TETRACHLOROETHYLENE

This substance was considered by previous working groups, in June 1978 and March 1987 (IARC, 1979, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

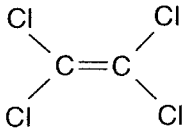
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 127-18-4
Chem. Abstr. Name: Tetrachloroethene
IUPAC Systematic Name: Tetrachloroethylene
Synonyms: Ethylene tetrachloride; PCE; 'per'; PER; perchlorethylene; perchloroethene; perchloroethylene; tetrachlorethylene; 1,1,2,2-tetrachloroethene; 1,1,2,2-tetrachloroethylene

1.1.2 Structural and molecular formulae and relative molecular mass



C_2Cl_4 Relative molecular mass: 165.83

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with an ether-like odour (Budavari, 1989)
(*b*) *Boiling-point*: 121 °C (Lide, 1993)
(*c*) *Melting-point*: –19 °C (Lide, 1993)
(*d*) *Density*: 1.6227 at 20 °C/4 °C (Lide, 1993)
(*e*) *Spectroscopy data*: Infrared (prism [5422]; grating [469]), ultraviolet [1485] and mass [1053] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).
(*f*) *Solubility*: Slightly soluble in water (0.15 g/L at 25 °C) (PPG Industries, Inc., 1994); soluble in ethanol, diethyl ether and benzene (Lide, 1993)
(*g*) *Volatility*: Vapour pressure, 9.975 mm Hg [1.33 kPa] at 13.8 °C (Hickman, 1993)

(*h*) *Stability*: Photooxidized in air with sunlight (half-time, about 12 h), giving phosgene and trichloroacetyl chloride (Gilbert *et al.*, 1982; Hickman, 1993)

(*i*) *Reactivity:* Incompatible with chemically active metals such as barium, lithium and beryllium and with caustic soda, sodium hydroxide, potash and strong oxidizers (United States National Institute for Occupational Safety and Health, 1994a)

(*j*) *Octanol/water partition coefficient (P)*: log P, 3.40 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 6.78 \times ppm$[1]

1.1.4 Technical products and impurities

Commercial grades of tetrachloroethylene available in the United States include a vapour degreasing grade, a dry cleaning grade, a technical or industrial grade for use in formulations, a high-purity, low-residue grade and a grade specifically formulated for use as a transformer fluid (Hickman, 1993). Isomerization and fluorocarbon grades have purities of 99.995% (Vulcan Chemicals, 1994). The various grades differ in the amount and type of added stabilizers. Stabilizers that have been used include amines, phenols and epoxides [not specified] in various combinations at levels of 0.01–0.35% (Gilbert *et al.*, 1982). Commercial grades should not contain more than 50 ppm [mg/L] water, 0.0005 wt% acidity (as hydrochloric acid) or 0.001 wt% insoluble residue (Hickman, 1993; Vulcan Chemicals, 1994; PPG Industries, Inc., 1994).

Trade names for tetrachloroethylene include Ankilostin, Antisol 1, Didakene, Dilatin PT, Fedal-Un, Nema, Perchlor, Perclene, PerSec, Tetlen, Tetracap, Tetraleno, Tetroguer and Tetropil.

1.1.5 Analysis

Selected methods for the analysis of tetrachloroethylene in various matrices are identified in Table 1. Several methods for the analysis of tetrachloroethylene in air, solids, liquids, water, food, blood and breath were reviewed by WHO (1984) and the United States Environmental Protection Agency (1985a).

Three gas chromatography/mass spectrometry (GC/MS) and three purge-and-trap GC methods for purgeable organics, including tetrachloroethylene, are typically used for aqueous samples (see also Table 1). The first (EPA Method 624 and APHA/AWWA/WEF Method 6210B) is a packed-column method useful for the determination of tetrachloroethylene in municipal and industrial wastes. A similar purge-and-trap method (EPA Method 503.1 and APHA/AWWA/WEF Method 6220C), which involves photoionization detection, is applicable for the determination of tetrachloroethylene in drinking-water and raw source water. The second method (EPA Method 524.1 and APHA/ AWWA/WEF Method 6210C), which is also a packed-column method, is applicable for the determination of tetrachloroethylene in drinking-water and raw source water. Similar purge-and-trap methods (EPA Methods 601 and 502.1 and APHA/-AWWA/WEF Methods 6230B and 6230C), which involve electrolytic conductivity or micro-coulometric detection, are applicable for the determination of tetrachloroethylene in municipal

[1]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

and industrial discharges (6230B) and in drinking-water and raw source water (6230C). The third group of GC/MS and purge-and-trap methods (EPA Method 524.2 and APHA/AWWA/-WEF Method 6210D; EPA Method 502.2 and APHA/AWWA/WEF Method 6230D) are identical to the previous ones, except that a capillary column is used. The second and third methods are intended primarily for the detection of large numbers of contaminants at low concentrations, which are not detectable with the first method (Greenberg *et al.*, 1992).

Table 1. Methods for the analysis of tetrachloroethylene

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg	Eller (1994)
	Draw air through Tenax sample tube; heat; desorb on cold trap	GC/MS	20 ng	US Environmental Protection Agency (1988a)
	Draw air into cryogenically cooled trap; heat	GC/FID or GC/EC	1–5 ng	US Environmental Protection Agency (1988a)
	Draw air into SUMMA® passivated stainless-steel canister; desorb on cold trap	GC/MS or GC/EC-FID-PID	NR	US Environmental Protection Agency (1988a)
Water	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD or GC/MCD	0.001–0.03 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/MS	0.3–1.9 µg/L	
	Purge and trap as above; desorb as vapour into capillary gas chromatographic column	GC/PID-ECD	0.02–0.05 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/MS	0.05–0.14 µg/L	
	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto gas chromatographic column	GC/PID	0.01 µg/L	US Environmental Protection Agency (1988b, 1994)
	Add internal standard (isotope-labelled tetrachloroethylene); purge, trap and desorb as above	GC/MS	10 µg/L	US Environmental Protection Agency (1994)
Liquid and solid wastes	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD	0.03 µg/L	US Environmental Protection Agency (1986a)
		GC/MS	5 µg/L (groundwater)[a] 5 µg/kg (soil/sediment)[a] 250–2500 µg/kg (liquid wastes)[a]	US Environmental Protection Agency (1986b)

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Food	Purge (inert gas) in water at 100 °C; trap on Tenax TA and XAD-4; elute with hexane	GC/ECD	0.4 ppb [µg/kg]	Heikes & Hopper, 1986; Heikes, 1987

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

[a] Practical quantification limit

The DuPont Pro-Tek® Organic Vapor Monitoring Badge has been used extensively in the dry cleaning industry to monitor time-weighted average exposures to tetrachloroethylene. The badge adsorbs vapours onto charcoal for subsequent gas chromatographic determination (International Fabricare Institute, 1987; Solet *et al.*, 1990). Good correlations have been reported between time-weighted average concentrations evaluated with passive dosimeters and conventional sampling pumps and concentrations in blood (Schaller & Triebig, 1987).

