1,1,2-TRICHLOROETHANE

Data were last evaluated in IARC (1991).

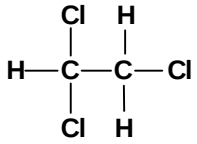
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 79-00-5
Chem. Abstr. Name: 1,1,2-Trichloroethane
IUPAC Systematic Name: 1,1,2-Trichloroethane
Synonym: Vinyl trichloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_2H_3Cl_3$ Relative molecular mass: 133.41

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with pleasant odour (Budavari, 1996)
(*b*) *Boiling-point*: 113.8°C (Lide, 1995)
(*c*) *Melting-point*: –36.6°C (Lide, 1995)
(*d*) *Solubility*: Insoluble in water; soluble in chloroform, diethyl ether, ethanol and many other organic liquids (Lide, 1995; Budavari, 1996)
(*e*) *Vapour pressure*: 2.5 kPa at 20°C; relative vapour density (air = 1), 4.6 (Verschueren, 1996)
(*f*) *Conversion factor*: $mg/m^3 = 5.46 \times ppm$

1.2 Production and use

Annual production of 1,1,2-trichloroethane in the United States in the early 1980s was estimated to be 186 000 tonnes (American Conference of Governmental Industrial Hygienists, 1992).

1,1,2-Trichloroethane is used primarily as an intermediate in the production of vinylidene chloride; other minor uses include as a solvent for fats, oils, waxes, resins and

other products, and as a process solvent in pharmaceutical manufacture (American Conference of Governmental Industrial Hygienists, 1992; Lewis, 1993; Snedecor, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

No national estimates of exposure were available to the Working Group.

1.3.2 *Environmental occurrence*

1,1,2-Trichloroethane may enter the atmosphere from its use in the manufacture of vinylidene chloride and its use as a solvent. It may also be discharged in wastewater associated with these uses and in leachates and volatile emissions from landfills. It has been detected at low levels in groundwater, drinking-water, wastewater, ambient water and ambient air (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 55 mg/m^3 as the threshold limit value for occupational exposures to 1,1,2-trichloroethane in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for 1,1,2-trichloroethane in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

1,1,2-Trichloroethane was tested for carcinogenicity in a two-year study in male and female B6C3F$_1$ mice and Osborne-Mendel rats by oral administration and in Sprague-Dawley rats by subcutaneous injection. In the study by oral administration, 1,1,2-trichloroethane produced hepatocellular neoplasms and adrenal phaeochromocytomas in mice of each sex but did not significantly increase the proportion of rats with neoplasms at any site relative to untreated controls. In the study in rats by subcutaneous injection, 1,1,2-trichloroethane did not increase the incidence of neoplasms.

In a screening assay for γ-glutamyltranspeptidase-positive foci in the liver of male Osborne-Mendel rats, 1,1,2-trichloroethane did not increase the number of foci in the liver after the initiation protocol (single injection), but the number was increased after the promotion protocol (repeated injections), after partial hepatectomy or after partial hepatectomy followed by initiation with *N*-nitrosodiethylamine (IARC, 1991).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

When [^{38}Cl]1,1,2-trichloroethane was administered by inhalation at a dose of about 5 mg per subject, about 3% of the compound was eliminated in the breath within 1 h, and urinary excretion of ^{38}Cl amounted less than 0.01% of the dose/min (IARC, 1991).

