1,1,1,2-TETRACHLOROETHANE

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

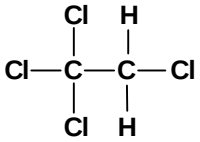
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 630-20-6
Chem. Abstr. Name: 1,1,1,2-Tetrachloroethane
IUPAC Systematic Name: 1,1,1,2-Tetrachloroethane
Synonym: (Chloromethyl)trichloromethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_2H_2Cl_4$ Relative molecular mass: 167.85

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (United States National Library of Medicine, 1997)
(*b*) *Boiling-point*: 130.5°C (Lide, 1995)
(*c*) *Melting-point*: –70.2°C (Lide, 1995)
(*d*) *Solubility*: Slightly miscible with water (1.1 g/L at 25°C); miscible in acetone, benzene, chloroform, diethyl ether and ethanol (Lide, 1995; United States National Library of Medicine, 1997)
(*e*) *Vapour pressure*: 1.9 kPa at 25°C (United States National Library of Medicine, 1997)
(*f*) *Conversion factor*: $mg/m^3 = 6.87 \times ppm$

1.2 Production and use

1,1,1,2-Tetrachloroethane has been used as a solvent and in the manufacture of insecticides, herbicides, soil fumigants, bleaches, other chlorocarbon solvents and paints and

varnishes (United States National Library of Medicine, 1997). It is present as an unisolated intermediate in some processes for the manufacture of trichloroethylene and tetrachloroethylene from 1,2-dichloroethane (IARC, 1986).

1.3 Occurrence

1.3.1 *Occupational exposure*

No data were available to the Working Group.

1.3.2 *Environmental occurrence*

Although 1,1,1,2-tetrachloroethane apparently is not produced or used commercially in large quantities, it may be formed incidentally during the manufacture of other chlorinated ethanes and released into the environment as air emissions or in wastewater. It has been detected at low levels in urban air, ambient air, drinking-water, ambient water, groundwater, wastewater and soil samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not recommended a threshold limit value for occupational exposures to 1,1,1,2-tetrachloroethane in workplace air.

No international guideline for 1,1,1,2-tetrachloroethane 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

1,1,1,2-Tetrachloroethane was tested for carcinogenicity by oral gavage in one study in mice and one study in rats. An increased incidence of hepatocellular adenomas was observed in mice of each sex and of hepatocellular carcinomas in females. The experiment in male rats gave negative results and that in female rats was inconclusive (IARC, 1986).

3.1 Oral administration

Rat: In a rat liver foci assay for tumour-initiating activity, groups of 10 male Osborne-Mendel rats were subjected to two-thirds partial hepatectomies and, 24 h later, were given 1,1,1,2-tetrachloroethane by gavage at the maximum tolerated dose (MTD) in corn oil. Six days after partial hepatectomy, the rats received 0.05% phenobarbital in

the diet for seven weeks, then control diets for seven further days, after which they were killed and their livers examined. The numbers of enzyme-altered foci in the liver were 0.77 ± 0.34 and 0.26 ± 0.19 foci/cm^2 (mean ± standard error) in the test and control (corn oil) groups, respectively. It was concluded that 1,1,1,2-tetrachloroethane did not show initiating activity in this system (Milman *et al*., 1988).

In a promotion study, groups of 10 rats were given an intraperitoneal injection of 30 mg/kg bw *N*-nitrosodiethylamine (NDEA) 24 h after a two-thirds partial hepatectomy. Six days later, the rats received 1,1,1,2-tetrachloroethane in corn oil at the MTD by gavage on five days per week for seven weeks. The rats were held for an additional seven days and then killed and the livers were examined. The numbers of enzyme-altered foci were 1.68 ± 0.44 foci/cm^2 in the treated group and 1.77 ± 0.49 foci/cm^2 in the control (corn oil) group. No promoting activity was observed (Milman *et al*., 1988).

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*

The metabolism of 1,1,1,2-tetrachloroethane and related chloroethanes has been reviewed (IARC, 1986).

In mice given a subcutaneous dose of 1.2–2.0 g/kg bw 1,1,1,2-tetrachloroethane, 21–62% was eliminated unchanged in exhaled air within 72 h. The major urinary metabolites in mice, rats, rabbits and guinea-pigs were trichloroethanol and its glucuronide conjugate; trichloroacetic acid was also excreted (IARC, 1986).

In the presence of oxygen, NADPH and rat liver microsomes, 1,1,1,2-tetrachloroethane undergoes little dechlorination. In contrast, NADPH-dependent reductive metabolism of 1,1,1,2-tetrachloroethane by hepatic microsomal fractions from rats yields 1,1-dichloroethylene as the major metabolite and 1,1,2-trichloroethane as a minor metabolite (IARC, 1986).

4.2 Toxic effects

The toxicity of 1,1,1,2-tetrachloroethane has been reviewed (Luotamo & Riihimäki, 1996).

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Short- and long-term administration of 1,1,1,2-tetrachloroethane induced hepatic damage; in long-term studies, central nervous system effects and renal mineralization were also observed (IARC, 1986).