1.2 Production and use

1.2.1 Production

Tetrachloroethylene was first prepared in 1821 by Faraday by thermal decomposition of hexachloroethane (Hickman, 1993). Many commercial processes have since been developed for the production of tetrachloroethylene. Either single or multiple products result.

In Europe, tetrachloroethylene is produced by oxychlorination of C_2 chlorinated hydrocarbons and by chlorination of C_1–C_3 hydrocarbons or their partially chlorinated derivatives. One company in Japan manufactures tetrachloroethylene by the chlorination of ethylene followed by thermal dehydrogenation (Linak *et al.*, 1992).

Between 1925 and the 1970s, the main commercial process for producing tetrachloroethylene in the United States involved the chlorination of acetylene to form tetrachloroethane, followed by dehydrochlorination to trichloroethylene (see monograph, this volume); the trichloroethylene was further chlorinated to pentachloroethane and dehydrochlorinated to form tetrachloroethylene. Owing partly to the high cost of acetylene, most tetrachloroethylene is now produced by chlorination and oxychlorination of other hydrocarbons (C_1–C_3) or chlorinated compounds. The raw materials include ethylene dichloride, methane, ethane, propane, propylene (see IARC, 1994a), propylene dichloride and various other chlorinated hydrocarbons (Linak *et al.*, 1992; Hickman, 1993).

Production of tetrachloroethylene has been declining. Table 2 shows the production of tetrachloroethylene in selected countries between 1941 and 1991. In 1992, annual capacity was 10 thousand tonnes in Austria, 30 thousand tonnes in Belgium, 62 thousand tonnes in France, 100 thousand tonnes in Germany and in Italy, 21 thousand tonnes in Spain and 130 thousand

tonnes in the United Kingdom. Tetrachloroethylene has been produced commercially in Japan since 1972; in 1992, seven plants in Japan had a capacity of 96 thousand tonnes. The only producer of tetrachloroethylene in Canada ceased production in 1992. Four companies in the United States had an annual capacity of 223 thousand tonnes of tetrachloroethylene (Linak *et al.*, 1992).

Table 2. Production of tetrachloroethylene in selected countries (thousand tonnes)

Year	Western Europe	Japan	USA
1941			5
1945			27
1955			81[a]
1960			95
1965			195
1970		NR	320
1975		48	308
1980	295	64	347
1981	290	57	313
1982	295	60	265
1983	300	61	248
1984	315	63	260
1985	315	71	225
1986	341	70	188
1987	323	84	215
1988	343	97	226
1989	317	91	218
1990	280	83	169
1991	NR	NR	109[b]

From Linak *et al.* (1992); NR, not reported

[a] From Su & Goldberg (1976)

[b] Preliminary

Tetrachloroethylene is also produced in Australia, Brazil, the Czech Republic, China, India, Mexico, Poland, Romania, the Russian Federation and South Africa (Chemical Information Services, Inc, 1994).

1.2.2 Use

Tetrachloroethylene is commercially important as a chlorinated solvent and as a chemical intermediate. In 1990, about 53% of world demand for tetrachloroethylene was for dry cleaning, and it was the cleaning fluid used by about 75% of all dry cleaners. About 23% was used as a chemical intermediate, principally for making 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113); 13% was used for metal cleaning and 11% for other uses (Linak *et al.*, 1992).

Tables 3–5 present the uses of tetrachloroethylene in western Europe, Japan and the United States (Linak *et al.*, 1992). Countries in the southern hemisphere are reported to receive only 1–2% of worldwide sales of tetrachloroethylene (Coopers & Lybrand, Ltd, 1993).

Table 3. Use of tetrachloroethylene in western Europe (thousand tonnes)

Year	Metal cleaning (vapour degreasing)	Metal cleaning (cold cleaning)	Dry cleaning	Precursor[a]	Other
1980	71	10	150	34	20
1984	61	5	133	36	15
1987	50	5	122	65	15
1990	45	5	115	60	10

From Linak *et al.* (1992); estimates

[a] Almost exclusively for production of 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113), dichlorotetrafluoroethane (CFC-114) and chloropentafluoroethane (CFC-115)

Table 4. Use of tetrachloroethylene in Japan (thousand tonnes)

Year	Metal cleaning	Dry cleaning	Other[a]
1980	10	26	20
1983	12	23	29
1987	11	25	63
1990	13	20	69

From Linak *et al.* (1992); estimates

[a] Almost exclusively for production of CFC-113, CFC-114 and CFC-115

Table 5. Use of tetrachloroethylene in the United States (thousand tonnes)

Year	Metal cleaning	Dry cleaning and textile processing	Precursor[a]	Other
1971	50	163	32	38
1974	54	193	39	45
1977	59	181	39	28
1980	45	172	50	59
1984	34	136	70	39
1987	27	127	84	14
1990	16	111	45	6

From Linak *et al.* (1992); estimates

[a] Almost exclusively for production of CFC-113, CFC-114 and CFC-115

In addition to its widespread use in dry cleaning, tetrachloroethylene has been used in the textile industry as a scouring solvent, for removing lubricants, oil and grime from fabrics, and as a carrier solvent for fabric dyes and finishes, as a water repellant and for sizing and desizing textiles. Tetrachloroethylene dissolves fats, greases, waxes and oils in fabric without harming the fibres (United States Agency for Toxic Substances and Disease Registry, 1990).