4.1.2 *Experimental systems*

1,1,2-Trichloroethane is rapidly absorbed after inhalation, oral administration and application to the skin in rodents. 1,1,2-Trichloroethane is extensively metabolized in mice given 100–200 mg/kg bw by intraperitoneal injection, 73–87 % of the dose being eliminated in the urine and 16–22% in expired air. Several urinary metabolites have been identified: chloroacetic acid, *S*-carboxymethyl-L-cysteine, thiodiacetic acid, 2,2-dichloroethanol and oxalic acid (IARC, 1991).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Upon administration of lethal doses of 1,1,2,-trichloroethane, signs of toxicity included sedation, gastric irritation, lung haemorrhage and liver and kidney damage, but at continued dosing at dose levels compatible with survival, no significant organ toxicity was observed (IARC, 1991). This was substantiated in a carcinogenicity study (United States National Cancer Institute, 1978), in which no gross or microscopic non-neoplastic changes were associated with administration of 1,1,2-trichloroethane (time-weighted average dose, 46 or 92 mg/kg bw per day by gavage for 78 weeks) to Osborne-Mendel rats of each sex and 195 or 390 mg/kg bw per day to B6C3F$_1$ mice of each sex.

A small but significant elevation of serum sorbitol dehydrogenase activity was observed 18 h after an intraperitoneal dose of 51 mg/kg bw 1,1,2-trichloroethane (1/8 of the LD_{50}), but not at a dose level of 25 mg/kg bw (Lundberg *et al*., 1986). After a single intragastric dose of 667 mg/kg bw 1,1,2 trichloroethane, serum glutamic pyruvic transaminase, sorbitol dehydrogenase and glutamate dehydrogenase activities showed elevations which peaked at 24 h in female Wistar rats. Cloudy swelling, vacuolar degeneration and scattered necrosis were observed in the liver. Electron spin resonance spectra from liver specimens were consistent with increased concentrations of free radicals (Liangfu & Tianju, 1992). In Sprague-Dawley rats, a single intraperitoneal dose of 200 mg/kg bw 1,1,2-trichloroethane induced an elevation of serum glutamic pyruvic transaminase activity and histological liver damage, while a dose of 167 mg/kg bw produced practically no effect. The hepatotoxicity of 1,1,2-trichloroethane was markedly potentiated by pre-

treatment with acetone. Hepatic glutathione content showed a slight decrease 2 h after administration of 1,1,2-trichloroethane; a very marked decrease was observed in acetone-pretreated animals (MacDonald *et al*., 1982).

When CD-1 mice were given 1,1,2-trichloroethane (4.4, 46 or 305 mg/kg bw for males and 3.9, 44 or 384 mg/kg bw for females) in the drinking-water for 90 days, very minor effects on weight gain or haematological or clinical chemical parameters were seen. A dose-dependent decrease in hepatic cytochrome P450 content and in aniline hydroxylase activity was observed in females (White *et al*., 1985). Cell-mediated immunity (delayed type hypersensitivity, popliteal lymph node proliferation, spleen lymphocyte response to concanavalin A) was not affected in these mice, while haemagglutination titres to sheep red blood cells were depressed in a dose-dependent manner in both sexes and the responsiveness of splenic lymphocytes to the B-cell mitogen lipopolysaccharide was decreased in females. In males, peritoneal exudate cells exhibited a decreased phagocytic capacity at the highest dose (Sanders *et al*., 1985).

4.3 Reproductive and developmental 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 Table 1 for references)

The genetic and related effects of 1,1,2-trichloroethane have been reviewed (Infante & Tsongas, 1982).

1,1,2-Trichloroethane gave conflicting results in the *Salmonella typhimurium* reverse mutation assay. Positive results were reported in only one study for strains TA100, TA104, and TA97. 1,1,2-Trichloroethane caused chromosome malsegregation in *Aspergillus nidulans* and morphological transformation of BALB/c-3T3 cells. It induced DNA damage in human lymphocyte cultures in the presence or absence of exogenous metabolic activation and micronuclei in the absence of metabolic activation. It bound to DNA, RNA and protein of lung, liver, kidney and stomach following treatment of rats and mice *in vivo*. Strong S-phase induction was observed in livers of treated mice, but unscheduled DNA synthesis was not seen in mouse or rat hepatocytes *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,2-Trichloroethane is used in the manufacture of vinylidene chloride. It has been detected in ground-, drinking-, waste- and ambient water and ambient air.

