1,3-DICHLOROPROPENE

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

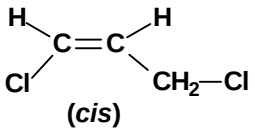
1. Exposure Data

1.1 Chemical and physical data

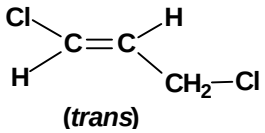
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 542-75-6
Chem. Abstr. Name: 1,3-Dichloro-1-propene
IUPAC Systematic Name: 1,3-Dichloropropene

1.1.2 *Structural and molecular formulae and relative molecular mass*



(*cis*)



(*trans*)

$C_3H_4Cl_2$ Relative molecular mass: 110.97

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Liquid with chloroform-like odour (Budavari, 1996)
(*b*) *Boiling-point*: 104°C (*cis*), 112°C (*trans*) (Verschueren, 1996)
(*c*) *Solubility*: Insoluble in water; soluble in acetone and toluene (Lewis, 1993)
(*d*) *Vapour pressure*: 5720 Pa at 25°C (*cis*), 4522 Pa at 25°C (*trans*); relative vapour density (air = 1), 3.83 (Verschueren, 1996)
(*e*) *Flash-point*: 35°C, open cup (Lewis, 1993)
(*f*) *Conversion factor*: $mg/m^3 = 4.54 \times ppm$

1.2 Use

1,3-Dichloropropene is used in organic synthesis and as a soil fumigant (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 2200 workers in the United States were potentially exposed to 1,3-dichloro-

propene (see General Remarks). Occupational exposures may occur in its manufacture and use in organic synthesis and as a soil fumigant.

1.3.2 *Environmental occurrence*

1,3-Dichloropropene is released into the air and in wastewater during its production and use as a soil fumigant and chemical intermediate. 1,3-Dichloropropene may also leach into groundwater. Considerable variation in the amounts of 1,3-dichloropropene lost by volatilization and degradation can be expected depending on the method of application, soil type, moisture and temperature. It has been detected in low levels in ambient air and drinking-water (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 4.5 mg/m^3 as the threshold limit value for occupational exposures to 1,3-dichloropropene in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established an international drinking-water guideline for 1,3-dichloropropene of 20 μg/L (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Technical-grade 1,3-dichloropropene (containing 1.0% epichlorohydrin (see this volume)) was tested for carcinogenicity by gavage in one experiment in mice and in one experiment in rats. In mice, it produced dose-related increases in the incidence of benign and/or malignant tumours of the urinary bladder, lung and forestomach. In male rats, it produced dose-related increases in the incidence of benign and malignant tumours of the forestomach and benign liver tumours; in female rats, it produced benign tumours of the forestomach. In one experiment, by subcutaneous administration in female mice, the *cis*-isomer produced malignant tumours at the injection site. In a two-stage skin application study in mice, the *cis*-isomer was not active as an initiator. A study in mice in which *cis*-1,3-dichloropropene was applied three times per week to the skin of mice for up to 85 weeks was inconclusive (IARC, 1986; Yang *et al*., 1986).

3.1 Inhalation exposure

3.1.1 *Mouse*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, 5–6 weeks of age, were exposed to technical-grade 1,3-dichloropropene (*cis*-isomer, 49.5%; *trans*-isomer, 42.6%;