Another major use of tetrachloroethylene was as a chemical intermediate in the manufacture of two-carbon chlorofluorocarbons (CFCs), principally CFC-113. As a result of international agreements to protect against depletion of the ozone layer, this use is rapidly being phased out (Linak *et al.*, 1992).

Tetrachloroethylene is also used for vapour and liquid degreasing and for cold cleaning of metals (Keil, 1979). In vapour degreasing, the part to be cleaned is placed in a zone of warm solvent vapour. The vapour condenses on the metal and subjects the surface to a solvent-flushing action. The liquid drops are collected in a reservoir and revaporized (Schneberger, 1981).

Tetrachloroethylene is also used in paint removers, printing inks, adhesive formulations, paper coatings, leather treatments and as a carrier solvent for silicones. It is used in aerosol formulations, e.g. water repellants, automotive cleaners, solvent soaps, silicone lubricants and spot removers. Tetrachloroethylene has also reportedly been used to remove soot from industrial boilers. Other reported uses are as an insulating fluid for power transformers, as a heat transfer medium, as an extractant in the pharmaceutical industry and as a pesticide and chemical intermediate. It has been reported to be used as an anthelminthic in the treatment of hookworm and some trematode infestations (Budavari, 1989; United States Agency for Toxic Substances and Disease Registry, 1990).

In a study of potential sources of indoor air pollution in the United States, 63 of 1159 (5.4%) common household products were found to contain tetrachloroethylene (Sack *et al.*, 1992).

1.3 Occurrence

1.3.1 Natural occurrence

Natural production of tetrachloroethylene has been reported in temperate, subtropical and tropical algae and in one red microalga (Abrahamsson *et al.*, 1995).

1.3.2 Occupational exposure

The National Occupational Exposure Survey conducted between 1981 and 1983 by the United States National Institute for Occupational Safety and Health (1994b) indicated that about 566 000 employees in 42 700 plants were potentially exposed to tetrachloroethylene. The estimate was based on a survey of United States companies and did not involve actual measurements of exposures. An independent estimate prepared by industry in 1994 indicated that about 450 000 workers in the United States may be exposed (Center for Emissions Control, 1994).

There is considerable potential exposure to tetrachloroethylene, by both skin contact and inhalation, during its use in dry cleaning and degreasing (Hake & Stewart, 1977). Acute cases of intoxication due to inhalation of tetrachloroethylene have been reported in the literature (Foot

et al., 1943; Coler & Rossmiller, 1953; Lob, 1957; Stewart *et al.*, 1961a; Dumortier *et al.*, 1964; Meckler & Phelps, 1966; Gold, 1969; Morgan, 1969; Stewart, 1969; Lackore & Perkins, 1970; Patel *et al.*, 1973; see also section 4.2.1).

Table 6 presents a range of exposures to tetrachloroethylene by occupation in the United States. Dry cleaning is specifically excluded, as occupational exposures in dry cleaning are covered in a separate monograph in this volume. Occupational exposure in dry cleaning was generally to 350–700 mg/m^3 in the 1970s and to 70–350 mg/m^3 in the late 1980s.

Table 6. Occupational exposures to tetrachloroethylene in the United States

No. of plants	Job, task or industry	No. of samples	Air concentration [mg/m^3]		Reference
			Mean	Range	
1	Degreasing, auto industry	Short-term	NR	[1573–2610]	Coler & Rossmiller (1953)
1	Urethane foam	3 (A)	0.6	0.344–0.714	Costello (1979)
1	Protective coatings	11	[2.7]	[ND–27]	Burroughs (1980)
1	Polyether urethane foam, car industry	3 (A) 9 (P)	2.1 4.2	0.4–4.2 < 0.03–8.0	White & Wegman (1978)
1	Degreasing, medical equipment	3 (A)	[106]	[48–197]	Tharr & Donahue (1980)
1	Degreasing	6 (P)	[271]	[34–1180]	Burgess (1981)
1	Degreasing, printing plates	4 (A) 2 (P)	78 57	25–99.3 28–86.4	Pryor (1977)
1	Cutlery manufacture, blade degreasing	2 (P)	[115]	[104–126]	Center for Chemical Hazard Assessment (1985)
1	Filling aerosol cans with carburettor cleaner	30 (A) 30 (P)	[311] [403]	[31–1248] [104–1010]	Hervin *et al.* (1972)
1	Coal testing laboratory	1 (P) Several (A)	[1010]	 [746–1315]	Jankovic (1980)
1	Automotive brake manufacture	11 (P) 11 (A)	103 145	10–350 10–350	Hervin & Lucas (1973)
8	Degreasing	14 24	[1220] (work in) [3282] (work out)	[170–2102] [542–12204]	Crowley *et al.* (1945)
60	Degreasing (11 non-condensing machines	68	[1498]	[163–5966]	Morse & Goldberg (1943)
1	Specialty packaging	4 (P) 5 (A)	[4] [15]	[1.4–5.4] [1.8–41]	Hanley (1993)
1	Rubber moulding	15 (P) 1 (A)	[17.6] [8]	[ND–36]	Cook & Parker (1994)
1	Plating, degreasing	1 (P) 1 (A)	11 2		Abundo *et al.* (1994)
14	Motion picture film processing	119 (P) 51 (A)	189 111	2.7–1606 2.2–965	Mosely (1980)

Table 6 (contd)

No. of plants	Job, task or industry	No. of samples	Air concentration [mg/m^3]		Reference
			Mean	Range	
1	Electroplating	5 (P)	[753]	[557–1253]	Daniels & Kramkowski (1986)
1	Degreasing, foundry	1 (P)	86.1		Hartle & Aw (1984)
		3 (A)	130.3	40.9–250	
1	Spray painting	9 (P)	21.4	4.4–50	Hartle & Aw (1983)
1	Automative parts, fasteners	2 (A)	1.3	1.1–1.5	Ahrenholz & Anderson (1982)
1	Motion picture film processing	4 (A)	9.5	6.5–11.3	Okawa & Coye (1982)
		7 (P)	16.4	7.8–54.5	
1	Graphic arts	4 (P)	13	0.01–30	Love (1982)
1	Painters, power plant	6 (P)	0.13	< 0.01–0.46	Chrostek & Levine (1981)
		2 (A)	0.29	< 0.01–0.88	
1	Taxidermy	9 (P)	403	0.01–1546	Gunter & Lybarger (1979)

NR, not reported; ND, not detected; A, area air sample; P, personal air sample (breathing zone)

In measurements made in Finland in 1982–85, 13 area samples taken in five plants for the manufacture of printing plates contained a mean of 9.6 ppm [65.1 mg/m^3] tetrachloroethylene, with a range of 3–19 ppm [20.3–129 mg/m^3]. The mean concentration in four samples taken in three plants where workers degreased metal parts was 3 ppm [20 mg/m^3], with a range of 1.8–5 ppm [12.2–33.9 mg/m^3] (Rantala *et al.*, 1992).

