3-CHLORO-2-METHYLPROPENE

1. Exposure Data

3-Chloro-2-methylpropene was considered by the *IARC Monographs* Working Group in 1995 (IARC, 1995). Since that time, new data have become available and these have been taken into consideration in the present evaluation.

1.1 Identification of the agent

1.1.1 Nomenclature

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

Chem. Abstr. Serv. Name:

3-Chloro-2-methylpropene

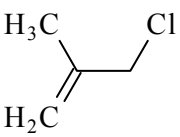
IUPAC Systematic Name:

3-Chloro-2-methylprop-1-ene

Synonyms: 3-Chloroisobutene; γ-chloroisobutylene; 3-chloro-2-methyl-1-propene; 3-chloro-2-methylprop-1-ene; methallyl chloride; 2-methylallyl chloride

Acronym: CMP

1.1.2 Structure and molecular formula, and relative molecular mass



Molecular formula: C_4H_7Cl

Relative molecular mass: 90.55 (IFA, 2015)

1.1.3 Physical and chemical properties of the pure substance

Description: Colourless, highly flammable liquid and vapour with a pungent odour; the substance may decompose when heated, explode when in contact with oxidizing agents, can polymerize and react dangerously with acids (IFA, 2015)

Impurities: Light and/or heat may form low concentrations of dimeric methallyl chloride (HSDB, 2014)

Density (at 20 °C): 0.93 g/cm³ (IFA, 2015)

Melting point: < −80 °C (IFA, 2015)

Boiling point: 72.2 °C (IFA, 2015)

Octanol/water partition coefficient (P): log K_{ow}, 2.48 (NTP, 2014)

Vapour pressure (at 20 °C): 13.5 kPa [101.7 mm Hg] (HSDB, 2014)

Vapour density: 3.1 (air = 1) (IFA, 2015)

Solubility: Moderately soluble in water (1.4 g/L at 25 °C) (NTP, 2014)

Stability: Lower explosion limit, ~2.3 vol. %; upper explosion limit, ~8.1 vol. % (IFA, 2015)

Flash point: −12 °C (IFA, 2015)

Conversion factor (at 101 kPa, 20 °C): 1 ppm = 3.76 mg/m³ (IFA, 2015)

1.1.4 Technical grade and impurities

3-Chloro-2-methylpropene is available commercially at purities ranging from 95% (technical grade) to 98%, with dimethyl-vinyl-chloride (1-chloro-2-methylpropene) as an impurity (IARC, 1995).

1.2 Production and use

1.2.1 Production

3-Chloro-2-methylpropene is produced by the chlorination of 2-methyl-1-propene (isobutylene) (HSDB, 2014).

Production of 3-chloro-2-methylpropene in the USA was estimated to be 12–24 million pounds [~5400–11 000 tonnes] in 1984 (NTP, 2014). Data filed between 1986 and 2006 under the Toxic Substances Control Act Inventory Update Rule of the United States Environmental Protection Agency (EPA) indicated a total annual production plus import of 3-chloro-2-methylpropene between 10 million and 50 million pounds [~4 500–23 000 tonnes] in the USA (NTP, 2014). In 2009, 3-chloro-2-methylpropene was produced by one manufacturer in Asia and was available from 18 suppliers (NTP, 2014). No information on European production or import of 3-chloro-2-methylpropene was available to the Working Group.

1.2.2 Use

3-Chloro-2-methylpropene is an important intermediate in the production of pesticides such as carbofuran, ethalfluralin, and fenbutatin oxide (HSDB, 2014). However, it can also be used as a fumigant for seeds of several vegetables, including cucumbers, tomatoes, onions and beetroot. In addition, 3-chloro-2-methylpropene is an intermediate in the manufacture of plastics and organic chemicals, in particular in the production of 2-methylepichlorohydrin (NTP, 2014).

1.3 Measurement and analysis

3-Chloro-2-methylpropene was analysed semi-quantitatively, among other volatile and semivolatile compounds, in air samples using gas chromatography-mass spectrometry after their sorption on TENAX®. The limit of detection of the method is 62 ng/m^3 ± 30% for 30 L of air sampled (Krost et al., 1982). No other specific methods of detection have been described for 3-chloro-2-methylpropene in the literature.

1.4. Occurrence and exposure

1.4.1 Natural occurrence

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

1.4.2 Environmental occurrence

3-Chloro-2-methylpropene was degraded by hydroxyl radicals and ozone in air, and its estimated half-lives were 10 and 27 hours by hydroxyl radicals and ozone, respectively (HSDB, 2014).