0.7% 1,2-dichloropropane with epoxidized soya bean as a stabilizer) by inhalation at concentrations of 0, 5, 20 or 60 ppm [0, 23, 91 or 272 mg/m^3] for 6 h per day on five days per week for 24 months. Ten mice of each sex per group were killed at six and 12 months. At the end of the study, necropsy and histopathological examination of all organs were performed. No sign of toxicity was recorded. Approximately 90% of male and 80–96% of female mice survived until the end of the study. Exposure-related histopathological alterations were observed in nasal tissues of male and female mice exposed to 60 ppm for 24 months, but not for six or 12 months. The alterations were characterized by hypertrophy and hyperplasia of the respiratory epithelium and degeneration of the olfactory epithelium. Hyperplastic changes also occurred in the epithelium of the urinary bladder. In male mice, there was a significant increase in the incidence of bronchioalveolar adenomas at the highest dose: 9/50 in controls compared with 6/50, 13/50 and 22/50 in the groups exposed to 5, 20 and 60 ppm, respectively (Lomax *et al*., 1989).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, 6–8 weeks of age were exposed to 1,3-dichloropropene (as described above). Hyperplastic and degenerative changes occurred to the nasal cavities as well as hyperplastic changes in the urinary bladder. No increase in tumour incidence was observed (Lomax *et al.*, 1989).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Isomers of *N*-acetyl-*S*-(3-chloroprop-2-enyl)-L-cysteine have been detected in urine samples of 1,3-dichloropropene applicators (Osterloh *et al*., 1984; Van Welie *et al*., 1989).

4.1.2 *Experimental systems*

In rats, 1,3-dichloropropene is absorbed rapidly, after either inhalation or oral administration, and is eliminated principally by metabolism (glutathione conjugation) within 24–48 h. The major urinary metabolite of *cis*-1,3-dichloropropene in rats is the mercapturic acid *N*-acetyl-*S*-(*cis*-3-chloroprop-2-enyl)-L-cysteine. Glutathione conjugation *in vitro* in rat liver cytosol of the *cis*-isomer occurs four to five times faster than that of the *trans*-isomer. 1,3-Dichloropropene is an alkylating agent and the *trans*-isomer is less reactive than the *cis*-isomer (IARC, 1986).

At higher inhalation exposure levels in rats, absorption mechanisms become saturated as a result of compromised respiration, while saturation of metabolism also occurs, presumably as result of limitations on glutathione *S*-transferase activity. Plasma elimination of 1,3-dichloropropene is biphasic, the half-life of the slower phase being roughly

25 to 45 min (Stott & Kastl, 1986). The plasma elimination half-life of the glutathione conjugate of 1,3-dichloropropene is about 17 h, irrespective of the inhalation exposure concentration (Fisher & Kilgore, 1989).

Both *cis*- and *trans*-isomers of 1,3-dichloropropene are conjugated with glutathione and excreted as mercapturic acids (55% *cis*-1,3-dichloropropene and 45% *trans*-1,3-dichloropropene in 24 h) in Wistar rats after intraperitoneal administration (Onkenhout *al*., 1986).

1,3-Dichloropropene was given in doses of 0, 25, 50 and 75 mg/kg bw intraperitoneally to male Fischer 344 rats. Excretion of the metabolite *N*-acetyl-*S*-(*cis*-3-chloroprop-2-enyl)-L-cysteine increased in a dose-dependent manner from 0 to 50 mg/kg 1,3-dichloropropene, but no further increase was seen at the 75-mg/kg dose, suggesting that, at higher doses, the metabolism pathway may be saturated or impaired (Osterloh & Xiwen, 1990).

Metabolic activation of 1,3-dichloropropene, as suggested by the use of specific inhibitors of metabolism in the *Salmonella typhimurium* gene mutation assay, proceeds via an hydrolytic-oxidative pathway; the first step of which is hydrolysis to chloroallyl alcohol, which is then oxidized to chloroacrolein (Neudecker & Henschler, 1986).

4.1.3 *Comparison of human and rodent data*

The principal metabolic pathway to mercapturic acids is presumably similar in humans and rodents. Because no data on kinetics or metabolic activation in humans are available, no quantitative comparison can be made.

4.2 Toxic effects

4.2.1 *Humans*

A 27-year-old previously healthy male worker who accidentally drank a solution containing 1,3-dichloropropene (mixture of *cis*- and *trans*-isomers) developed gastrointestinal distress, adult respiratory distress syndrome, haematological and hepatorenal functional impairment, and died 40 h after ingestion (Hernandez *et al*., 1994).

