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TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS

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International Agency for Research on Cancer

World Health Organization

1,1,2,2-TETRACHLOROETHANE

1,1,2,2-Tetrachloroethane was considered by previous IARC Working Groups in 1979, 1987, and 1998 (IARC, 1979, 1987, 1999). New data have since become available and these have been taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

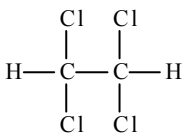
Chem. Abstr. Serv. Reg. No.: 79-34-5

Chem. Abstr. Serv Name: 1,1,2,2-Tetrachloroethane

IUPAC Systematic Name: 1,1,2,2-Tetrachloroethane

Synonym: Acetylene tetrachloride, *sym*-tetrachloroethane

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

Description: Nonflammable, heavy, mobile liquid with sweetish, suffocating, chloroform-like odour (O'Neil, *et al.*, 2006)

Boiling-point: 146.5 °C (O'Neil *et al.*, 2006)

Melting-point: –44 °C (O'Neil *et al.*, 2006)

Density: 1.587 at 25 °C, relative to H_2O at 4 °C (O'Neil, *et al.*, 2006)

Solubility: Very sparingly soluble in water (1 g/350 mL at 25 °C); Soluble in acetone, benzene and chloroform, miscible with methanol, ethanol, diethyl ether, petroleum ether, carbon tetrachloride, carbon disulfide, dimethylformamide and oils. Has the highest solvent power of the chlorinated hydrocarbons (Haynes, 2012; O'Neil *et al.*, 2006)

Volatility: Vapour pressure, 1 kPa at 32.4 °C (Haynes, 2012)

Octanol/water partition coefficient (P): log P, 2.39 (Haynes, 2012)

Conversion factor: mg/m^3 = 6.87 × ppm, calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

Table 1.1 Methods for the analysis of 1,1,2,2-tetrachloroethane

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Air collected in specially prepared canister; desorb on cold trap	GC/MS	0.09–0.28 ppm	EPA (1999a)
		GC/ECD	NR	
		GC/FID	NR	
		GCPID	NR	
	Analyte collected on sorbent tube; thermally desorb to GC	GC/MS	NR	EPA (1999b)
		GC/ECD	NR	
		GC/FID	NR	
		GCPID	NR	
Water	Purge with inert gas and trap; desorb to GC	GC/PID	NR	EPA (1988)
		GC/HECD	0.01 µg/L	EPA (1995a)
	Purge with inert gas and trap; desorb to GC	GC/MS	0.04 µg/L	EPA (1988), EPA (1995b)
Liquid and solid wastes	Purge with inert gas and trap	GC/PID	NR	EPA (1996a)
		GC/HECD	0.01 µg/L	
	Purge with inert gas and trap and various other methods	GC/MS	5 µg/kg (soil/sediment) 500 µg/kg (wastes) 5 µg/L (ground water)	EPA (1996b)

ECD, electron capture detection; FID, flame ionization detection; GC, gas chromatography; HECD, Hall electrolytic conductivity detection; MS, mass spectrometry; MCD, microcoulometric detection; NR, not reported; PID, photoionization detection

1.1.4 Technical products and impurities

1,1,1,2-Tetrachloroethane is found as an impurity in technical-grade 1,1,2,2-tetrachloroethane (HSDB, 2012).

1,1,2,2-Tetrachloroethane is available in research quantities at purities of > 98% and > 95% (Sigma Aldrich, 2012).

Trade names for 1,1,2,2-tetrachloroethane include Freon 130, F130 and HCC 130 (Springer Materials, 2013).

1.1.5 Analysis

Methods for the analysis of volatile organic compounds have been reviewed by Delinsky *et al.*, (2005) and Demeestere *et al.* (2007). Selected methods for the analysis of 1,1,2,2-tetrachloroethane in various matrices are identified in Table 1.1.

1.2 Production and use

1.2.1 Production process

(a) Manufacturing processes

1,1,2,2-Tetrachloroethane is manufactured by chlorination of ethylene; by catalytic chlorination of ethane; or by chlorination of 1,2-dichloroethane (O'Neil *et al.*, 2001). When ethylene is used as a feedstock, 1,1,2,2-tetrachloroethane is not usually isolated initially, but is thermally cracked to produce other products (Mertens, 1993). To produce 1,1,2,2-tetrachloroethane of high purity, chlorination of acetylene has been used.

(b) Production volume

In the 1960s, production of 1,1,2,2-tetrachloroethane in the USA was > 100 000 tonnes per year (OECD SIDS, 2002). Because 1,1,2,2-tetrachloroethane is no longer used as a solvent, production has since dramatically decreased (ATSDR, 2008). Production worldwide has been reported to be

Table 1.2 Concentration of 1,1,2,2-tetrachloroethane in air

Location	Concentration		Comments	Reference
	Mean	Range		
Outdoor air				
Eight remote sites; North & South Atlantic	NR	0.2–1.7 ppt	Background tropospheric levels	Class & Ballschmiter (1986)
Tarragona, Spain	0.1 µg/m³	NR–0.7 µg/m³	Near large industrial complex	Ramírez *et al.* (2012)
Hamburg, Germany	NR	0.08–0.6 µg/m³	12 sites	Bruckmann *et al.* (1988)
Dallas, TX, USA	0.3[a] ppb	0.2 – 0.4 ppb	Ambient air near natural gas wells	Rich (2011)
Missoula, MT, USA	< 0.06[a] ng/m³	ND–0.3 ng/m³	Ambient outdoor air	Ward *et al.* (2009)
MN, USA	0.06 µg/m³	NR–6.87 µg/m³	25 outdoor sites in state (1991–1998)	Pratt *et al.* (2000)
Country-wide, USA	5.4 ppt	ND–4800 ppt	853 urban/suburban sites	ATSDR (2008)
Los Angeles, CA, USA	16.6 ppt	NR	Outdoor air	Singh *et al.* (1981)
Phoenix, AZ, USA	17.0 ppt	NR	Outdoor air	Singh *et al.* (1981)
Oakland, CA, USA	7.1 ppt	NR	Outdoor air	Singh *et al.* (1981)
Kuwait City, Kuwait	1188 µg/m³	0–17 604 µg/m³	Outdoor air	Bouhamra (1997)
Indoor air				
Missoula, MT, USA	< 0.06[a] ng/m³	ND–2.0 ng/m³	Indoor air, 80 homes	Ward *et al.* (2009)
Knoxville, TN, USA	13.0 µg/m³	NR	Indoor air, 8 homes	ATSDR (2008)
Kuwait City, Kuwait	3458 µg/m³	0–26 521 µg/m³	Indoor air	Bouhamra (1997)

[a] Median
ND, not detected; NR, not reported

between 10 000 and 100 000 tonnes per year, and most production occurred in China (OECD SIDS, 2002).