Environmental exposure to 3-chloro-2-methylpropene was monitored at concentrations of 110–400 µg/m^3 in ambient air in an industrial area near Curtis Bay, MD, USA. The source of the emission was not reported, but four halogenated hydrocarbons, including 3-chloro-2-methylpropene, analysed in this study were speculated to come from the same source (Pellizzari, 1982).

1.4.3 Occupational exposure

No data on occupational exposure to 3-chloro-2-methylpropene were available to the Working Group.

1.4.4 Exposure of the general population

No data on exposure to 3-chloro-2-methylpropene were available to the Working Group.

1.5 Regulations and guidelines

No occupational exposure limits have been reported for 3-chloro-2-methylpropene (IFA, 2015). According to the risk phrases of the Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations, 3-chloro-2-methylpropene is harmful if swallowed (H302) and if inhaled (H332), causes severe skin burns and eye damage (H314), may cause an allergic skin reaction (H317) and is toxic to aquatic life with long-lasting effects (H411) (ECHA, 2015).

The United States National Toxicology Program (NTP) states that 3-chloro-2-methylpropene "is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals" (NTP, 2014). The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK) has designated 3-chloro-2-methylpropene as a substance for which there is some evidence of carcinogenicity (Category 3B) (MAK, 2015).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3-Chloro-2-methylpropene was evaluated previously by an IARC Monographs Working Group (IARC, 1995) which concluded that there was *limited evidence* in experimental animals for its carcinogenicity.

See Table 3.1

3.1 Mouse

3.1.1 Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 8 weeks) were given technical-grade 3-chloro-2-methylpropene (two different lots; purity, 93% and > 95%, respectively, containing 5% and 3.6% dimethylvinylchloride [1-chloro-2-methylpropene, an IARC Group 2B carcinogen with *sufficient evidence* in experimental animals (IARC, 1995)], respectively) in corn oil by gavage at doses of 0, 100, or 200 mg/kg body weight (bw) on 5 days per week for 103 weeks (Chan et al., 1986; NTP, 1986). Mean body weights of the males given 200 mg/kg bw and of all treated females were significantly lower (by less than 10%) than those of vehicle controls throughout most of the study. Survival in the treated groups was not significantly lower than that in vehicle controls; the numbers of survivors at the end of the experiment (105 weeks) were: 26 male controls, 37 males at 100 mg/kg bw and 32 males at 200 mg/kg bw; and 37 female controls, 43 females at 100 mg/kg bw and 27 females at 200 mg/kg bw.

In males, the incidence of forestomach squamous cell papilloma was: 3/49 controls, 19/49 at 100 mg/kg bw ($P < 0.001$ by the Fisher's exact test); and 30/49 at 200 mg/kg bw ($P < 0.001$ by the Fisher's exact test) (dose-related increase at $P < 0.001$ by the Cochran-Armitage trend test); that of squamous cell carcinoma was: 0/49 controls, 5/49 at 100 mg/kg bw ($P = 0.028$ by the Fisher's exact test) and 7/49 at 200 mg/kg bw ($P = 0.006$ by the Fisher's exact test) (dose-related increase at $P = 0.008$ by the Cochran-Armitage trend test); and that of forestomach squamous cell papilloma or carcinoma (combined) was: 3/49 controls, 24/49 at 100 mg/kg bw ($P < 0.001$ by the Fisher's exact test) and 36/49 at 200 mg/kg bw ($P < 0.001$ by the Fisher's exact test) (dose-related increase at $P < 0.001$ by the Cochran-Armitage trend test). The historical incidence of forestomach squamous cell papilloma or carcinoma (combined) in male mice at the study laboratory

Table 3.1 Studies of carcinogenicity with 3-chloro-2-methylpropene in experimental animals

Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M) 8 wk 105 wk NTP (1986)	Gavage Purity, ≥ 93% Corn oil 0, 100, 200 mg/kg bw 5 days/wk for 103 wk 50/group 26, 37, 32	*Forestomach* Squamous cell papilloma: 3/49, 19/49, 30/49 Squamous cell carcinoma: 0/49, 5/49, 7/49 Squamous cell papilloma or carcinoma (combined): 3/49, 24/49, 36/49	Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P < 0.001$ at 100 and 200 mg/kg bw (Fisher's exact test) Trend test: $P = 0.008$ (Cochran-Armitage test) Incidental tumour test: $P = 0.028$ and $P = 0.006$ at 100 and 200 mg/kg bw, respectively (Fisher's exact test) Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P < 0.001$ at 100 and 200 mg/kg bw (Fisher's exact test)	Principal strengths: GLP, large number of animals per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 3.6–5%
Mouse, B6C3F$_1$ (F) 8 wk 105 wk NTP (1986)	Gavage Purity, ≥ 93% Corn oil 0, 100, 200 mg/kg bw 5 days/wk for 103 wk 50/group 37, 43, 27	*Forestomach* Squamous cell papilloma: 0/50, 15/48, 29/44 Squamous cell carcinoma: 0/50, 1/48, 2/44 Squamous cell papilloma or carcinoma (combined): 0/50, 16/48, 31/44	Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P < 0.001$ at 100 and 200 mg/kg bw (Fisher's exact test) NS Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P < 0.001$ at 100 and 200 mg/kg bw (Fisher's exact test)	Principal strengths: GLP, large number of animals per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 3.6–5% Incidence of forestomach squamous cell papilloma or carcinoma (combined) in historical controls: study laboratory, 0/145; NTP studies, 4/1027

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, BDF_1 (M) 6 wk 104 wk Katagiri et al. (2000)	Whole-body inhalation Purity, 95% vapour 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50/group 40, 44, 43, 46	*Forestomach* Squamous cell papilloma: 1/50, 0/49, 3/50, 4/50 Squamous cell carcinoma: 0/50, 0/49, 1/50, 0/50 *Harderian gland* Adenoma: 3/50, 7/49, 9/50, 5/50	 Trend test: $P = 0.0392$ (Peto's test) NS NS	Principal strengths of the study: GLP, large number of animals per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 1.4% Incidence of Harderian gland adenoma in historical controls: 30/598 (5.0%), 2.0–10.0% (Ohnishi et al., 2013)
Mouse, BDF_1 (F) 6 wk 104 wk Katagiri et al. (2000)	Whole-body inhalation Purity, 95% vapour 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50/group 29, 29, 31, 33	*Forestomach* Squamous cell papilloma: 1/50, 0/48, 5/50, 4/49 Squamous cell carcinoma: 0/50, 0/48, 0/50, 0/49 *Harderian gland* Adenoma: 0/50, 4/48, 7/50, 8/49	 Trend test: $P = 0.0437$ (Peto's test) NS Trend test: $P = 0.0056$ (Peto's test) and $P = 0.0061$ (Cochran-Armitage test) Incidence: $P = 0.0101$ and $P = 0.0051$ at 100 and 200 ppm, respectively (Fisher's exact test)	Principal strengths of the study: GLP, large number of mice per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 1.4% Incidence of Harderian gland adenoma in historical controls: 29/849 (3.4%), 0–12.0%

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/N (M) 8 wk 105 wk NTP (1986)	Gavage Purity, ≥ 93% Corn oil 0, 75, 150 mg/kg bw 5 days/wk for 103 wk 50/group 30, 25, 17	*Forestomach* Squamous cell papilloma: 1/50, 5/50, 30/48 Squamous cell carcinoma: 0/50, 0/50, 2/48 *Kidney* Renal tubular cell adenoma: 0/50, 1/50, 0/49 Renal tubular cell adenocarcinoma: 0/50, 1/50, 1/49 Renal transitional cell carcinoma: 0/50, 0/50, 1/49 *Urinary bladder* Transitional cell papilloma: 0/48, 0/49, 1/46 *Testis* Interstitial cell tumours: 36/50, 43/50, 43/48	Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P < 0.001$ at 150 mg/kg bw (Fisher's exact test) NS NS NS NS Trend test: $P < 0.001$ (life-table test), $P = 0.003$ (incidental tumour test) and $P = 0.015$ (Cochran-Armitage test) Incidence: $P = 0.009$ (life-table test at 75 mg/kg bw), $P < 0.001$ (life-table test at 150 mg/kg bw), $P = 0.012$ (incidental tumour test at 150 mg/kg bw) and $P = 0.025$ (Fisher's exact test at 150 mg/kg bw)	1-Chloro-2-methylpropene, 3.6–5% Incidence of renal tubular cell tumours, renal transitional cell tumours and urinary bladder tumours in historical corn oil-vehicle controls at the study laboratory: 1/150, 0/150 and 0/150, respectively Incidence of testicular (interstitial cell) tumours in historical controls: 92.0 ± 6.9%, study laboratory; 90.4 ± 5.7%, all NTP studies