4.2.2 *Experimental systems*

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to 0, 10, 30, 90 or 150 ppm [0, 45, 136, 409 or 681 mg/m^3] technical grade 1,3-dichloropropene (*cis*, 48.6%; *trans*, 42.3%) vapours for 6 h per day on five days per week for 13 weeks (Stott *et al*., 1988). At the end of the exposure, slight degeneration of the nasal olfactory epithelium and mild hyperplasia of the nasal respiratory epithelium were observed in rats exposed to 150 ppm 1,3-dichloropropene. All male and female Fischer 344 rats exposed to 90 or 150 ppm and two of the 10 rats exposed to 30 ppm 1,3-dichloropropene exhibited minimally detectable hyperplasia of the respiratory epithelium. Exposure to 90 or 150 ppm 1,3-dichloropropene also produced diffuse, moderate hyperplasia of the olfactory epithelium in female B6C3F$_1$ mice.

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed by inhalation to 0, 5, 20 or 60 ppm [0, 23, 91 or 272 mg/m^3] 1,3-dichloropropene (*cis*, 49.5%; *trans*, 42.6%)

for 6 h per day on five days per week for up to two years. Significant morphological alterations in the nasal tissues of rats exposed to 60 ppm and mice exposed to 20 or 60 ppm 1,3-dichloropropene were found at the end of the study (Lomax *et al.*, 1989).

Treatment with buthionine sulfoximine (0.2 M in 0.58% NaCl, 4 mL/kg bw) (to inhibit glutathione synthesis) 4 h before dosing with 1,3-dichloropropene or with diethyl maleate (3.1 M in corn oil, 0.4 mL/kg bw) (to deplete glutathione) or corn oil itself 1 h before dosing with 1,3-dichloropropene at 50 and 75 mg/kg bw resulted in elevations of *N*-acetylglucosaminidase excretion. In contrast, treatment with aminooxyacetic acid (0.125 M in 0.85% NaCl, 4 mL/kg bw) (which inhibits β-lyase activity) 1 h before 1,3-dichloropropene injection prevented the 1,3-dichloropropene-induced release of *N*-acetylglucosaminidase from the renal tubule. These results suggest that the nephrotoxic effects of 1,3-dichloropropene may be mediated through the mercapturic acid metabolites in the kidney, rather than glutathione depletion (Osterloh & Xiwen, 1990).

1,3-Dichloropropene was administered to male and female Fischer 344 rats and B6C3F_1 mice for 13 weeks (0, 5, 15, 50 or 100 mg/kg bw per day to rats or 0, 15, 50, 100 or 175 mg/kg bw per day to mice) in the diet by mixing a microencapsulated formulation of 1,3-dichloropropene into animal feed (microencapsulated in a 80/20% starch/sucrose matrix; 1,3-dichloropropene consisted of 50.7% *cis*-, 45.1% *trans*-isomers). There was a decrease in the body weights of male and female rats ingesting more than 5 and 15 mg/kg bw per day, respectively, and a decrease in body weights of mice in all treatment groups relative to controls. A low degree of basal cell hyperplasia in the non-glandular portion of the stomach of male and female rats exposed to more than 15 mg/kg bw per day was also observed, but the severity of the damage was somewhat diminished after a four-week recovery period during which the rats were not exposed to 1,3-dichloropropene. The authors established a no-observed-adverse-effect level for rats as 5 mg/kg bw per day, and a no-observed-adverse-effect levels in mice as 15 mg/kg bw per day (Haut *et al.*, 1996).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

In a study of 64 men employed in the production of chlorinated compounds [time-weighted average exposures, < 1 ppm [4.5 mg/m^3] 1,3-dichloropropene, 3.1 mg/m^3 allyl chloride and 3.8 mg/m^3 epichlorohydrin], sperm counts and percentages of normal sperm were similar in the study group and among 63 controls. The volunteer participation rate for the study group was 64% (IARC, 1986).