1.2.2 Use

In the past, 1,1,2,2-tetrachloroethane was used as a solvent, for degreasing metals, in paint removers, varnishes, lacquers, photographic film, rust removers, resins and waxes, extraction of oils and fats, and as an alcohol denaturant, in organic synthesis (Lewis, 1993). It has also been used in the manufacture of cyanogen chloride, polymers, and tetrachloro-alkylphenol, and as a solvent in the preparation of adhesives (Mackison *et al.*, 1981). Previously it was used in soil sterilization, as a weed killer, and in insecticide formulations, but is currently not registered in the USA for any of these purposes (ATSDR, 2008). Less common uses included in the determination of theobromine in cacao, as an immersion fluid in crystallography, in the biology laboratory to produce pathological changes in the gastrointestinal tract, liver and kidneys (O'Neil *et al.*, 2001), in the estimation of the water content of tobacco and many drugs, and as a solvent for impregnation of furs with chromium chloride (Sittig, 1985).

The primary current use of 1,1,2,2-tetrachloroethane is as a feedstock or chemical intermediate in the manufacture of trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene (ATSDR, 2008).

1.3 Occurrence

1.3.1 Natural occurrence

1,1,2,2-Tetrachloroethane is not known to occur as a natural product.

Table 1.3 Regulations and guidelines worldwide for 1,1,2,2-tetrachlorethane

Country or region	Concentration (mg/m³)	Interpretation	Carcinogenicity
Australia	6.9	TWA[a]	–
Austria	7	TWA	–
Belgium	7	TWA	–
Canada, Quebec	6.9	TWA	–
Denmark	7	TWA	–
France	7	TWA	–
Germany	7	TWA	TRGS 905 K3[b], MAK Category 3B[c]
New Zealand	6.9	TWA	–
Poland	5	TWA	–
Singapore	6.9	TWA	–
Spain	7	TWA	–
Switzerland	7	TWA	–
USA			–
NIOSH	7	TWA	–
OSHA	35	TWA	–
EPA	–	–	Group C[d]
ACGIH	–	–	A3[e]
NTP	–	–	Not listed

[a] Eight-hour time-weighted average
[b] Substances that are possibly carcinogenic for humans and thus give cause for concern.
[c] Substances that are proven/possibly carcinogenic and therefore give reason for concern. There are clues for carcinogenic effects which, however, are not enough for allocation into a different category.
[d] Possible human carcinogen
[e] Confirmed animal carcinogen with unknown relevance to humans.
ACGIH, American Conference of Industrial Hygienists; EPA, United States Environmental Protection Agency; MAK, [Maximale Arbeitsplatz-Konzentration] Maximum Workplace Concentration; NTP, National Toxicology Program; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; TRGS, Technical Rules for Hazardous Substances
From GESTIS-database on hazardous substances (IFA, 2012)

1.3.2 Environmental occurrence

1,1,2,2-Tetrachloroethane is primarily released to the atmosphere and to surface water as fugitive emissions during its production or use as a chemical intermediate (ATSDR, 2008). It was estimated that 1.4 tonnes of 1,1,2,2-tetrachloroethane were released to the atmosphere from 20 manufacturing and processing facilities in the USA in 2005 (ATSDR, 2008).

(a) Air

Table 1.2 presents some recent data on levels of 1,1,2,2-tetrachloroethane in air.

(b) Water

A nationwide study in the USA reported a mean concentration of 1,1,2,2-tetrachloroethane of 0.6 µg/L (range, 0.1–25 µg/L) in ground and surface water (ATSDR, 2008). Another study in the USA reported a range of 9000–17 000 µg/L in a river near a military testing site in the state of Maryland (Burton *et al.*, 2002).

1.3.3 Occupational exposure

In a large cross-sectional survey of small- to medium-scale industries in Japan in 1995–96, no use of 1,1,2,2-tetrachloroethane was reported (Ukai *et al.*, 1997). Two more recent (2009–2010) cross-industry surveys on use of organic solvents

in almost 1500 workplaces and 1900 laboratories in Japan confirmed this finding (Nagasawa *et al.*, 2011a, b).

1.3.4 Exposure of the general population

In Mexico City, 90 volunteers who lived near air-pollution monitoring stations wore personal samplers for 24 hours. 1,1,2,2-Tetrachlorethane was only detected in 3 out of 105 personal airspace monitors (Serrano-Trespalacios *et al.*, 2004). In studies in the USA of 1235 people in 2003–04 and 3131 people in 2005–06, 1,1,2,2-tetrachloroethane was not detected in blood (CDC, 2013).

1.4 Regulations and guidelines

Several countries have set time-weighted average (TWA) doses of 7 mg/m^3, including Australia, Austria, Belgium, Canada, Denmark, France, Germany, Japan, New Zealand, Singapore, Spain, Switzerland, and the National Institute for Occupational Safety and Health in the USA (Table 1.3). In the USA, the Occupational Safety and Health Administration has set a TWA dose of 35 mg/m^3.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Oral administration

In one study conducted by the US National Cancer Institute, male and female B6C3F$_1$ mice were given 1,1,2,2-tetrachloroethane by gavage in corn oil for 78 weeks, and observed for up to 90 weeks (NCI, 1978). Male mice were initially given 1,1,2,2-tetrachloroethane at a dose of 0 (n = 20), 100 (n = 50), or 200 (n = 50) mg/kg bw per day, 5 days per week, for 18 weeks. At week 19, the lower and higher doses were increased to 150 and 300 mg/kg bw per day, respectively, for 3 weeks, then increased again to 200 and 400 mg/kg bw, for 5 weeks, and finally decreased to 150 and 300 mg/kg bw for the remaining 52 weeks of treatment. The TWA doses were 0, 142, and 282 mg/kg bw per day. A significant dose-dependent trend in the incidence of hepatocellular carcinoma was observed at termination of the study. The incidence rates in the groups at the lower and higher doses were higher than in the controls. [The Working Group noted the alteration in the doses administered over time, the small number of mice in the control group, the limited duration of exposure, the increased mortality due to tubular nephrosis in weeks 69–70 in the group at the higher dose, and that the mice were housed in the same room as animals treated with several other volatile agents.]