1.3.3 Environmental occurrence

Tetrachloroethylene has been reported in air, rainwater, surface water, drinking-water, seawater, marine sediments, marine invertebrates, fish, waterbirds, marine mammals, foods and human tissues (McConnell *et al.*, 1975). Human exposure to tetrachloroethylene has been estimated by modelling multiple exposure pathways (McKone & Daniels, 1991).

(a) Air

Concentrations of tetrachloroethylene in air have been reported in numerous studies. Table 7 presents levels measured in remote, rural, urban and suburban locations worldwide. In a compilation of the results of surveys of ambient air in the United States before 1981 (Brodzinsky & Singh, 1983; United States Agency for Toxic Substances and Disease Registry, 1990), representing 2553 monitoring points, the mean concentrations were 160 ppt [1.1 μg/m^3] in rural areas, 790 ppt [5.4 μg/m^3] in urban communities and 1300 ppt [8.8 μg/m^3] in areas near sources of tetrachloroethylene emissions. A similar study, conducted by the United States Environmental Protection Agency (1985a), estimated the average ambient levels to be 40 ppt [0.3 μg/m^3] in the northern hemisphere and 12 ppt [0.08 μg/m^3] in the southern hemisphere. The average urban

level was reported to be 800 ppt [5.4 μg/m^3]. According to the United States Environmental Protection Agency (1993) Toxic Chemical Release Inventory, industrial releases of tetrachloroethylene to the environment were 16 335 tonnes in 1988, 12 527 tonnes in 1989, 10 183 tonnes in 1990 and 7596 tonnes in 1991; however, total emissions to the atmosphere, including those from dry cleaning, were estimated to be 87 000 tonnes in 1991 (United States Environmental Protection Agency, 1991)

Table 7. Concentrations of tetrachloroethylene in air

Area	Concentration [ng/m^3]		Reference
	Mean	Range	
Remote			
Atlantic Ocean			
Northern hemisphere	[230]		Penkett (1982)
Northern hemisphere	[197]		Singh *et al.* (1983)
Southern hemisphere	[34]		
Northern hemisphere	[380]		Rasmussen & Khalil (1982)
Southern hemisphere	[95]		
Northern hemisphere		[102–203]	Class & Ballschmiter (1986)
Southern hemisphere		[14–68]	
Northern hemisphere	[102]		Class & Ballschmiter (1987)
Southern hemisphere	[14]		
Northern hemisphere	[88]		European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Southern hemisphere	[20]		
Pacific Ocean			European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Northern hemisphere	[54]		
Southern hemisphere	[20]		
Rural			
Southern Washington, USA	[136]		Grimsrud & Rasmussen (1975)
Western Ireland	[190]		Lovelock (1974)
Rural California, USA	[210]		Singh *et al.* (1977)
Central Michigan, USA		200–300	Russell & Shadoff (1977)
Southern Germany		[197–1763]	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Netherlands		[136–407]	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Brittany, France		[136–183]	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
USA, 577 sites	[1085]		European Centre for Ecotoxicology and Toxicology of Chemicals (1995)

Table 7 (contd)

Area	Concentration [ng/m^3]		Reference
	Mean	Range	
Urban and suburban			
Germany, 92 sites	6600		Bauer (1991)
Tokyo, Japan	[8136]		Ohta *et al.* (1976)
Brussels, Belgium		[6441–21 700]	Su & Goldberg (1976)
Geneva, Switzerland	[46 104]		Su & Goldberg (1976)
Russian Federation		[203–1356]	Su & Goldberg (1976)
Paris, France	[2102]		Su & Goldberg (1976)
Grenoble, France	[9153]	[6507–12 204]	Su & Goldberg (1976)
Kyoto, Japan	[9492]		Su & Goldberg (1976)
Tokyo, Japan	[15 594]		Su & Goldberg (1976)
New York City, NY, USA	[9017]	[1085–71 936]	Evans *et al.* (1979)
Houston, TX, USA	[2644]	[< 678–30 510]	Evans *et al.* (1979)
Detroit, MI, USA	[3119]	[678–14 916]	Evans *et al.* (1979)
Los Angeles, CA, USA	[10 034]	[1180–14 001]	Singh *et al.* (1981)
Phoenix, AZ, USA	[6739]	[875–25 066]	Singh *et al.* (1981)
Oakland, CA, USA	[2054]	[359–9831]	Singh *et al.* (1981)
Bochum, Germany	6100	1100–67 000	Bauer (1981)
Frankfurt, Germany		700–1800	Bauer (1981)
Munich, Germany		< 1000–25 000	Bauer (1981)
Milan, Italy (polluted)		9500–14 800	Ziglio *et al.* (1983)
Yokohama and Kawasaki, Japan		[2712–4543]	Urano *et al.* (1988)
Turin, Italy		[4746–13 357]	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Fonte, Portugal		[197–949]	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
San Diego, CA, USA	[1831]		Douglas *et al.* (1993)
San Francisco, CA, USA	[1559]		Douglas *et al.* (1993)
Sacramento, CA, USA	[475]		Douglas *et al.* (1993)

The concentrations of tetrachloroethylene in New Jersey (United States) were 6 μg/m^3 in the autumn of 1981, 6.2 μg/m^3 in the summer of 1982 and 4.2 μg/m^3 in the winter of 1983. The mean indoor air concentrations were 45, 11 and 28 μg/m^3, respectively. The mean outdoor air level in Los Angeles, CA, in February 1984 was 10 μg/m^3 (Wallace, 1986), and the geometric mean concentrations of tetrachloroethylene in three cities in New Jersey were 0.45 ppb [3.05 μg/m^3] (n = 38), 0.31 ppb [2.10 μg/m^3] (n = 37) and 0.24 ppb [1.63 μg/m^3] (n = 35) in summer 1981 (Harkov *et al.*, 1984).