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/N (F) 8 wk 105 wk NTP (1986)	Gavage Purity, ≥ 93% Corn oil 0, 75, 150 mg/kg bw 5 days/wk for 103 wk 50/group 31, 32, 26	*Forestomach* Squamous cell papilloma: 1/50, 1/50, 10/50 *Subcutis* Fibroma: 0/50, 2/50, 4/50	Trend test: $P < 0.001$ (Cochran-Armitage test) Incidental tumour test: $P = 0.004$ at 150 mg/kg bw (Fisher's exact test) NS	Principal strengths of the study: GLP, large number of rats per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 3.6–5% Incidence of subcutaneous fibroma in historical controls at study laboratory: 2/150
Rat, F344/DuCrj (M) 6 wk 104 wk MHLW (1998b)	Whole-body inhalation Purity, 95% Vapour 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 39, 35, 33, 30	*Thyroid gland* Follicular cell adenoma: 2/50, 0/50, 2/50, 6/50 Follicular cell adenoma or adenocarcinoma (combined): 4/50, 4/50, 3/50, 10/50	Trend test: $P = 0.00213$ (Cochran-Armitage test) Trend test: $P = 0.0388$ (Cochran-Armitage test)	Principal strengths of the study: GLP, large number of animals per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 1.4%
Rat, F344/DuCrj (F) 6 wk 104 wk MHLW (1998b)	Whole-body inhalation Purity, 95% Vapour 0, 50, 100, 200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 40, 45, 44	*Any tumour type* No significant increase	NS	Principal strengths of the study: GLP, large number of animals per group, multiple doses tested, and covered most of the lifespan 1-Chloro-2-methylpropene, 1.4%

bw, body weight; F, female; GLP, good laboratory practice; M, male; NS, not significant; wk, week

and that in NTP studies was 2/147 and 7/1005, respectively. Evidence of metastasis or invasion of other organs was observed in two males at 100 mg/kg bw and three males at 200 mg/kg bw. The incidence of forestomach epithelial hyperplasia was significantly increased in all treated males.

In females, the incidence of forestomach squamous cell papilloma was: 0/50 controls, 15/48 at 100 mg/kg bw ($P < 0.001$ by the Fisher's exact test) and 29/44 at 200 mg/kg bw ($P < 0.001$ by the Fisher's exact test) (dose-related increase at $P < 0.001$ by the Cochran-Armitage trend test); that of forestomach squamous cell carcinoma was: 0/50 controls, 1/48 at 100 mg/kg bw and 2/44 at 200 mg/kg bw; and that of forestomach squamous cell papilloma or carcinoma (combined) was: 0/50 controls, 16/48 at 100 mg/kg bw ($P < 0.001$ by the Fisher's exact test) and 31/44 at 200 mg/kg bw ($P < 0.001$ by the Fisher's exact test) (dose-related increase at $P < 0.001$ by the Cochran-Armitage trend test). The historical incidence of forestomach squamous cell papilloma or carcinoma (combined) in female mice at the study laboratory and in NTP studies was 0/145 and 4/1027, respectively. Evidence of metastasis or invasion of other organs was observed in one female mouse at 200 mg/kg bw. The incidence of forestomach epithelial hyperplasia was significantly increased in females at 200 mg/kg bw.

[The strengths of this study included compliance with good laboratory practice, large numbers of animals, the evaluation of multiple dose levels and a duration that involved most of the lifespan.]

3.1.2 Inhalation

Groups of 50 male and 50 female BDF_1 (C57BL/6NCrj × DBA/2NCrj) mice (age, 6 weeks) were exposed to technical-grade 3-chloro-2-methylpropene (purity, 95%, containing 1.4% 1-chloro-2-methylpropene) by whole-body inhalation at a concentration of 50, 100 or 200 ppm for 6 hours per day on 5 days per week for 104 weeks (MHLW, 1998a; Katagiri et al., 2000). The control mice were handled in the same manner and exposed to clean air in similar chambers. A significant decrease in body weight was observed in all exposed groups. Survival in the treated groups was slightly higher than that in the controls; the numbers of survivors at the end of the experiment were: 40/50 male controls, 44/50 males at 50 ppm, 43/50 males at 100 ppm, and 46/50 males at 200 ppm; and 29/50 female controls, 29/48 females at 50 ppm, 31/50 females at 100 ppm, and 33/49 females at 200 ppm.