Table 1. Genetic and related effects of 1,1,2-trichloroethane

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SAF, *Salmonella typhimurium*, forward mutation (Ar2 test)	–		500	Roldán-Arjona *et al*. (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[c]	–	4000	Barber *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	–	5	Strobel & Grummt (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[d]	–	NG	Mersch-Sunderman (1989)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–[c]	–	NG	Mersch-Sunderman (1989)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	+	5	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	3000	Rannug *et al*. (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–[c]	–	4000	Barber *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[c]	–	4000	Barber *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Strobel & Grummt (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[d]	–	NG	Mersch-Sunderman (1989)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	5	Strobel & Grummt (1987)
SAS *Salmonella typhimurium* TA97, reverse mutation	–[d]	–	NG	Mersch-Sunderman (1989)
ANG, *Aspergillus nidulans* strain P1, genetic crossing-over	–	NT	1000	Crebelli *et al.* (1988)
ANN, *Aspergillus nidulans* strain P1, aneuploidy	+	NT	1000	Crebelli *et al.* (1988)
TBM, Cell transformation, BALB/c-3T3 cells	(+)[c]	NT	25	Tu *et al*. (1985)
DIH, DNA damage, human lymphocytes *in vitro*	+	+	333	Tafazoli & Kirsch-Volders (1996)
MIH, Micronucleus test, human lymphocytes *in vitro*	(+)	–	133	Tafazoli & Kirsch-Volders (1996)
UPR, Unscheduled DNA synthesis, Fischer 344 rat hepatocytes *in vivo*	–		1000 po × 1	Mirsalis *et al*. (1989)
UVM, Unscheduled DNA synthesis, B6C3F$_1$mouse hepatocytes *in vivo*	–		1000 po × 1	Mirsalis *et al*. (1989)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
BVD, DNA binding (covalent), BALB/c mouse liver, kidney, lung and stomach *in vivo*	+		0.8 ip × 1	Mazzullo *et al*. (1986)
BVD, DNA binding (covalent),Wistar rat liver, kidney, lung and stomach *in vivo*	+		0.8 ip × 1	Mazzullo *et al*. (1986)
BVP, Binding to RNA/protein, BALB/c mouse liver, kidney, lung and stomach *in vivo*	+		0.8 ip × 1	Mazzullo *et al*. (1986)
BVP, Binding to RNA/protein, Wistar rat liver, kidney, lung and stomach *in vivo*	+		0.8 ip × 1	Mazzullo *et al*. (1986)
S-phase synthesis induction, mouse hepatocytes *in vivo*	+		500 po × 1	Mirsalis *et al*. (1989)

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

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

[c] Closed container

[d] Negative in closed container, standard test or spot

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,2-Trichloroethane was tested for carcinogenicity in a two-year study in male and female B6C3F_1 mice and Osborne-Mendel rats by oral administration and in Sprague-Dawley rats by subcutaneous injection. In the study by oral administration, 1,1,2-trichloroethane produced hepatocellular neoplasms and adrenal phaeochromocytomas in mice of each sex but did not significantly increase the proportion of rats with neoplasms at any site relative to untreated controls. In the study in rats by subcutaneous injection, 1,1,2-trichloroethane did not increase the incidence of neoplasms.

5.4 Other relevant data

1,1,2-Trichloroethane bound to DNA, RNA and protein and caused strong S-phase induction but not unscheduled DNA synthesis in rodents *in vivo*. It induced DNA damage and micronuclei in human lymphocytes and cell transformation in BALB/c-3T3 cells *in vitro*. 1,1,2-Trichloroethane caused chromosomal malsegregation in fungi and showed some evidence of mutagenicity in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 1,1,2-trichloroethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,1,2-trichloroethane.

Overall evaluation

1,1,2-Trichloroethane is *not classifiable as to its carcinogenicity to humans (Group 3).*

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