(b) Occurrence in air near dry cleaning shops

In 1990 in New York State, the levels of tetrachloroethylene in 12-h samples of air inside apartments located above dry cleaners were 300–55 000 μg/m^3 (mean, 13 000 μg/m^3) for morning samples, compared with < 6.7–103 μg/m^3 (mean, 28 μg/m^3) in control apartments. Afternoon 12-h samples contained 100–36 500 μg/m^3 (mean, 10 000 μg/m^3), while those from control apartments contained < 6.7–77 μg/m^3. The concentrations of tetrachloroethylene in apartments above dry cleaners using transfer machines were 1730–17 000 μg/m^3 (mean, 7500 μg/m^3) in the morning and 1350–14 000 (7900) in the afternoon; those in apartments above dry-to-dry machines were 300–440 μg/m^3 (mean, 370 μg/m^3) in the morning and 100–160 (130) in the afternoon. The ambient morning levels outside the apartments were 195–2600 μg/m^3 (mean, 1000 μg/m^3), and those in the afternoon were 66–1400 μg/m^3 (mean, 580 μg/m^3). The ambient levels outside the control apartments were < 6.7–21 μg/m^3 (mean, 8.4 μg/m^3) in the morning and < 6.7–6.9 μg/m^3 (mean, 3.9 μg/m^3) in the afternoon (Schreiber *et al.*, 1993).

Levels as high as 197 mg/m^3 were detected in an apartment next to a dry cleaning facility that operated transfer machines in New York State in 1990. In an apartment 30 feet [9.1 m] from a dry cleaners, the level was 1.5 mg/m^3. Shops in a mall where there was a dry cleaning establishment had levels as high as 50.4 mg/m^3. The air levels were 1.5 mg/m^3 in a fish market in the mall, 34.5 mg/m^3 in a pizza parlour and 15.7 mg/m^3 in a delicatessen (New York Department of Health, 1994).

Tetrachloroethylene was determined in the alveolar air of 136 people living near 12 dry cleaning shops in the Netherlands. The geometric mean concentration in the breath of residents was 5 mg/m^3 in apartments above the dry cleaning shops, 1 mg/m^3 in houses next door to the shops, 0.2 mg/m^3 in the next house and < 0.1 mg/m^3 in a house across the street from the shop. The mean alveolar air concentration of 18 employees in the dry cleaning shops was 73 mg/m^3 (Verberk & Scheffers, 1980).

In an apartment above a dry cleaning shop in Switzerland, 0.1 mg/m^3 tetrachloroethylene and 1 mg/m^3 CFC-113 were measured. At the counter of the shop, the concentrations were 10 mg/m^3 tetrachloroethylene and 150 mg/m^3 CFC-113, while in the room where the dry cleaning took place, 25 mg/m^3 tetrachloroethylene and 1000 mg/m^3 CFC-113 were measured (Grob *et al.*, 1991).

The concentrations of tetrachloroethylene in the air of five apartments in the vicinity of dry cleaners in Germany in 1987 were 17.1–2296 μg/m^3; the concentrations outside the apartments were 3.07–138 μg/m^3 (Reinhard *et al.*, 1989).

Elevated levels of tetrachloroethylene have been measured in the homes of dry cleaning workers that were not near dry cleaning shops. For example, the levels in six homes in New Jersey were 21–560 μg/m^3 (European Centre for Ecotoxicology and Toxicology of Chemicals, 1995), and those in 25 homes in Italy were 25–9600 μg/m^3 (Aggazzotti *et al.*, 1994). The concentrations were suggested to result from the exhaled breath and clothing of the workers (Thompson & Evans, 1993).

Off-gassing of tetrachloroethylene from dry cleaned clothes has also been studied. A concentration of 9.3 mg/m^3 was measured 2 min after deposition into a private car of a cleaned down-filled jacket, which increased to 24.8 mg/m^3 108 min after deposition (Gulyas &

Hemmerling, 1990). Levels of 70–2100 mg/m^3 were reported inside a car containing dry cleaned clothes in another study (Jensen & Ingvordsen, 1977).

The concentrations of tetrachloroethylene in the air of four homes in Japan where there were freshly dry cleaned clothes were 1.3–7.4 μg/m^3 (mean, 2.6 μg/m^3). The levels outside the homes were 0.3–1.6 μg/m^3 (mean, 1.2 μg/m^3) (Kawauchi & Nishiyama, 1989). Levels up to 300 μg/m^3 were measured at seven of nine houses in New Jersey when freshly dry cleaned clothes were brought home (Thomas *et al.*, 1991).

(c) Water

Tetrachloroethylene occurs ubiquitously at low levels in water supplies and frequently occurs as a contaminant of groundwater, owing to its widespread use and physical characteristics. Table 8 presents measurements of tetrachloroethylene in surface waters, groundwater and drinking-water.

Table 8. Concentrations of tetrachloroethylene in water

Location (year)	Concentration (μg/L)		
	Mean	Range	Reference
Surface waters			
Seawater			
Eastern Pacific		0.0001–0.0021	Singh *et al.* (1983)
North Atlantic		0.00012–0.0008	Pearson & McConnell (1975); Murray & Riley (1973)
Coastal waters			
Sweden, coast	0.007		European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Greece, northern coast		0.27–3	Fytianos *et al.* (1985)
Jackfish Bay, Canada		2.1–190	Comba *et al.* (1994)
Birmingham, United Kingdom		0.02–500	Rivett *et al.* (1990); Burston *et al.* (1993)
Rainwater			
Los Angeles, CA, 1982	0.021		Kawamura & Kaplan (1983)
La Jolla, CA	0.006		Su & Goldberg (1976)
Portland, OR		0.0008–0.009	Ligocki *et al.* (1985)
Germany	0.08		European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Switzerland		< 0.010–0.115	European Centre for Ecotoxicology and Toxicology of Chemicals (1995)
Kobe, Japan	0.050		European Centre for Ecotoxicology and Toxicology of Chemicals (1995)

Table 8 (contd)