Histopathological evaluation revealed a significant positive trend in the incidence of forestomach squamous cell papilloma in males and females ($P = 0.0392$ and $P = 0.0437$ by Peto's trend test, respectively). The incidence of squamous cell papilloma was 1/50 controls, 0/49 at 50 ppm, 3/50 at 100 ppm, and 4/50 at 200 ppm in males, and 1/50 controls, 0/48 at 50 ppm, 5/50 at 100 ppm, and 4/49 at 200 ppm in females. A forestomach squamous cell carcinoma was also observed in one male mouse at 100 ppm. The incidence of forestomach epithelial hyperplasia was also significantly increased ($P \leq 0.01$) in males and females at 200 ppm. In addition, a significant positive trend was found in the incidence of Harderian gland adenoma in female mice ($P = 0.0056$ by Peto's trend test, $P = 0.0061$ by the Cochran-Armitage trend test) with an incidence of 0/50 controls, 4/48 at 50 ppm, 7/50 at 100 ppm ($P = 0.0101$ by the Fisher's exact test) and 8/49 at 200 ppm ($P = 0.0051$ by the Fisher's exact test). The incidence in the groups exposed to 100 and 200 ppm was higher than the maximum incidence (29/849, 3.4%; 0–12.0%) in historical controls at the institute performing this experiment using female BDF_1 mice. The incidence of Harderian gland adenoma in males was: 3/50 controls, 7/49 at 50 ppm, 9/50 at 100 ppm, and 5/50 at 200 ppm (historical control incidence in male BDF_1 mice: 30/598 (5.0%); range, 2.0–10.0%; Ohnishi et al., 2013).

[The strengths of this study included compliance with good laboratory practice, large numbers of animals, the evaluation of multiple dose levels and a duration that involved most of the lifespan.]

3.2 Rat

3.2.1 Oral administration

Groups of 50 male and 50 female Fischer 344/N rats (age, 8 weeks) were given technical-grade 3-chloro-2-methylpropene (two different lots; purity, 93% and > 95%, respectively, containing 5% and 3.6% dimethylvinylchloride [1-chloro-2-methylpropene, an IARC group 2B carcinogen with *sufficient evidence* in experimental animals (IARC, 1995)], respectively) in corn oil by gavage at doses of 0, 75, or 150 mg/kg bw on 5 days per week for 103 weeks (Chan et al., 1986; NTP, 1986). The mean body weight of the males given 150 mg/kg bw was significantly lower than that of the vehicle controls, beginning at week 10 of the study. The mean body weights of males given 75 mg/kg bw and of all treated females were comparable with those of the vehicle controls throughout the study. Survival was marginally reduced among males receiving 150 mg/kg bw; the numbers of survivors at the end of the experiment (105 weeks) were: 30 male controls, 25 males at 75 mg/kg bw and 17 males at 150 mg/kg bw; and 31 female controls, 32 females at 75 mg/kg bw, and 26 females at 150 mg/kg bw.

A dose-related increase in the incidence of squamous cell papilloma of the forestomach was observed in both males and females ($P < 0.001$ by the Cochran-Armitage trend test): 1/50 male controls, 5/50 males at 75 mg/kg bw, 30/48 males at 150 mg/kg bw ($P < 0.001$ by the Fisher's exact test), 1/50 female controls, 1/50 females at 75 mg/kg bw, and 10/50 females at 150 mg/kg bw ($P = 0.004$ by the Fisher's exact test). Forestomach squamous cell carcinomas were observed in 2 of the male rats bearing forestomach squamous cell papillomas at 150 mg/kg bw but not in controls or animals given 75 mg/kg bw. Consequently, the incidence was significantly increased (with a significant positive trend) for papilloma and carcinoma (combined) in males at 150 mg/kg bw. The historical incidence of forestomach squamous cell papilloma at the study laboratory and in NTP studies was 0/147 and 5/1062 in male rats, and 1/150 and 5/1073 in female rats, respectively. The incidence of basal cell or epithelial hyperplasia (combined) of the forestomach in groups of treated males and that of basal cell hyperplasia in groups of treated females was also increased. In addition to forestomach tumours in males, a significant increase and positive trend in the incidence ($P < 0.001$ by the life-table trend test, $P = 0003$ by the incidental tumour trend test, $P = 0.015$ by the Cochran-Armitage trend test) of testicular interstitial cell tumours was observed: 36/50 controls, 43/50 at 75 mg/kg bw ($P = 0.009$ by the life-table test), and 43/48 at 150 mg/kg bw ($P < 0.001$ by the life-table test, $P = 0.012$ by the incidental tumour test, $P = 0.025$ by the Fisher's exact test), which was within the historical control range. The historical incidence for this tumour at the study laboratory was 92.0% ± 6.9% (138/150), and that in all NTP studies was 90.4% ± 5.7% (985/1090). [The Working Group concluded that it was uncertain that these testicular tumours were related to treatment.]