The initial doses to female mice were 0 (n = 20), 100 (n = 50), and 200 (n = 50) mg/kg bw. At week 19, the lower and higher doses were increased to 150 and 300 mg/kg bw per day, respectively, for 3 weeks, then increased again to 200 and 400 mg/kg bw per day for 5 weeks, and finally decreased to 150 and 300 mg/kg bw per day for the remaining 52 weeks of treatment. The TWA doses were the same as for males. A significant positive trend in the incidence of hepatocellular carcinoma was observed in female mice at termination of the study. The incidence of hepatocellular carcinoma was higher at both doses

Table 3.1 Studies of carcinogenicity in experimental animals given 1,1,2,2-tetrachloroethane by gavage

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M) 90 wk NCI (1978)	0, 142, 282 mg/kg bw per day[a], in corn oil, for 78 wk 20, 50, 50/group	Hepatocellular carcinoma: 1/18, 13/50, 44/49	Cochran–Armitage trend test and Fisher exact test $P < 0.005$ (lower dose), $P < 0.001$ (higher dose), $P < 0.001$ (trend)	Purity, > 90% Variation of dose with time. Mice housed in same room where other volatile agents were studied. High mortality in higher-dose group due to tubular nephrosis (wk 69–70).
Mouse, B6C3F$_1$ (F) 90 wk NCI (1978)	0, 142, 282 mg/kg bw per day[a], in corn oil, for 78 wk 20, 50, 50/group	Hepatocellular carcinoma: 0/20, 30/48, 43/47	Cochran Armitage trend test and Fisher exact test $P < 0.001$ (lower dose), $P < 0.001$ (higher dose), $P < 0.001$ (trend)	Purity, > 90% Variation of dose with time. Mice housed in same room where other volatile agents were studied. High mortality in high-dose group (cause not identified).
Rat, Osborne-Mendel (M) 110 wk NCI (1978)	0, 62, 108 mg/kg bw per day[a], in corn oil, for 78 wk 20, 50, 50/group	Liver neoplastic nodules [liver adenoma] or hepatocellular carcinoma (combined): 0/20, 0/50, 3/49 [carcinoma, 2/49] Haemangiosarcoma: 0/20, 2/50, 3/49	NS	Purity, > 90% Variation of dose with time. Rats housed in same room where other volatile agents were studied. Early mortality at higher dose. The liver tumour incidence in high-dose animals was increased compared to historical controls.
Rat, Osborne-Mendel (F) 110 wk NCI (1978)	0, 43, 76 mg/kg bw per day[a], in corn oil, for 78 wk 20, 50, 50/group	Endometrial stromal polyp: 0/20, 8/50, 4/48	NS	Purity, > 90% Variation of dose with time. Rats housed in same room where other volatile agents were studied. Early mortality at both doses.

[a] Time-weighted average doses (see also text)

F, female; M, male; NS, not significant; wk, week

than in controls. [The Working Group noted the alteration in the doses administered over time, the small number of mice in the control group, the limited duration of exposure, the increased mortality due to unidentified causes in the group at the higher dose, and that the mice were housed in the same room as animals treated with several other volatile agents.]

3.2 Rat

Oral administration

In one study conducted by the US National Cancer Institute, male and female Osborne-Mendel rats were given 1,1,2,2-tetrachloroethane by gavage in corn oil for 78 weeks, and observed for up to 110 weeks (NCI, 1978). Male rats were initially given 1,1,2,2-tetrachloroethane at 0 (*n* = 20), 50 (*n* = 50), and 100 (*n* = 50) bw per day, 5 days per week. At week 15, the lower and higher doses were increased to 65 and 130 mg/kg bw per day, respectively. At week 33, treatment of rats at the higher dose was suspended for 1 week, then continued for a further 4 weeks. This dosing cycle of "1 week off" and "4 weeks on" was maintained until the end of treatment at week 78. The TWA doses were 0, 62, and 108 mg/kg bw per day. An increase in the incidence of liver neoplastic nodules [adenoma] or hepatocellular carcinoma (combined) was observed at the higher dose (0 out of 20, 0 out of 50, 3 out of 49 [carcinoma, 2 out of 49]). This increase was not statistically significant when compared with concurrent controls, but was significant compared with historical controls. The incidence of liver neoplastic nodules [adenoma] or hepatocellular carcinoma (combined) in male Osborne-Mendel rats among historical controls was 9 out of 975 (0.9% [carcinoma: 2 out of 975, 0.2%]; Goodman *et al.*, 1980). The increase in the incidence of haemangiosarcoma (0 out of 20, 2 out of 50, 3 out of 49) was not statistically significant compared with concurrent controls or historical controls (25 out of 975 [2.6%]; Goodman *et al.*, 1980). [The Working Group noted that the power of this study was reduced by the frequent changes in the doses administered, the small number of rats in the control group, the limited duration of exposure, and that the rats were housed in the same room as animals treated with several other volatile agents.]

Like the males, the female rats initially were given 1,1,2,2-tetrachloroethane at a dose of 0 (*n* = 20), 50 (*n* = 50), or 100 (*n* = 50) mg/kg bw per day (NCI, 1978). At week 26, the lower and higher doses were reduced to 40 and 80 mg/kg bw per day, respectively. Beginning at week 33, dosing was suspended for 1 week and then continued for a further 4 weeks. This dosing cycle of 1 week off and 4 weeks on was maintained until the end of treatment at week 78. The TWA doses were 0, 43, and 76 mg/kg bw per day. Survival was found to be reduced with increasing dose. No treatment-related increase in the incidence of liver tumours was noted, but there was an increase in the incidence of endometrial stromal polyps at the lower dose (0 out of 20, 8 out of 50, 4 out of 48). This increase was not statistically significant when compared with concurrent controls, but was significant compared with the incidence in historical controls. The incidence of endometrial stromal polyps in female Osborne-Mendel rats among historical controls was 43 out of 970 (4.4%; Goodman *et al.*, 1980). [The Working Group noted the frequent changes in the doses administered, the increased mortality in both dose groups, that the rats were housed in the same room as animals treated with several other volatile agents, and that the group of rats receiving the higher dose was reduced by 10 in the first 5 weeks of the study (including 8 rats with pneumonia). Reduced survival, the small number of rats in the control group, and the limited duration of exposure reduced the sensitivity of this study to adequately characterize the carcinogenic potential of the test agent.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Absorption

(a) Humans

No data on absorption of orally administered 1,1,2,2-tetrachloroethane in humans were identified by the Working Group. However, systemic toxicities after ingestion indicated absorption from the gastrointestinal tract in humans. The extent of absorption has not been characterized. One study reported on the absorption of 1,1,2,2-tetrachloroethane administered by inhalation (Morgan *et al.*, 1970). Volunteers inhaled ^{38}Cl-labelled 1,1,2,2-tetrachloroethane from a bulb in a single breath, which they held for 20 seconds. Approximately 97% of the inhaled dose was absorbed systemically, while only 3% was excreted as the parent compound in exhaled breath.

Estimates of the human blood:air partition coefficient *in vitro* averaged about 114 (Meulenberg & Vijverberg, 2000), indicating considerable respiratory uptake of 1,1,2,2-tetrachloroethane from inhaled air under equilibrium conditions.

(b) Experimental systems

Numerous studies indicated that 1,1,2,2-tetrachloroethane is readily absorbed after exposure by either oral or inhalation in rodents, but fewer data are available on the quantitative extent of absorption. Hanley *et al.* (1988) exposed male Osborne-Mendel rats and B6C3F$_1$ mice to ^{14}C-labelled 1,1,2,2-tetrachloroethane at a dose of 10 ppm (68.7 mg/m^3) as vapour for 6 hours, and recovered between 92% and 98% of the body burdens of radioactivity as metabolites, indicating very high uptake in both species at this level of exposure.