Location (year)	Concentration (μg/L)		Reference
	Mean	Range	
Rivers			
USA, five states, surface water (14% of samples positive)		max, 21	Dyksen & Hess (1982)
Rhine, Germany		0.2–78	Dietz & Traud (1973); Bauer (1978); Bauer (1981); Hellmann (1984)
Elbe		0.2–9.9	Hellmann (1984)
Mosel		0.3–1.3	Hellmann (1984)
Rhine, Switzerland	~ 1		Zürcher & Giger (1976); Zoeteman *et al.* (1980)
Lake Zurich		0.07–1.4	Zürcher & Giger (1976); Schwarzenbach *et al.* (1979)
Danube	0.6		Bolzer (1982)
Netherlands		0.1–1.5	Herbert *et al.* (1986)
Drinking-water			
Zagreb, Croatia		0.36–7.8	Skender *et al.* (1993)
China, southern	0.2		Trussell *et al.* (1980)
Egypt	0.3		Trussell *et al.* (1980)
Australia, southern	0.1		Trussell *et al.* (1980)
New Jersey, USA, 1981–83	0.4		Wallace *et al.* (1987)
New Jersey, USA	7.7	max, 14	Cohn *et al.* (1994)
Woburn, MA, USA		66–212	Lagakos *et al.* (1986)
Germany, 1977	0.6	< 0.1–35.3	Bauer (1981)
Finland, south, 1992, two industrialized cities		≤ 200	Vartiainen *et al.* (1993)
Germany, 1985–86, > 90% of drinking-water supplies		51% < 0.001 40% 0.001–0.5 9% > 5	Bauer (1991)
Milan, Italy		2–68	Ziglio *et al.* (1985)
Groundwater			
Japan, 1983–84, 41 wells	23 samples, GM of 1.27 33 samples, GM of 0.94 35 samples, GM of 0.92		Kido *et al.* (1989)
USA, CA, 945 water supplies		max, 0.58–69	Westrick *et al.* (1984)
USA, five sites, 28% of samples positive		max, 1500	Dyksen & Hess (1982)
Netherlands, 1976		max, 22	Zoeteman *et al.* (1980)

GM, geometric mean

Tetrachloroethylene was reported in drinking-water in the Cape Cod, MA, region of the United States in the late 1970s (Webler & Brown, 1993). About 650 miles [1046 km] of vinyl-lined asbestos–cement water pipes were found to have contaminated the municipal water supply with tetrachloroethylene. The concentrations ranged from 1600–7750 µg/L at sites of low use to 1.5–80 µg/L in areas of medium and high use (Aschengrau *et al.*, 1993). A peak of 18 mg/L was found in a vinyl-coated asbestos–cement water pipe in Falmouth, MA (Wakeham *et al.*, 1980).

In a computerized database on water quality in the United States, the reported median concentrations of tetrachloroethylene in 1983–84 were 5.0 µg/L in industrial effluents (10.1% detectable, 1390 samples), 0.1 µg/L (38% detectable, 9323 samples) in ambient water, < 5.0 µg/kg dry weight (5% detectable, 359 samples) in sediment and < 50 µg/kg (7.0% detectable, 101 samples) in biota (Staples *et al.*, 1985).

The United States Environmental Protection Agency (1985b) estimated in 1985 that 11 430 000 individuals (5.3% of the United States population using municipal water supplies) were exposed to tetrachloroethylene at concentrations ≥ 0.5 µg/L. In addition, 874 000 individuals (0.4% of the United States population) were exposed to levels > 5 µg/L.

In the National Organic Monitoring Survey in the United States in 1976–77, 113 drinking-water samples were found to contain tetrachloroethylene at concentrations of 0.2–3.1 µg/L. In the National Screening Program in 1977–81, 142 drinking-water samples were reported to contain levels from traces to 3.2 µg/L. In the Community Water Supply Survey, 452 drinking-water samples contained 0.5–30 µg/L. An aggregate of various state reports on 1652 drinking-water samples showed a range of trace levels to 3000 µg/L (Thomas, 1989).

1.3.4 Food

The concentrations in milk and meat products in Switzerland ranged from 3 to 3490 µg/kg. The total daily intake was calculated to be 160 µg/day (Zimmerli *et al.*, 1982).

In the United Kingdom, tetrachloroethylene was found at concentrations of 0.3–13 µg/kg in dairy products, 0.9–5.0 µg/kg in meat, 7 µg/kg in margarine, 0.01–7 µg/kg in oils, 3 µg/kg in instant coffee, 3 µg/kg in tea and 0.7–2.0 µg/kg in fruits and vegetables (McConnell *et al.*, 1975). In the United Kingdom, 81 of 98 samples of olive oil contained < 10 µg/kg and the other 17 contained 1–70 µg/kg tetrachloroethylene (Norman, 1991).

In the United States, tetrachloroethylene was found in 93 of 231 food samples (40%) at a mean concentration of 13 µg/kg (1–124 µg/kg). Residues were determined in a variety of cereals (mean, 22 µg/kg; range, 1–108 µg/kg), in corn oil (21 µg/kg), pork and beans (2 µg/kg), peas (2 µg/kg), onion rings (5 µg/kg), fried potatoes (9 µg/kg), a wide variety of baked goods (mean, 12 µg/kg; range, 3–48 µg/kg), peanut butter (3 µg/kg), pecan nuts (120 µg/kg), dairy products (mean, 9 µg/kg; range, 2–30 µg/kg), milk chocolate (20 µg/kg), meat products (mean, 13 µg/kg; range, 1–124 µg/kg), baby foods (mean, 2.5 µg/kg; range, 1–5 µg/kg), bananas (2 µg/kg), grapes (1 µg/kg) and avocados (14 µg/kg) (Daft, 1988).

The concentrations of tetrachloroethylene in fish in the United Kingdom were 0.3–11 µg/kg in tissue and 1–41 µg/kg in liver, with an average concentration in water of 0.12 µg/L. Molluscs from Liverpool Bay contained a mean of 4 µg/kg on a dry weight basis, with a range of 1–15 µg/kg (Pearson & McConnell, 1975). In Lake Pontchartrain, LA (United States), tetrachloro-

ethylene was found at a concentration of 3.3 ppb [μg/kg] in clams and 10 ppb in oysters; the concentration in the sediment was reported to be 0.3 ppb wet weight (Ferrario *et al.*, 1985).