A non-significant increase in tumours was observed in the kidney and urinary bladder of male rats and in the subcutaneous tissue of female rats. One renal tubular cell adenoma was observed in one male given 75 mg/kg bw and renal tubular cell adenocarcinomas were observed in another male given 75 mg/kg bw and in one male given 150 mg/kg bw. At 150 mg/kg bw, a renal transitional cell carcinoma was observed in one male and a transitional cell papilloma was observed in the urinary bladder of another. No renal tubule tumours, renal transitional cell tumours or urinary bladder tumours were observed in male or female controls. The historical incidence

of renal tubular cell tumours and renal transitional cell tumours in corn oil vehicle-control male rats at the study laboratory was 1/150 and 0/150, respectively, and that in NTP studies was 4/1091 and 1/1091 (1 transitional cell papilloma), respectively; that of urinary bladder tumours in male rats treated with corn oil vehicle was 0/150 at the study laboratory and 0/1040 in NTP studies. [The Working Group concluded that it was uncertain that these kidney and urinary bladder tumours were related to treatment.] Subcutaneous fibromas were observed in 2/50 females at 75 mg/kg bw and in 4/50 females at 150 mg/kg bw. No such subcutaneous tumour was seen in control female rats. The historical incidence of subcutaneous fibroma in control female rats at the study laboratory and in NTP studies was 2/150 and 13/1095, respectively [the Working Group concluded that these subcutaneous tumours may have been related to treatment] (NTP, 1986).

[The strengths of this study included compliance with good laboratory practice, large numbers of animals, the evaluation of multiple dose levels and a duration that involved most of the lifespan.]

3.2.2 Inhalation

Groups of 50 male and 50 female Fischer 344/DuCrj rats (age, 6 weeks) were exposed to technical-grade 3-chloro-2-methylpropene (purity, 95%, containing 1.4% 1-chloro-2-methylpropene) by whole-body inhalation at a concentration of 50, 100 or 200 ppm for 6 hours per day on 5 days per week for 104 weeks. The control rats were handled in the same manner and exposed to clean air in similar chambers. Growth rates were slightly suppressed in males treated with 100 or 200 ppm and in females treated with 200 ppm compared with the respective controls. Survival in the treated males was slightly lower than that in controls; the numbers of male survivors at the end of the experiment were: 39 controls, 35 at 50 ppm, 33 at 100 ppm and 30 at 200 ppm. Survival in the treated females tended to be higher than that in controls; the numbers of female survivors at the end of the experiment were: 38 controls, 40 at 50 ppm, 45 at 100 ppm and 44 at 200 ppm. Histopathological evaluation revealed a slightly increased incidence of thyroid follicular cell adenoma and of thyroid follicular cell adenoma or adenocarcinoma (combined) in treated males. The incidence of thyroid follicular cell adenoma in males was 2/50 controls, 0/50 at 50 ppm, 2/50 at 100 ppm, and 6/50 at 200 ppm (significant positive trend at $P = 0.00213$ by the Cochran-Armitage trend test). The incidence of thyroid follicular cell adenoma or adenocarcinoma (combined) in males was 4/50 controls, 4/50 at 50 ppm, 3/50 at 100 ppm and 10/50 at 200 ppm (significant positive trend at $P = 0.0388$ by the Cochran-Armitage trend test). The historical control incidence of thyroid follicular cell adenoma in male Fischer 344 rats at the study laboratory was 8/899 (0.9%; range, 0–4%). No significant increase in the incidence of tumours was observed in treated female Fischer 344/DuCrj rats (MHLW, 1998b). [The strengths of this study included compliance with good laboratory practice, large numbers of animals, the evaluation of multiple dose levels and a duration that involved most of the lifespan.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Humans

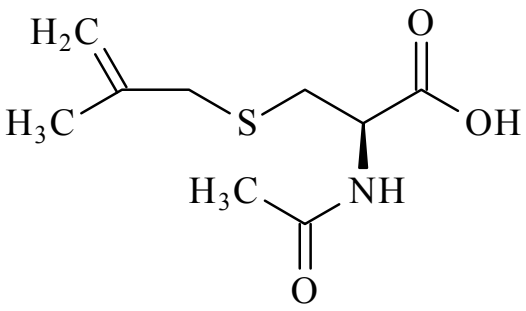
No data were available to the Working Group.