4.3.2 *Experimental systems*

Pregnant Fischer 344 rats and New Zealand White rabbits were exposed by inhalation to 0, 20, 60 or 120 ppm [0, 91, 272 or 545 mg/m^3 air] 1,3-dichloropropene (47.7% *cis*, 42.4% *trans*) for 6 h per day during gestation days 6–15 (rats) or 6–18 (rabbits). Dose-dependent decreases in maternal weight gain and food consumption were observed in rats at all doses of 1,3-dichloropropene, and in rabbits at 60 and 120 ppm. In spite of

maternal toxicity, no evidence of teratogenetic or embryotoxic response was observed in rats or rabbits at any of the doses tested (Hanley *et al*., 1987).

Breslin *et al*. (1989) conducted a two-generation reproduction study in Fischer 344 rats with 1,3-dichloropropene (92% technical product). Male and female Fischer 344 rats were exposed by inhalation to 0, 10, 30 or 90 ppm [0, 45, 136 or 409 mg/m^3] 1,3-dichloropropene for 6 h per day on five days per week for two generations. The parental F_0 and F_1 generations were each bred twice. Parental effects (decreased body weights, histopathological effects on nasal mucosa) occurred only at the highest concentration of 1,3-dichloropropene. No adverse effect on reproductive parameters or neonatal growth or survival was found in either of the F_1 or F_2 litters, even at the 90 ppm dose.

Male and female Wistar rats were exposed by inhalation to concentrations of 0, 10, 30 or 90 ppm (v/v) of a mixture of vapours containing 28.1% *cis*-1,3-dichloropropene, 25.6% *trans*-1,3-dichloropropene, 25.6% 1,2-dichloropropane, 20.7% other chemicals (D-D) for 6 h per day on five days per week for 10 weeks. Treated males were paired with untreated virgin females, and treated females were paired with untreated males. Exposure to the vapours produced no adverse effect on the libido, fertility or morphology of the reproductive tracts of rats of either sex (Linnett *et al*., 1988).

Relative testicular weights of Fischer 344 male rats exposed by inhalation to 90 and 150 ppm [409 and 681 mg/m^3] 1,3-dichloropropene (*cis*, 48.6%; *trans*, 42.3%) for 6 h per day on five days per week for 13 weeks were increased and thymus weights of female rats exposed to 150 ppm 1,3-dichloropropene were decreased relative to controls (Stott *et al*., 1988). Changes in testicular or thymic weights at the lower doses of 10 and 30 ppm were not observed.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

1,3-Dichloropropene was mutagenic in *Salmonella typhimurium*, with or without metabolic activation. In one study, the *cis*-isomer was reported not to be mutagenic to *Salmonella typhimurium* TA100 without metabolic activation, and to become active only after exposure to oxygen and consequent generation of autooxidation products. Glutathione was shown to efficiently inhibit the mutagenicity in *Salmonella* of *cis*- and *trans*-1,3-dichloropropene both with and without metabolic activation. There was no difference in the *Salmonella* mutagenicity between *cis*- and *trans*-1,3-dichloropropene.

In one study, a mixture of *cis*- and *trans*-1,3-dichloropropene gave positive results for induction of mutations in *Drosophila melanogaster*.

A mixture of *cis*- and *trans*-1,3-dichloropropene caused sister chromatid exchanges in human lymphocytes *in vitro* as well as in other cultured mammalian cells. It also induced unscheduled DNA synthesis and DNA strand breaks. However, it was negative for induction of chromosomal aberrations in Chinese hamster ovary CHO cells.

Table 1. Genetic and related effects of 1,3-dichloropropene

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***trans*-1,3-Dichloropropene**				
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	10	De Lorenzo *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	10	Creedy *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Neudecker & Henschler (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	10	De Lorenzo *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	122	Neudecker *et al.* (1977)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	+	+	25	De Lorenzo *et al*. (1977)
***cis*-1,3-Dichloropropene**				
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	10	De Lorenzo *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5	Creedy *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Neudecker & Henschler (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	20	Watson *et al*. (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	10	De Lorenzo *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	122	Neudecker *et al.* (1977)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	+	+	25	De Lorenzo *et al*. (1977)
Mixture of *trans*- + *cis*-1,3-dichloropropene				
PRB, SOS-Chromotest, DNA damage in *Escherichia coli* PQ37	+	NT	365	Von der Hude *et al*. (1988)
SAF, *Salmonella typhimurium* TA98, forward mutation (rifampicin resistance)	+	NT	200	Vithayathil *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	55	Stolzenberg & Hine (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	17	Haworth *et al*. (1983)