The concentration of tetrachloroethylene in sediment and marine animal tissue collected near the discharge zone of the waste treatment plant of Los Angeles County, CA, was 2.9 μg/L in the effluent and < 0.5 μg/kg in sediment and in various marine animals (range, < 0.3–29 μg/kg wet tissue) (Gossett *et al.*, 1983).

Tetrachloroethylene has frequently been found at higher levels in fatty foods in residences and markets near dry cleaning establishments (Vieths *et al.*, 1987, 1988; Reinhard *et al.*, 1989). In Germany, the concentrations of tetrachloroethylene in foods in a supermarket near a dry cleaning shop were 110 μg/kg in margarine, 7 μg/kg in herb butter, 36 μg/kg in a cheese spread, 21 μg/kg in butter, 25 μg/kg in flour and 36 μg/kg in cornstarch. The concentrations found in foods taken into a dry cleaning shop were 2 μg/kg in a fruit sherbert, 1330 μg/kg in chocolate-coated ice cream, 4450 μg/kg in chocolate- and nut-coated ice cream and 18 750 μg/kg in an ice-cream confection (Vieths *et al.*, 1988). Butter obtained from a supermarket located near a dry cleaning establishment contained concentrations of 100–> 1000 ppb [μg/kg], whereas butter obtained from other shops generally contained < 50 ppb (Miller & Uhler, 1988). The concentrations in butter in apartments above a coin-operated dry cleaners in Hamburg, Germany, were as high as 58 000 μg/kg (Gulyas *et al.*, 1988). Concentrations of 500–5000 ppb were found in four of 56 margarine samples bought from supermarkets in the Washington DC metropolitan area; the concentrations in the remaining samples were 100–500 μg/kg in one, 50–100 μg/kg in one, < 50 μg/kg in nine, < 4 μg/kg in 18 and undetectable in 23 (Entz & Diachenko, 1988).

1.3.5 Other

Tetrachloroethylene was reported as a contaminant of cosmetic products (range, 0.3–400 μg/L) and of cough mixtures (range, 0.2–97.1 μg/kg) (Bauer, 1981). In Germany, the mean daily intake of tetrachloroethylene from air, food, and water has been estimated to range from 113 to 144 μg/day (Bauer, 1981; von Düszeln *et al.*, 1982).

1.3.6 Biological monitoring

The results of the United States Third National Health and Nutrition Survey showed a mean blood concentration of tetrachloroethylene in 590 non-occupationally exposed volunteers of 0.19 μg/L (Ashley *et al.*, 1994).

The median blood level of tetrachloroethylene in people not occupationally exposed to volatile halogenated hydrocarbons in Germany was 0.4 μg/L (range, < 0.1–3.7 μg/L), whereas the ranges were 1.7–29.2 μg/L in the blood of nine motor vehicle mechanics, 0.4–0.7 μg/L in three painters, 0.5–1.1 μg/L in three precision instrument makers and 17.6–2497.9 μg/L (mean, 748.8 μg/L) in six dry cleaners and pressers (Hajimiragha *et al.*, 1986).

In a Japanese factory where tetrachloroethylene was used for degreasing, the air concentrations were 30–220 ppm [203–1492 mg/m^3] (geometric mean, 92 ppm [624 mg/m^3]); the geometric mean concentration of total trichloro compounds in urine was 50.7 mg/L (Ikeda *et al.*, 1980).

In a metal degreasing process in the Republic of Korea, the mean concentration of tetrachloroethylene in the air was 22.4 ppm [152 mg/m^3] (range, 0–61 ppm [0–414 mg/m^3]). The mean blood concentration was 0.85 mg/L (range, 0.2–2.5 mg/L), and the mean concentration of trichloroacetic acid in urine was 1.76 mg/L (range, 0.6–3.5 mg/L) (Jang *et al.*, 1993).

In an ongoing biological monitoring study of workers in various occupations exposed to trichloroethylene, tetrachloroethylene or 1,1,1-trichloroethane conducted by the Finnish Institute of Occupational Health, 11 534 samples representing 3976 workers in 600 workplaces were obtained for the three compounds between 1965 and 1983. Of these workers, 94.4% were monitored for one solvent, 5.2% for two solvents and 0.4% for three solvents. The mean concentrations of tetrachloroethylene measured in blood samples collected between 1974 and 1983 were 0.7 μmol/L [116 μg/L] for men and 0.4 μmol/L [66 μg/L] for women (Anttila *et al.*, 1995). A maximal concentration of 0.5 μmol/L [83 μg/L] tetrachloroethylene was measured in the blood of Finnish workers manufacturing printing plates (Rantala *et al.*, 1992).

Tetrachloroethylene was detected at a geometric mean concentration of 0.069 μg/L (range, < 0.015–2.54 μg/L) in the blood of 31 of 39 subjects in Zagreb, Croatia, with no known exposure to solvents. The geometric mean concentration in drinking-water was 1.98 μg/L (range, 0.36–7.80 μg/L) (Skender *et al.*, 1993). Similar observations were made in 79 subjects (Skender *et al.*, 1994).

Tetrachloroethylene was detected in seven of 42 samples of breast milk from the general population in four urban areas of the United States (Pellizzari *et al.*, 1982). In a case of jaundice and hepatomegaly reported in a six-week-old breast-fed infant in Halifax, Canada, the mother's blood was found to contain 3000 μg/L and her milk contained 10 000 μg/L. The father, who worked as a leather and suede cleaner at a dry cleaning plant, had a blood level of 30 000 μg/L. The mother regularly visited her husband at the plant during lunch (Bagnell & Ellenberger, 1977; see also section 4.3.1, p. 195).

In a study of non-occupationally exposed nursing mothers in the United States in 1985, the concentrations of tetrachloroethylene in milk ranged from undetectable to 43 μg/L (mean, 6.2 μg/L). Those in personal air samples were 1.1–210 μg/m^3 (mean, 27 μg/m^3), and their blood concentrations were 2.9–8.7 μg/L (Schreiber, 1992, 1993).