When 1,1,1,2-tetrachloroethane was administered to male Fischer 344/N rats by gavage at 0.62 or 0.124 mmol/kg once daily for 21 days, hyaline nephropathy, consisting of hyaline droplet accumulation, and an increased incidence of tubule regeneration were observed. Granular casts and an increased proliferating cell nuclear antigen labelling index were observed at the higher dose level (United States National Toxicology Program, 1996).

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)

1,1,1,2-Tetrachloroethane induced reverse but not forward mutation in *Salmonella typhimurium*: one of two studies reported that 1,1,1,2-tetrachloroethane induced mutations in strain TA100 and TA98 in the presence or absence of exogenous metabolic activation. A weak mutagenic response was reported for strain TA104 and results for strain TA97 were positive in the presence of exogenous metabolic activation. 1,1,1,2-Tetrachloroethane induced recombination but not mutation or aneuploidy in *Saccharomyces cerevisiae* and induced genetic crossing-over and aneuploidy in *Aspergillus nidulans* in the absence of metabolic activation. Sex-linked recessive lethal mutations were not induced in *Drosophila melanogaster*.

1,1,1,2-Tetrachloroethane induced gene mutations in the mouse lymphoma $tk^{+/-}$ assay only in the presence of an exogenous metabolic activation system. It did not increase the frequency of chromosomal aberrations in Chinese hamster lung fibroblasts or ovary cells but did induce sister chromatid exchanges in Chinese hamster ovary cells and aneuploidy in Chinese hamster lung fibroblasts in the absence of exogenous activation. 1,1,1,2-Tetrachloroethane did not induce cell transformation in BALB/c-3T3 cells.

One study reported that 1,1,1,2-tetrachloroethane covalently bound to DNA in rat and mouse lung, liver, kidney and stomach following a single treatment by intraperitoneal injection.

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

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SAF, *Salmonella typhimurium*, forward mutation, arabinose resistance	–	–	150	Roldán-Arjona *et al*. (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	(+)	(+)	25	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	125	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	5	Strobel & Grummt (1987)
SCG, *Saccharomyces cerevisiae* strain D7, gene conversion, *trp* locus	+	–	168	Bronzetti *et al*. (1989)
ANG, *Aspergillus nidulans* strain P1, genetic crossing-over	+	NT	400	Crebelli *et al*. (1988)
SCR, *Saccharomyces cerevisiae*, reverse mutation, *ilv* locus	–	–	1679	Bronzetti *et al*. (1989)
SCN, *Saccharomyces cerevisiae* strain D61.M, aneuploidy	–	NT	1340	Whittaker *et al*. (1990)
ANN, *Aspergillus nidulans* strain P1, aneuploidy	+	NT	200	Crebelli *et al*. (1988)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		1500 µg/mL inj	Foureman *et al*. (1994)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	+	200	McGregor *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	?	200	Sofuni *et al*. (1996)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	–	248	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	506	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts *in vitro*	–	–	200	Matsuoka *et al*. (1996)
AIA, Aneuploidy, Chinese hamster lung fibroblasts *in vitro*	+	+	100	Matsuoka *et al*. (1996)
TBM, Cell transformation, BALB/c-3T3 mouse cells	–	NT	250	Tu *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
BID, Binding (covalent) to calf thymus DNA *in vitro*	NT	+	9.6	Colacci *et al*. (1989)
BVD, Binding (covalent) to DNA, BALB/c mouse lung, liver, kidney and stomach *in vivo*	+		1.46 ip × 1	Colacci *et al*. (1989)
BVD, Binding (covalent) to DNA, Wistar rat lung, liver, kidney and stomach *in vivo*	+		1.46 ip × 1	Colacci *et al*. (1989)

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

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw /day; inj, injection; ip, intraperitoneal

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,1,1,2-Tetrachloroethane is an intermediate in one process for the manufacture of trichloroethylene and tetrachloroethylene and has been reported to occur as an impurity in these widely used products. It has been detected at low levels in ambient air and in drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,1,2-Tetrachloroethane was tested for carcinogenicity by oral administration by gavage in one study in mice and one study in rats. An increased incidence of hepatocellular adenomas was observed in mice of each sex and of hepatocellular carcinomas in females. The experiment in male rats gave negative results and that in female rats was inconclusive. In one small experiment in rats, no initiating or promoting activity of 1,1,1,2-tetrachloroethane was demonstrated.

5.4 Other relevant data

In a single study, 1,1,1,2-tetrachloroethane bound covalently to DNA in rats and mice *in vivo*. It induced gene mutations, sister chromatid exchanges and aneuploidy, but not chromosomal aberrations, in rodent cell cultures. It did not induce sex-linked recessive mutation in *Drosophila* or mutations or aneuploidy in yeast. 1,1,1,2-Tetrachloroethane induced gene conversion in yeast, genetic crossing-over and aneuploidy in fungus and gene mutations in bacteria.

5.5 Evaluation

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

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

Overall evaluation

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

6. References

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