Table 1 (contd)

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation (1,3-dichloropropene purified by chromatography)	–	NT	500	Talcott & King (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	Talcott & King (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	17	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	–	50	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	NT	200	Vithayathil *et al.* (1983)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		5750 ppm feed	Valencia *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocations	–		5750 ppm feed	Valencia *et al.* (1985)
DIA, DNA fragmentation, Chinese hamster lung V79 cells *in vitro*	+	NT	200	Martelli *et al.* (1993)
DIA, DNA fragmentation, rat primary hepatocytes *in vitro*	+	NT	20	Martelli *et al.* (1993)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	35	Martelli *et al.* (1993)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	–	11	von der Hude *et al.* (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	30	Loveday *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	100	Loveday *et al.* (1989)
DIH, DNA fragmentation, human hepatocytes *in vitro*	+	NT	35	Martelli *et al.* (1983)
UIH, Unscheduled DNA synthesis, human hepatocytes *in vitro*	+	NT	35	Martelli *et al.* (1983)
SHL, Sister chromatid-exchange, human lymphocytes *in vitro*	+	+	11	Kevokordes *et al.* (1996)
DVA, DNA fragmentation, rat liver, kidney and gastric mucosa *in vivo*	+		62.5 ip × 1	Ghia *et al.* (1993)

Table 1 (contd)

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
URP, Unscheduled DNA synthesis, rat hepatocytes *in vivo*	–		125 po × 1	Ghia *et al*. (1993)
MVR, Micronucleus test, rat bone-marrow, spleen and liver cells *in vivo*	–		125 po × 1	Ghia *et al*. (1993)
MVM, Micronucleus test, NMRI mice bone-marrow cells *in vivo*	+		187 po × 1	Kevekordes *et al*. (1996)
SPF, Sperm morphology, (C57BL/6 × C3H)F_1 mice *in vivo*	–		75 ip × 5	Osterloh *et al*. (1983)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; po, oral; ip, intraperitoneal

A mixture of *cis*- and *trans*-1,3-dichloropropene has given contradictory results in the mouse micronucleus assay. In the most recent study, it was positive in female (but not in male) NMRI mice. On the other hand, it did not induce micronuclei in the bone marrow, spleen or liver of partially hepatectomized rats, nor did it cause unscheduled DNA synthesis in rat hepatocytes *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Dichloropropene is used in organic synthesis and as a soil fumigant. It can be released into the air and waste water and can occur to some extent in ground water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Technical-grade 1,3-dichloropropene (containing 1.0% epichlorohydrin), when given by gavage, produced tumours of the urinary bladder, lung and forestomach in mice and of the liver and forestomach in rats. Inhalation exposure produced an increase in the incidence of bronchioalveolar adenomas in mice. No increase in tumours was seen in rats. After subcutaneous administration to mice, the *cis*-isomer produced malignant tumours at the site of injection.

5.4 Other relevant data

The principle metabolic pathway of 1,3-dichloropropene is conjugation with glutathione and elimination as mercapturic acids. Enzymatic conjugation with glutathione and non-enzymatic alkylation proceed more rapidly with the *cis*-isomer than with the *trans*-isomer. At the concentrations used in rodent carcinogenicity studies by inhalation, significant morphological alterations in the nasal tissues were observed. No teratogenic or embryotoxic effects were observed in rats and rabbits exposed by inhalation to the mixed isomers.

1,3-Dichloropropene induces micronuclei in the bone marrow of female mice, as well as sister chromatid exchanges and DNA damage in cultured mammalian cells. It is mutagenic to bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,3-dichloropropene were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed isomers of 1,3-dichloropropene (technical grade).

Overall evaluation

1,3-Dichloropropene (technical-grade) is *possibly carcinogenic to humans (Group 2B)*.

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