Gargas & Andersen (1989) conducted experiments on closed-chamber, whole-body inhalation in rats, and found a decline in chamber concentrations with time, consistent with an equilibrium alveolar gas-exchange model in which uptake by inhalation was largely determined by the partition coefficient. Estimates of the blood:air partition coefficient in rats *in vitro* averaged about 142 (Meulenberg & Vijverberg, 2000), indicating considerable respiratory uptake of 1,1,2,2-tetrachloroethane from inhaled air under equilibrium conditions. While the estimated blood:air partition coefficient for rats was slightly higher than that for humans, absorption would be expected to be similar since > 99% of the compound reaching the alveolar region would be absorbed into the blood in both species.

Hanley *et al.* (1988) gave male Osborne-Mendel rats and B6C3F$_1$ mice a single oral dose of radiolabelled 1,1,2,2-tetrachloroethane at 150 mg/kg in corn oil. Only 4–6% of the radiolabel was recovered in the faeces 72 hours after exposure, while > 90% was found as metabolites in both species, indicating complete absorption in rats and mice within 72 hours. Mitoma *et al.* (1985) exposed groups of male Osborne-Mendel rats to 1,1,2,2-tetrachloroethane at a dose of 25 or 100 mg/kg bw per day, and B6C3F$_1$ mice at 50 or 200 mg/kg bw per day, 5 days per week, for 4 weeks, followed by a single dose of radiolabelled compound, and recovered 79% of the administered dose as metabolites in rats and 68% in mice in 48 hours. Because metabolite recovery may not be complete, the results of this study were consistent with the virtually complete absorption estimated by Hanley *et al.* (1988).

Absorption also occurs via the dermal route. When 0.5 mL or 1 mL of 1,1,2,2-tetrachloroethane was applied to the skin of mice or guinea-pigs and the dose site occluded to prevent evaporation, all of the applied dose was absorbed within 30 minutes (Tsuruta, 1975; Jakobson *et al.*, 1982).

4.1.2 Distribution

(a) Humans

No data on tissue distribution of 1,1,2,2-tetrachloroethane were available to the Working Group. Meulenberg & Vijverberg (2000) used empirical regression models to predict tissue:air partition coefficients of volatile organic compounds based on measured saline:air and oil:air partition coefficients. Based on their predictions, tissue:blood partition coefficients in humans were estimated to range from 1.1 (kidney) to 38 (fat), depending on the lipid content of the tissues. These values suggested that 1,1,2,2-tetrachloroethane would be widely distributed to tissues after systemic delivery.

(b) Experimental systems

No data on the tissue distribution of 1,1,2,2-tetrachloroethane were available to the Working Group. Gargas *et al.* (1989) measured tissue:blood partition coefficients in the range of 0.7 (muscle) to 40 (fat), suggesting that 1,1,2,2-tetrachloroethane would be widely distributed to tissues after systemic delivery.

4.1.3 Metabolism

(a) Humans

No data on the metabolism of 1,1,2,2-tetrachloroethane in humans were available to the Working Group.

(b) Experimental systems

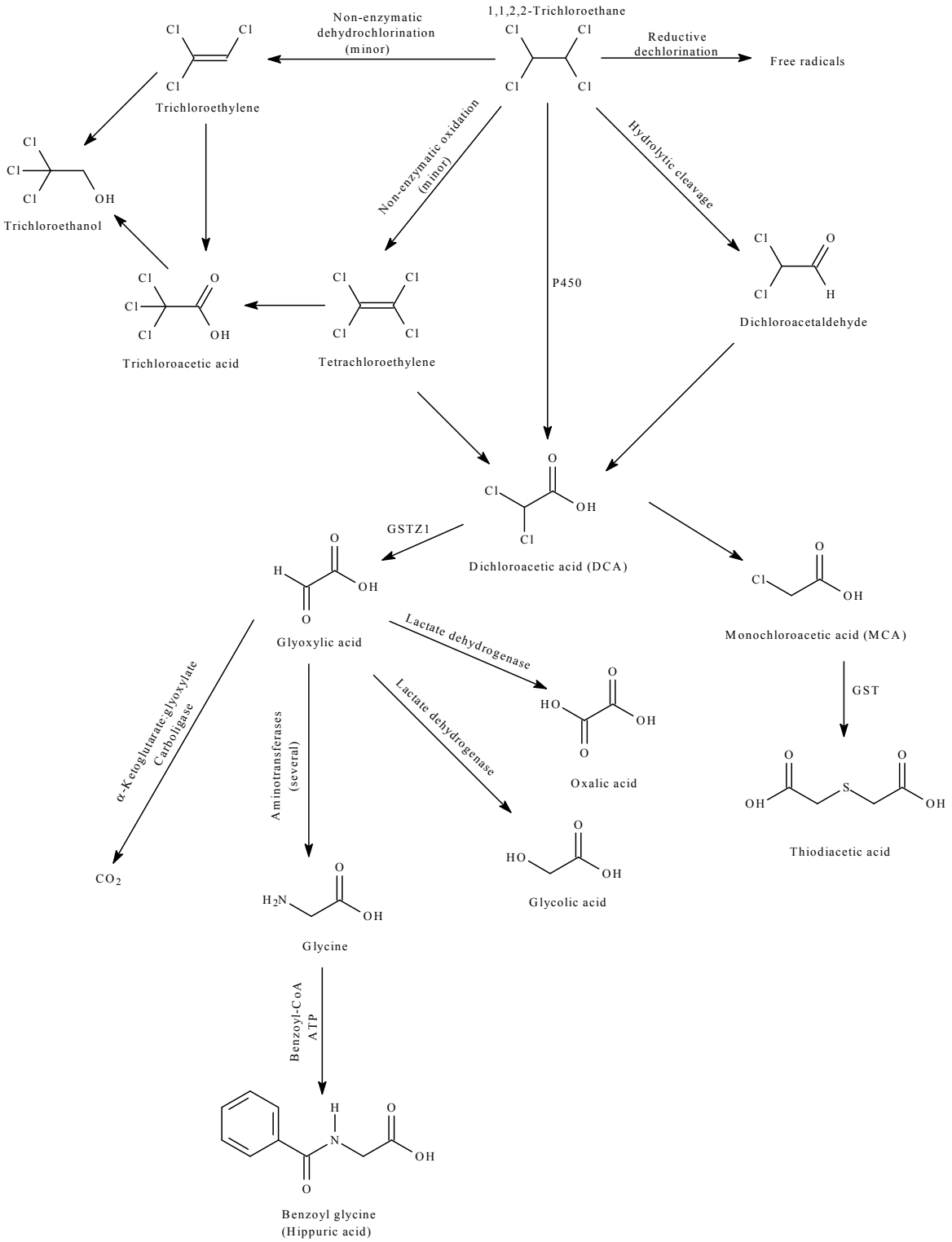
The metabolism of 1,1,2,2-tetrachloroethane is extensive in rodents, with 68–96% of the administered dose recovered as metabolites in mice and rats (Yllner, 1971; Mitoma *et al.*, 1985; Hanley *et al.*, 1988). Hanley *et al.* (1988) conducted quantitative recovery studies of 1,1,2,2-tetrachloroethane administered orally or by inhalation in rats and mice and showed that > 90% of the absorbed dose was metabolized.

