVM, Micronucleus induction, mouse bone-marrow cells *in vivo*	–		250 ip	90.7	Shelby *et al.* (1993)

[a]+, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an adequate study); 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; inh, inhalation; ip, intraperitoneal

(Eder *et al.*, 1982). In standard assays, the compound was more weakly mutagenic to TA100; it was mutagenic to TA1537 only in the presence of an exogenous metabolic system.

Induction of somatic recombination was observed in *Drosophila melanogaster*, in the *white/white*$^+$ eye mosaic assay, after larvae had been exposed by inhalation to 3-chloro-2-methylpropene of unknown purity.

The frequencies of both large and small colonies in the L5178Y mouse lymphoma *tk* locus assay, indicative of intragenic changes at the thymidine kinase locus and chromosomal rearrangements, respectively, were increased by treatment with 3-chloro-2-methylpropene (purity, 90.7%) in the absence of metabolic activation.

3-Chloro-2-methylpropene (purity, 90.7%) induced chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells both in the presence and absence of metabolic activation.

Micronuclei were not induced in bone-marrow cells of male B6C3F1 mice treated intraperitoneally with 3-chloro-2-methylpropene (purity, 90.7%) at doses up to 250 mg/kg bw.

[A quantitative comparison with results obtained with 1-chloro-2-methylpropene indicates that the genotoxicity of 3-chloro-2-methylpropene cannot be accounted for by the presence of 1-chloro-2-methylpropene.]

5. Summary and Evaluation

5.1 Exposure data

3-Chloro-2-methylpropene is produced commercially as a chemical intermediate. It has had limited use as an insecticide and grain fumigant.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

3-Chloro-2-methylpropene containing 5% 1-chloro-2-methylpropene (see monograph, p. 315) was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. Tumours of the forestomach were induced in mice and rats of each sex.

5.4 Other relevant data

No data were available on the toxicokinetics or toxic effects of 3-chloro-2-methylpropene in humans. It is rapidly absorbed, extensively metabolized and rapidly excreted after oral administration to rats. Most of the excretory products were found in urine; a mercapturic acid was the main metabolite. Considerable amounts were exhaled, some as carbon dioxide.

After repeated oral administrations, 3-chloro-2-methylpropene induced liver necrosis in rats and mice and kidney necrosis in mice; it also induced forestomach hyperplasia in rats.

No data were available on the effects of 3-chloro-2-methylpropene on reproduction in humans or experimental animals.

Micronuclei were not induced in the bone marrow of mice treated *in vivo* in a single study. 3-Chloro-2-methylpropene induced gene mutation, sister chromatid exchange and chromosomal aberrations in rodent cells in single studies. It was mutagenic to insects and bacteria. The genotoxic effects of this compound cannot be attributed solely to the presence of 1-chloro-2-methylpropene as an impurity.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 3-chloro-2-methylpropene.

There is *limited evidence* in experimental animals for the carcinogenicity of 3-chloro-2-methylpropene.

Overall evaluation

3-Chloro-2-methylpropene *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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

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