4.1.2 Experimental systems

The toxicokinetics of 3-chloro-2-methylpropene in experimental systems was reviewed in *IARC Monographs* Volume 63 (IARC, 1995). At that time, only one study was available (Ghanayem & Burka, 1987). The reported data indicated extensive absorption and rapid excretion in rats after a single dose or up to four daily doses of 150 mg/kg bw of 3-chloro-2-methylpropene (stated purity, 93%; containing ~5% 1-chloro-2-methylpropene [dimethylvinyl chloride] by oral gavage. Distribution to the tissues was rapid and the highest concentrations were found in the forestomach, liver and kidney. Excretion was primarily via the urine but large amounts were exhaled, partly as carbon dioxide.

The major 3-chloro-2-methylpropene metabolite in rat urine was characterized as *N*-acetyl-*S*-(2-methylpropenyl)cysteine, presumably formed by direct conjugation of glutathione with the allylic carbon of 3-chloro-2-methylpropene (see Fig. 4.1), followed by catabolism to the mercapturate (Ghanayem & Burka, 1987).

Fig. 4.1 Structure of *N*-acetyl-*S*-(2-methylpropenyl)cysteine, the major metabolite of 3-chloro-2-methylpropene in rat urine



4.2 Mechanisms of carcinogenesis

The evidence on the key characteristics of carcinogens (Smith et al., 2016) concerning whether 3-chloro-2-methylpropene is genotoxic, induces chronic inflammation and alters cell proliferation, cell death or nutrient supply is summarized below.

4.2.1 Genetic and related effects

See Table 4.1

(a) Humans

No data in exposed humans were available to the Working Group.

(b) Experimental systems

3-Chloro-2-methylpropene is considered to be an electrophilic agent. The genotoxicity of 3-chloro-2-methylpropene was reviewed in *IARC Monographs* Volume 63 (IARC, 1995). Most of the studies reported were conducted with compounds that were 90.7% pure (the remaining material being primarily 1-chloro-2-methylpropene). The test preparations were mutagenic to *Salmonella typhimurium* TA100 in the presence and absence of metabolic activation and to strain TA1537 in the presence of an exogenous metabolic system. Single studies also reported the induction of somatic recombination in *Drosophila melanogaster*, mutation at the *Tk* locus in mouse L5178Y lymphoma cells, and sister-chromatid exchange and chromosomal aberrations in Chinese hamster cells, but not micronucleus formation in the bone marrow of mice treated in vivo.

An earlier study reported the induction of unscheduled DNA synthesis in HeLa cells by 3-chloro-2-methylpropene (purity, 100%; reported in Eder et al., 1982) at a minimum dose of 10^{-3} mol/L [90.55 µg/mL] (Schiffmann et al., 1983). [The Working Group noted that no statistical analysis was presented.]

Table 4.1 Genetic and related effects of 3-chloro-2-methylpropene

Species	End-point	Test	Results		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Human, HeLa cell line	DNA damage	Unscheduled DNA synthesis	(+)	NT	10^{-3} mol/L [90.55 µg/mL]	Stated purity, 100% (Eder et al., 1982); no statistical analysis presented; the lowest dose was one to two orders of magnitude higher than that for other structurally related compounds; lethal dose NR	Schiffmann et al. (1983)
Drosophila melanogaster	Mutation	Sex-linked recessive lethal mutations	+	NA	4500 ppm		Foureman et al. (1994)
Drosophila melanogaster	Mutation	Heritable translocation test	–	NA	5000 ppm		Foureman et al. (1994)
Drosophila melanogaster	Mutation	Somatic mutation and recombination test	+	NA	2.75 µg/L (50% lethal concentration)		Chroust et al. (2007)

+, positive; –, negative; (+), weakly positive; HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NT, not tested

An additional study in *Drosophila melanogaster* (analysed purity, 93.3%) reported a positive result for the induction of sex-linked recessive lethal mutations in post-meiotic and meiotic germ cells of adult males fed 3-chloro-2-methylpropene. The same test sample gave negative results for the induction of reciprocal translocations (Foureman et al., 1994). 3-Chloro-2-methylpropene [purity not specified] also gave positive results in the wing spot test in *Drosophila melanogaster* when administered by inhalation at the 50% lethal concentration (Chroust et al., 2007). A quantitative structure–activity relationship multivariate analysis of a series of structurally similar halogenated aliphatic compounds, including 3-chloro-2-methylpropene, indicated that nucleophilic superdelocalizability of the halogen atom (calculated by quantum mechanics) was a good structural parameter to predict the toxicity and genotoxicity of these compounds, consistent with the direct reactivity or bioactivation at the halogenated carbon (Chroust et al., 2007).