The major pathway appears to be via oxidation to dichloroacetic acid, the major urinary metabolite detected in mice after intraperitoneal injection (Yllner, 1971) and in studies *in vitro* with rat liver microsomal and nuclear cytochrome P450 enzymes (Halpert & Neal, 1981; Halpert, 1982; Casciola & Ivanetich, 1984). The expiration of carbon dioxide (CO_2) and the presence of glyoxylic acid and oxalic acid in urine reported by Yllner (1971) are consistent with this pathway, since dichloroacetic acid can be further metabolized to glyoxylic acid to form oxylic acid and CO_2 (Fig. 4.1).

Yllner (1971) and Mitoma *et al.* (1985) reported trichloroethanol and/or trichloroacetic acid as urinary excretion products. Yllner (1971) also reported small amounts (0.2% to 0.4% of dose) of trichloroethylene and tetrachloroethylene in expired air. Yllner (1971) found that small amounts of 1,1,2,2-tetrachloroethane undergo non-enzymatic degradation to trichloroethylene in neutral aqueous solution, and suggested this pathway to explain the presence of trichloroethylene. Yllner (1971) suggested that a minute amount of 1,1,2,2-tetrachloroethane can be non-enzymatically converted to tetrachloroethylene. Trichloroethylene formation may explain the presence of trichloroethanol in urine, and either trichloroethylene or tetrachloroethylene could explain the presence of trichloroacetic acid. However, the source of trichloroethanol and trichloroacetic acid has not been conclusively demonstrated.

Multiple cytochrome P450 isozymes (CYP) are likely to be involved in the formation of dichloroacetic acid, as demonstrated by studies reporting increased metabolism following pretreatment with phenobarbital (Halpert 1982; Casciola & Ivanetich, 1984), xylene (Halpert 1982), or ethanol (Sato *et al.* 1980). Isozymes induced by these chemicals include members of the CYP subfamilies, CYP2A, CYP2B, CYP2E, and CYP3A (Omiecinski *et al.*, 1999).

Fig. 4.1 Metabolism of 1,1,2,2-tetrachloroethane



The reader is referred to the *Monographs* on trichloroethylene, tetrachloroethylene, trichloroacetic acid, dichloroacetic acid and 1,1,1,2-tetrachloroethane in this Volume for additional details on the metabolic pathway of 1,1,2,2-trichloroethylene.

Among several halogenated aliphatic hydrocarbons tested for their ability to decrease hepatic CYP content in rats, 1,1,2,2-tetrachloroethane was the second most active after carbon tetrachloride (Vainio *et al.*, 1976). Further evidence for the importance of CYP in the metabolism of 1,1,2,2-tetrachloroethane was obtained by Halpert (1982), who demonstrated covalent binding of a radiolabelled 1,1,2,2-tetrachloroethane metabolite to rat liver microsomes or a reconstituted mono-oxygenase system. On the basis of recovery of metabolites, 1,1,2,2-tetrachloroethane is metabolized by CYP to dichloroacetyl chloride, which can covalently bind to various nucleophilic groups or be hydrolysed to release dichloroacetic acid.

Halpert *et al.* (1986) also showed that incubation of a reconstituted system containing the phenobarbital-inducible form of CYP with 1,1,2,2-tetrachloroethane resulted in destruction of the haeme moiety. This provided further evidence of the role of CYP in the metabolism of 1,1,2,2-tetrachloroethane.

Tomasi *et al.* (1984) used electron spin resonance spectroscopy with spin trapping to demonstrate the formation of free radical intermediates in incubations of isolated hepatocytes from rats with eight aliphatic haloalkanes, including 1,1,2,2-tetrachloroethane. Formation of free radicals was demonstrated for 1,1,2,2-tetrachloroethane under both normoxic and hypoxic conditions.

Paolini *et al.* (1992) provided further evidence that 1,1,2,2-tetrachloroethane undergoes CYP-dependent oxidative metabolism to generate free radical intermediates that may cause lipid peroxidation and oxidative injury to the liver. Male and female mice were given a single oral dose of 1,1,2,2-tetrachloroethane (300 or 600 mg/kg bw). Analysis by electron spin resonance spectroscopy with spin trapping showed formation of a trichloroethyl free radical, the structure of which was not confirmed.

Thompson *et al.* (1985) investigated the reductive metabolism of several haloethanes, including 1,1,2,2-tetrachloroethane, by rat liver microsomes. Metabolism was NADPH-dependent, occurred only under anaerobic conditions, and led to formation of 1,2-dichloroethylene. Thus, depending on oxygenation status, CYP can catalyse both the oxidative and reductive metabolism of 1,1,2,2-tetrachloroethane.

Bolt (1987) compared metabolic rates of 1,1,2,2-tetrachloroethane between mice and rats, and found higher metabolic rates in mice. However, Mitoma *et al.* (1985) reported greater total metabolism in rats compared with mice (79% versus 68%).

4.1.4 Excretion

(a) Humans

No data on excretion of 1,1,2,2-tetrachloroethane in humans were available to the Working Group.

(b) Experimental systems

In experimental animals, 1,1,2,2-tetrachloroethane is eliminated primarily as expired CO_2 and metabolites in urine, with a small amount expired unchanged (Yllner 1971; Ikeda & Ohtsuji, 1972; Mitoma *et al.* 1985; Hanley *et al.* 1988). Of the metabolites, major fractions (25–50%) were exhaled as CO_2, approximately 20% excreted in urine and approximately 5% excreted in faeces (Hanley *et al.*, 1988). Yllner (1971) reported similar findings in mice given an intraperitoneal injection of ^{14}C-labelled tetrachloroethane (about half the dose expired as CO_2, and about 30% excreted in urine). A small percentage (4%) was expired unchanged, and the remaining was retained in the carcass. Mitoma *et al.* (1985) characterized the overall metabolic disposition of several chlorinated hydrocarbons, including 1,1,2,2-tetrachloroethane, in Osborne-Mendel rats and B6C3F$_1$ mice after administration of 25% or 100% of the maximum tolerated dose. In

their study, a smaller fraction was expired as CO_2 (2% in rats and 10% in mice), and a larger fraction excreted (46% in rats and 30% in mice), after repeated oral dosing for 4 weeks. The patterns of elimination in rats and mice were qualitatively similar (Mitoma *et al.* 1985; Hanley *et al.* 1988). Elimination was fairly rapid, with a large fraction excreted in the first 24 hours, but significant amounts remained in the urine and expired air at 48–72 hours after exposure (Yllner, 1971).