4.2.2 Other mechanisms

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

In a 13-week study on the toxicity of 3-chloro-2-methylpropene (same material as that used in the 2-year bioassay), inflammation and necrosis of the liver were observed in treated rats and mice, and necrosis of cortical tubules was observed in the kidney of mice. In the 2-year study, a dose-dependent increase in the incidence of forestomach inflammation was

observed in treated male and female mice. The incidence of inflammation in the nasal cavity and of nephropathy/nephrosis was higher in exposed groups than in the controls in male and female mice and rats (NTP, 1986).

The incidence and severity of epithelial cell proliferation of the forestomach was increased in Fischer 344/N rats given 3-chloro-2-methylpropene at 150 mg/kg bw, but not at 75 mg/kg bw, by gavage on 5 days per week for 2 weeks (Ghanayem et al., 1986). A strong association between early forestomach mucosal cell proliferation and forestomach neoplasia was observed in treated rats and mice in the 2-year carcinogenicity bioassay conducted by the NTP, in which 3-chloro-2-methylpropene (technical grade, containing 5% dimethylvinyl chloride) was administered by gavage (Chan et al., 1986; NTP, 1986).

In the nasal cavity, eosinophilic exudate associated with atrophy of the olfactory epithelia, respiratory metaplasia of the olfactory epithelia and olfactory gland, and eosinophilic changes in the respiratory and olfactory epithelia were observed in male and female BDF_1 mice exposed to 3-chloro-2-methylpropene (stated purity, 95%) at 0, 50, 100, or 200 ppm on 5 days per week for 104 weeks (Katagiri et al., 2000).

4.3 Data relevant to comparisons across agents and end-points

3-Chloro-2-methyl propene was not tested by the Tox21 and ToxCast™ research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013). Analyses of other compounds evaluated in this volume with high-throughput screening results are presented in the *Monograph* on 1-bromopropane in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

No additional data were available to the Working Group.

5. Summary of Data Reported

5.1 Exposure data

3-Chloro-2-methylpropene is available commercially at purities ranging from 95% (technical grade) to 98%, with dimethylvinyl chloride (1-chloro-2-methylpropene) as an impurity. 3-Chloro-2-methylpropene is an important intermediate in the production of pesticides, is used as a fumigant for seeds and is also an intermediate in the manufacture of plastics and other organic chemicals. Apart from a single study of environmental exposure published in 1982, no data on environmental or occupational exposure were available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Technical-grade 3-chloro-2-methylpropene was tested for carcinogenicity by oral administration (gavage) in one study in male and female mice and in one study in male and female rats, and by whole-body inhalation in one study in male and female mice and in one study in male and female rats.

In the study in mice treated by gavage, technical-grade 3-chloro-2-methylpropene caused a significantly increased incidence (with a significant positive trend) 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.

In the study in mice treated by inhalation, administration of technical-grade 3-chloro-2-methylpropene resulted in a significantly increased positive trend in the incidence of forestomach squamous cell papilloma in males and females. It also caused a significantly increased incidence (with a significant positive trend) of adenoma of the Harderian gland in females.

In the study in rats treated by gavage, technical-grade 3-chloro-2-methylpropene 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 the study in rats treated by inhalation, exposure to technical-grade 3-chloro-2-methylpropene resulted in a significant positive trend in the incidence of follicular cell adenoma and of follicular cell adenoma or adenocarcinoma (combined) of the thyroid gland in males. No significant increase in the incidence of tumours was observed in female rats.

5.4 Mechanistic and other relevant data

3-Chloro-2-methylpropene is considered to be an electrophilic agent. The main urinary metabolite is a mercapturate conjugate. No data were available on the toxicokinetics of 3-chloro-2-methylpropene in humans. In rats given 3-chloro-2-methylpropene by oral administration, the compound is rapidly absorbed, distributed (primarily to the forestomach, liver and kidney) and excreted. Urinary excretion predominates, although large amounts are exhaled, partly as carbon dioxide.

With respect to the key characteristics of human carcinogens, there is *strong* evidence that 3-chloro-2-methylpropene is genotoxic, and these effects can operate in humans. 3-Chloro-2-methylpropene 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*. Only one study of DNA damage in human (HeLa) cells in vitro was available, but the results were positive.

There is *moderate* evidence that 3-chloro-2-methylpropene induces chronic inflammation. 3-Chloro-2-methylpropene 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 3-chloro-2-methylpropene alters cell proliferation. Proliferation of the epithelial cells of the forestomach was increased in rats exposed to 3-chloro-2-methylpropene.

There were few data 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 immortalization).

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Technical-grade 3-chloro-2-methylpropene is *possibly carcinogenic to humans* (*Group 2B*).

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