4.2 Genotoxicity and related effects

4.2.1 Humans

No data on the genotoxicity of 1,1,2,2-tetrachloroethane in humans were available to the Working Group.

4.2.2 Experimental systems

Several studies on genotoxicity with 1,1,2,2-tetrachloroethane were available to the Working Group. These are summarized in Table 4.1 and discussed below.

(a) Covalent binding

Colacci *et al.* (1987) found significant radiolabelling of DNA, RNA, and proteins from the liver, kidney, lung and stomach of male Wistar rats and BALB/c mice after intraperitoneal injection of radiolabelled 1,1,2,2-tetrachloroethylene.

Eriksson & Brittebo (1991) gave intravenous injections of ^{14}C-labelled 1,1,2,2-tetrachloroethane to C57B1 mice. Autoradiography showed selective localization of radiolabel in the nasal olfactory mucosa, epithelia of the trachea, bronchi and bronchioles, and squamous epithelia of the oral cavity, tongue and oesophagus. Homogenates of olfactory mucosa and liver were compared for their ability to activate radiolabelled 1,1,2,2-tetrachloroethane and bound radiolabel. For both processes, the capacity of the olfactory mucosa was higher than that of the liver. In addition, the effects of a CYP inhibitor, metyrapone, were consistent with 1,1,2,2-tetrachloroethane undergoing oxidative metabolism.

[The Working Group noted that the binding observed may be the result of a free radical formed via reductive dechlorination; as discussed above, free radical intermediates have been detected by spin-trapping techniques (Tomasi *et al.*, 1984; Paolini *et al.*, 1992; ATSDR, 1996). Alternatively, it may be the result of metabolic incorporation after metabolism through dichloroacetic acid to glycine.]

(b) DNA damage

Mirsalis *et al.* (1989) conducted *in vivo* to *in vitro* assays of DNA repair in hepatocytes and measurements of S-phase synthesis activity with 24 chemicals, including 1,1,2,2-tetrachloroethane. In the assay for DNA repair in hepatocytes, F344 rats or B6C3F$_1$ mice were given 1,1,2,2-tetrachloroethane by oral gavage and hepatocytes were isolated and incubated with radiolabelled thymidine. 1,1,2,2-Tetrachloroethane failed to induce unscheduled DNA synthesis in either rats or mice, and produced equivocal results with respect to S-phase synthesis activity in mice.

(c) Mutation and cytogenetic effects

Sofuni *et al.* (1996) reported on a collaborative study involving 42 Japanese laboratories to assess and compare a large battery of chemicals in the assay for clastogens in mouse lymphoma cells *in vitro*, using the microwell method. The results for 1,1,2,2-tetrachloroethane were inconclusive, with positive, negative, and unacceptable [high background] results reported.

As shown in Table 4.1, 1,1,2,2-tetrachloroethane has given negative results in several strains of *Salmonella typhimurium* (TA100, TA1530, TA104, TA1535, TA1537, TA1538, TA98) with and without exogenous metabolic activation. A few positive results have been reported by Strubel & Grummt (1987), in the TA98, TA97 or TA100 strains with and without metabolic activation.

Table 4.1 Genetic and related effects of 1,1,2,2-tetrachloroethane

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli pol A, differential toxicity (spot)	+	NT	16 000/disc	Brem *et al.* (1974); Rosenkranz (1977)
Salmonella typhimurium, forward mutation, arabinose resistance	–	–	150	Roldán-Arjona *et al.* (1991)
Salmonella typhimurium TA100, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
Salmonella typhimurium TA100, reverse mutation	–	–	500	Haworth *et al.* (1983)
Salmonella typhimurium TA100, reverse mutation	(+)	+	125	Strubel & Grummt (1987)
Salmonella typhimurium TA1530, reverse mutation	+	NT	1680/disc	Brem *et al.* (1974); Rosenkranz (1977)
Salmonella typhimurium TA104, reverse mutation	–	(+)	500	Strubel & Grummt (1987)
Salmonella typhimurium TA1535, reverse mutation	–	NT	1680/disc	Brem *et al.* (1974); Rosenkranz (1977)
Salmonella typhimurium TA1535, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
Salmonella typhimurium TA1535, reverse mutation	–	–	500	Haworth *et al.* (1983)
Salmonella typhimurium TA1537, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
Salmonella typhimurium TA1537, reverse mutation	–	–	500	Haworth *et al.* (1983)
Salmonella typhimurium TA1538, reverse mutation	–	NT	1680/disc	Brem *et al.* (1974); Rosenkranz (1977)
Salmonella typhimurium TA1538, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	–	–	500	Haworth *et al.* (1983)
Salmonella typhimurium TA98, reverse mutation	(+)	+	5	Strubel & Grummt (1987)
Salmonella typhimurium TA97, reverse mutation	+	+	5	Strubel & Grummt (1987)
Saccharomyces cerevisiae strain D7, gene conversion, *trp*5 locus	+	NT	875	Callen *et al.* (1980)
Saccharomyces cerevisiae strain D7, homozygosis, *ade*2 locus	+	NT	875	Callen *et al.* (1980)
Aspergillus nidulans strain P1, genetic crossing-over	–	NT	640	Crebelli *et al.* (1988)
Saccharomyces cerevisiae strain D7, reverse mutation, *ilv*1 locus	+	NT	875	Callen *et al.* (1980)
Aspergillus nidulans strain P1, aneuploidy	+	NT	320	Crebelli *et al.* (1988)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–	NT	1500 ppm, feed	Woodruff *et al.* (1985)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	56	Galloway *et al.* (1987)
Sister chromatid exchange, BALB/c 3T3 cells *in vitro*	+	+	500	Colacci *et al.* (1992)
Chromosomal aberration, Chinese hamster ovary cells *in vitro*	–	–	653	Galloway *et al.* (1987)
Chromosomal aberration, mouse lymphoma assay *in vitro*	+/–	+/–	100–600 µg/mL	Sofuni *et al.* (1996)

Table 4.1 (continued)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cell transformation, BALB/c 3T3 mouse cells	–	NT	250	Tu *et al.* (1985)
Cell transformation, BALB/c 3T3 mouse cells	(+)	+	125	Colacci *et al.* (1990)
Cell transformation, BALB/c 3T3 mouse cells	NT	+	62.5	Colacci *et al.* (1992)
Unscheduled DNA synthesis, B6C3F_1 mouse hepatocytes *in vivo*	–	NT	1000 p.o. × 1	Mirsalis *et al.* (1989)
DNA binding (covalent), calf thymus DNA *in vitro*	–	+	10	Colacci *et al.* (1987)
DNA and RNA binding, male BALB/c mouse liver, kidney, lung and stomach *in vivo*	+	NT	1.46 i.p. × 1	Colacci *et al.* (1987)
DNA and RNA binding, male Wistar rat liver, kidney, lung and stomach *in vivo*	+	NT	1.46 i.p. × 1	Colacci *et al.* (1987)
Binding to protein, male BALB/c mouse lung, liver, kidney and stomach *in vivo*	+	NT	1.46 i.p. × 1	Colacci *et al.* (1987)
Binding to protein, male Wistar rat lung, liver, kidney and stomach *in vivo*	+	NT	1.46 i.p. × 1	Colacci *et al.* (1987)
Rat-liver foci assay for tumour initiation and promotion	+	NT	100	Milman *et al.* (1988)

[a] +, positive; (+), weakly positive; –, negative

[b] Unless otherwise specified, tests *in vitro*, μg/mL; tests *in vivo*, mg/kg bw per day.

HID, highest ineffective dose; i.p., intraperitoneal; LED, lowest effective dose; NT, not tested; p.o., oral

However, 1,1,2,2-tetrachloroethane was reported to lack mutagenicity in the TA98 and TA100 strains in two other published reports of tests at much higher exposures (Nestmann *et al.*, 1980; Haworth *et al.*, 1983). 1,1,2,2-Tetrachloroethane also gave positive results in the TA1530 strain without metabolic activation (Brem *et al.*, 1974).

1,1,2,2-Tetrachloroethane did not induce chromosomal aberrations in Chinese hamster ovary cells (Galloway *et al.*, 1987). 1,1,2,2-Tetrachloroethane induced sister chromatid exchanges in Chinese hamster ovary cells and mouse BALB/c 3T3 cell cultures *in vitro* (Galloway *et al.*, 1987; Colacci *et al.*, 1992).

Brem *et al.* (1974) assessed the ability of a series of haloalkanes, haloethanols, and haloacetaldehydes to induce mutations in *S. typhimurium* or to inhibit growth of DNA polymerase-deficient (pol A^+/pol A^-) *Escherichia coli*. 1,1,2,2-Tetrachloroethane was weakly mutagenic in both assays.

Roldán-Arjona *et al.* (1991) examined the association between mutagenicity of 16 halogenated aliphatic hydrocarbons, including 1,1,2,2-tetrachloroethane, in the Ames test in *S. typhimurium* and their documented carcinogenicity. 1,1,2,2-Tetrachloroethane was not mutagenic either in the presence or absence of metabolic activation from rat liver S9 fraction (9000 × *g* supernatant), and caused concentration-dependent lethality.

Callen *et al.* (1980) studied the mutagenicity of several halogenated aliphatic hydrocarbons, including 1,1,2,2-tetrachloroethane, in *Saccharomyces cerevisiae*. 1,1,2,2-Tetrachloroethane induced mitotic gene convertants and recombinants when incubated with yeast cells in log phase.

Crebelli *et al.* (1988) tested a series of halogenated solvents for induction of mitotic segregation in *Aspergillus nidulans* diploid strain P1. 1,1,2,2-Tetrachloroethane significantly increased the frequency of morphologically abnormal colonies that produced euploid whole-chromosome segregants (haploids and non-disjunctional diploids), but not the frequency of genetic crossing-over.

Woodruff *et al.* (1985) found that 1,1,2,2-tetrachloroethane did not increase the frequency of sex-linked recessive lethal mutation in *Drosophila melanogaster*.

(d) Cell transformation

Tu *et al.* (1985) found that 1,1,2,2-tetrachloroethane gave negative results at concentrations up to 250 µg/mL in an assay for the induction of transformation of BALB/c-3T3 cells *in vitro* in the absence of exogenous metabolic activation.

Colacci *et al.* (1990) demonstrated that 1,1,2,2-tetrachloroethane is capable of inducing transformation of BALB/c 3T3 cells *in vitro* either in the presence or absence of metabolic activation from rat liver S9 fraction. The highest concentration of 1,1,2,2-tetrachloroethane, 1000 µg/mL, induced transformation in a S9-independent manner, while lower concentrations (< 500 µg/mL) exhibited a requirement for S9 fraction that was inversely related to concentration. These results were consistent with metabolic activation being necessary for transformation, exogenous activation being necessary at lower concentrations and endogenous activation being adequate at higher concentrations.

In a subsequent study, BALB/c 3T3 cells transformed by exposure to 1,1,2,2-tetrachloroethane gave positive results in an assay for chemoinvasion in athymic mice (Colacci *et al.*, 1993).

4.3 Nongenotoxic mechanisms of carcinogenesis

4.3.1 Mechanisms related to liver carcinogenesis

(a) Cytotoxicity

(i) Humans

Zheng *et al.* (2012) evaluated the effects of exposure to 1,1,2,2-tetrachloroethane in 18 workers in a factory processing plastic products. Measurements of several parameters in serum considered indicative of liver damage, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and γ-glutamyltranspeptidase (GGT), showed increases of 3- to 25-fold on admission to the hospital. Histological findings were also indicative of liver injury, including crowded hepatic plates that were lobular with swollen, fatty and ballooned degeneration of hepatocytes. Lymphocytes and neutrophils were found in the hepatic sinusoids. Infiltration of Kupffer cells was found in the majority of samples.

(ii) Experimental systems

In long-term studies, rats and mice were given diets containing 1,1,2,2-tetrachloroethane at doses up to 108 mg/kg bw per day (rats) or 284 mg/kg bw per day (mice) for 78 weeks (NCI, 1978). Hepatic fatty metamorphosis was observed in male rats at the highest dose, but not in female rats, or either species of mouse tested.

In a study of toxicity, male and female F344/N rats and B6C3F$_1$ mice were given feed containing 1,1,2,2-tetrachloroethane (enclosed in starch microcapsules to minimize evaporation) at dietary concentrations of up to 4600 ppm (rats) or 9100 ppm (mice) for 14 weeks (NTP, 2004). Body weights were significantly decreased compared with controls in rats at doses of up to 1180 ppm, and in mice at doses up to 2300 ppm. The liver was the primary target for toxicity. In rats, histological changes in the liver (cytoplasmic vacuolization, hepatocellular hypertrophy and necrosis, and hepatocellular mitotic alterations) and alterations in plasma enzymes indicative of decreased liver function were observed.

Dahlström-King *et al.* (1990) used suspensions of isolated rat hepatocytes to develop a model to study the cytotoxicity of chlorinated hydrocarbons *in vitro*. To validate the model, the acute cytotoxicity of four compounds known to be hepatotoxic *in vivo* and four compounds known to be not hepatotoxic *in vivo* was determined by measuring release of alanine aminotransferase from cells incubated for 30–180 minutes. Acute cytotoxicity in the model *in vitro* was found to be poorly correlated with hepatotoxicity *in vivo*. Thus, although carbon tetrachloride is the most potent hepatotoxicant *in vivo* of the eight chlorinated hydrocarbons tested, 1,1,2,2-tetrachloroethane was actually more potent than carbon tetrachloride in the isolated cell suspension.

In the study by Cottalasso *et al.* (1998), male Sprague-Dawley rats received a single dose of 1,1,2,2-tetrachloroethane (574 mg/kg bw) and were killed after 5, 15, 30, or 60 minutes. The activity of serum aspartate aminotransferase and alanine aminotransferase, and concentrations of hepatic triglycerides were significantly higher in exposed rats than in controls, while the activity of microsomal glucose 6-phosphatase was decreased.

(b) Oxidative stress

Gavino *et al.* (1984) incubated slices of various rat tissues with one of several halogenated hydrocarbons and measured release of total ethane and pentane as a measure of lipid peroxidation. Rats were also made either vitamin E-deficient or given excess iron (iron overload) to prime the oxidative-stress response. Bromotrichloromethane produced the largest release of total ethane and pentane from the liver. Release of total ethane and pentane from 1,1,2,2-tetrachloroethane was somewhat lower,

but equivalent to that from carbon tetrachloride and 1,1,2,2-tetrabromoethane, and was higher than that from tetrachloroethylene. Release of total ethane and pentane occurred from several tissues, with intestine, brain and kidney producing greater releases than the liver.

Paolini *et al.* (1992) detected conjugated dienes in male and female mice given 1,1,2,2-tetrachloroethane as a single oral dose (300 or 600 mg/kg bw), providing evidence for 1,1,2,2-tetrachloroethane-induced lipid peroxidation *in vivo* as part of the mechanism of hepatotoxicity.

(c) Promotion of GGT-positive foci

Story *et al.* (1986) examined the ability of 1,1,2,2-tetrachloroethane to induce liver tumours, using GGT activity as a preneoplastic marker in the liver of young male Osborne-Mendel rats, with or without phenobarbital induction. 1,1,2,2-Tetrachloroethane increased the formation of GGT-positive foci only when rats were first induced with phenobarbital. The ability of 1,1,2,2-tetrachloroethane to initiate or promote tumour formation in livers of young adult male Osborne Mendel rats was investigated (Story *et al.*, 1986; Milman *et al.*, 1988). After partial hepatectomy, 1,1,2,2-tetrachloroethane was given at the maximum tolerated dose in either the initiation phase followed by phenobarbital, or in the promotion phase preceded by diethylnitrosamine. 1,1,2,2-Tetrachloroethane was found to modestly increase the number of GGT-positive foci during the initiation phase and strongly increase the number of GGT-positive foci in the promotion protocol.

4.4 Other adverse effects

4.4.1 Kidney

In long-term studies by the National Cancer Institute, rats and mice were given diets containing 1,1,2,2-tetrachloroethane at a dose of up to 108 mg/kg bw per day (rats) or 284 mg/kg bw per day (mice) for 78 weeks(NCI, 1978). In mice, the toxic effects observed in the kidney were acute tubular nephrosis in males, hydronephrosis in females, and chronic kidney inflammation in both sexes.

4.4.2 Central nervous system

1,1,2,2-Tetrachloroethane has a sedative effect in humans and animals (IARC, 1999; ATSDR, 2007). The relevance of neurotoxicity to cancer hazard is unknown.

4.5 Mechanistic considerations

Limited information is available to characterize the absorption, distribution, metabolism and excretion of 1,1,2,2-tetrachloroethane in humans and experimental animals. High absorption was shown experimentally in humans. High absorption is also suggested by the high blood:air partition coefficient that has been measured in human blood. In animals, several studies have shown that 1,1,2,2-tetrachloroethane is readily absorbed orally or by inhalation; dermal absorption has also been shown in mice. Although no direct data on distribution were available, estimated tissue:blood partition coefficients indicate that 1,1,2,2-tetrachloroethane would be widely distributed in humans and animals, especially to tissues with a high lipid content. No data on metabolism or excretion in humans were available. In animals, the major metabolite is dichloroacetic acid (via cytochrome P450-mediated oxidation). Glyoxylic acid and CO_2, metabolites of dichloroacetic acid, have been measured in exposed animals, further supporting formation of dichloroacetic acid. Trichloroethylene and tetrachloroethylene are minor metabolites formed via a non-enzymatic pathway. Formation of a carbon-centred radical has been reported in two studies; however, the identity and quantity of this radical species have not been characterized.

Although some positive results for genotoxicity were reported, most studies of mutagenesis in bacteria gave negative results. A few studies have indicated possible clastogenic effects and one study showed binding to DNA and protein.

Evidence for liver toxicity is available from studies in humans and animals, including studies with human hepatocytes *in vitro*. Suggested mechanisms for liver carcinogenesis in rodents include cytotoxicity (*in vivo* and *in vitro*) and oxidative stress (*in vivo* and *in vitro*). One study showed the potential for 1,1,2,2-tetrachloroethane to promote GGT-positive foci in rat liver. Other target tissues for the adverse health outcomes associated with 1,1,2,2-tetrachloroethane are the liver, kidney, and central nervous system.

5. Summary of Data Reported

5.1 Exposure data

1,1,2,2-Tetrachloroethane has been used in small amounts in many applications, mainly as a solvent and for degreasing metals. The primary current use is as a chemical intermediate in the manufacture of chlorinated solvents. Very low concentrations have been reported in ambient and indoor air, and in surface water near contaminated areas.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,2,2-Tetrachloroethane was evaluated for carcinogenicity in one study in rats and in one study in mice treated by gavage in corn oil. Survival was reduced in male and female mice, and in female rats. There was an increase in the trend and the incidence of hepatocellular carcinoma in male and female mice. The incidence of hepatocellular tumours in exposed male rats was greater than that in historical controls.

5.4 Mechanistic and other relevant data

Little information was available from studies on absorption and distribution in humans. In experimental animals, it is likely that 1,1,2,2-tetrachloroethane is absorbed readily and distributed widely throughout the body. No data on metabolism or excretion in humans were available; in rodents, metabolism produces dichloroacetic acid and then glyoxylic acid which, along with several other metabolites, including CO_2, are excreted in the urine and breath. Trichloroethylene and tetrachloroethylene may also be formed from 1,1,2,2-tetrachloroethane, albeit in lesser amounts. 1,1,2,2-Tetrachloroethane is weakly genotoxic. Major target tissues for adverse health outcomes are the liver, kidney, and the central nervous system. Based on cancer findings in animals and toxicity findings in animals and humans, the evidence for liver as a target tissue is strong. The evidence for nongenotoxic mechanisms of carcinogenesis in the liver is moderate. 1,1,2,2-Tetrachloroethane is also toxic to the kidney and has a sedative effect in humans and animals. No data on potential inter-individual variability in response to the adverse effects of 1,1,2,2-tetrachloroethane were available.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

1,1,2,2-Tetrachlorethane *is possibly carcinogenic to humans (Group 2B).*

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