In a study in the Netherlands, the mean concentrations of tetrachloroethylene in alveolar air were 24 μg/m^3 for six children in a school located near a factory and 2.8 μg/m^3 in 11 control children; the indoor ambient air levels were 13 μg/m^3 in the school near the factory and 1–3 μg/m^3 in the control school. The mean alveolar air concentrations of 10 residents on the first floor of a retirement home located near a chemical waste dump was 7.8 μg/m^3, whereas that of 19 residents on higher floors was 1.8 μg/m^3 (Monster & Smolders, 1984).

Tetrachloroethylene was found at concentrations of 0.4–29.2 μg/kg in the body fat of eight people *post mortem* in the United Kingdom, with an average of 7.9 μg/kg wet weight (McConnell *et al.*, 1975). The maximal concentration of tetrachloroethylene in fat from the cadavers of 15 people who had lived in industrialized areas of Germany was 36.9 μg/kg wet weight, with an average of 14 μg/kg (Bauer, 1981).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for tetrachloroethylene in a number of countries are presented in Table 9. In 1947, the American Conference of Governmental Industrial Hygienists (ACGIH) reduced its recommended threshold limit value from 200 ppm (1370 mg/m^3) to 100 ppm (670 mg/m^3). It was reduced again in 1984 to 50 ppm (335 mg/m^3) and was further reduced in 1993 to 25 ppm (170 mg/m^3) (Coler & Rossmiller, 1953; American Conference of Governmental Industrial Hygienists, 1984, 1994).

WHO (1993) has established a guideline for tetrachloroethylene in drinking-water of 40 µg/L. In Switzerland, the tolerance limit for tetrachloroethylene in food is 0.05 mg/kg, while that in the fat of meat and milk is 0.2 mg/kg (Grob *et al.*, 1991).

The ACGIH (1994) has recommended several biological exposure indices for tetrachloroethylene. That for exhaled air before the last shift of a work week is 10 ppm [67.8 mg/m^3]; that for blood before the last shift of the work week is 1 mg/L; and that for trichloroacetic acid in urine at the end of the work week is 7 mg/L. It is noted that measurement of trichloroacetic acid in urine is a nonspecific, semiquantitative determinant of exposure to tetrachloroethylene.

Biological indices for tetrachloroethylene have been reported; in Finland: tetrachloroethylene in blood, 6 µmol/L [995 µg/L] (Aitio *et al.*, 1995); in Germany: tetrachloroethylene in blood, 1 mg/L; in alveolar air, 9.5 ml/m^3 (Deutsche Forschungsgemeinschaft, 1993) and in Switzerland: tetrachloroethylene in blood, 1 mg/L; trichloroacetic acid in urine, 7 mg/L; tetrachloroethylene in alveolar air, 9.5 ml/m^3 (Schweizerische Unfallversicherungsanstalt, 1994).

In some countries, emissions of tetrachloroethylene from dry cleaning establishments are specifically regulated. In Germany, for example, the concentration of tetrachloroethylene in the air leaving a dry cleaning machine may be no higher than 2000 mg/m^3. Tetrachloroethylene concentrations in air emissions from dry cleaning plants must not exceed 20 mg/m^3, and the concentration in the outlet air of the workroom cannot exceed 35 mg/m^3. The threshold value for tetrachloroethylene in a neighbouring apartment is 0.1 mg/m^3. The concentration in contaminated water from distillation and in the water from the drying cycle must not exceed 0.5 mg/m^3 (Kurz, 1992).

2. Studies of Cancer in Humans

2.1 Case reports

Ratnoff and Gress (1980) in the United States reported a case of polycythemia vera in a 44-year-old salesman who distributed tetrachloroethylene to dry cleaning plants and checked for leaks. He had been exposed transiently to concentrations of 50–1000 ppm [339–6780 mg/m^3]. Polycythemia vera had been diagnosed in his father, who was the director of the chemical distribution company, at the age of 53 years.

Jalihal and Barlow (1984) reported a case of myeloid leukaemia diagnosed in a 60-year-old dry cleaner in the United Kingdom. He had had heavy exposure for many years first to trichloroethylene and later to tetrachloroethylene.

Table 9. Occupational exposure limits and guidelines for tetrachloroethylene

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1993	335	TWA, suspected carcinogen
		1005	STEL
Austria	1987	345	TWA
Belgium	1993	339	TWA
		1368	STEL
Brazil	1987	525	TWA; skin notation
Bulgaria	1993	170	TWA
		685	STEL
Canada (Saskatchewan)	1987	335	TWA
		420	STEL; 5 min
Chile	1987	536	TWA; skin notation
China	1987	670	TWA
Czech Republic	1993	250	TWA
		1250	STEL
Denmark	1993	200	TWA; skin notation
Egypt	1993	35	TWA
Finland	1993	335	TWA
		520	STEL
France	1993	335	TWA
Germany	1993	345	TWA; suspected carcinogen
Indonesia	1987	670	TWA
Italy	1987	600	TWA; skin notation
Japan	1993	335	TWA
Mexico	1987	670	TWA
Netherlands	1994	240	TWA; skin notation
Poland	1993	60	TWA; skin notation
Republic of Korea	1993	170	TWA
		685	STEL
Romania	1987	400	TWA
		500	STEL
Russian Federation	1993	339	TWA
Sweden	1993	70	TWA
		170	STEL
Switzerland	1993	345	TWA; skin notation
		678	STEL
United Kingdom	1994	335	TWA
		1000	STEL
USA			
ACGIH	1994	170	TWA; animal carcinogen
		685	STEL
NIOSH	1994	None	TWA; carcinogen
OSHA	1994	678	TWA
		1356	Ceiling
		2034	PEAK; 5 min in any 3 h

Table 9 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation
Venezuela	1987	670	TWA; skin notation
		1000	STEL; skin notation

From Cook (1987); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); United Kingdom Health and Safety Executive (1994); US National Institute for Occupational Safety and Health (NIOSH) (1994a,c); US Occupational Safety and Health Administration (OSHA) (1994)
TWA, time-weighted average; STEL, short-term exposure limit; Ceiling, level not to be exceeded during any part of the workday

2.2 Cohort studies

Olsen *et al.* (1989) studied a cohort of 2610 white men employed for one or more years between 1956 and 1980 in a chemical company in Louisiana, United States. Tetrachloroethylene was one of many chemicals produced in the plant. The cohort was followed until 1 January 1981, and vital status was ascertained for 98.9% of the men. The expected numbers of deaths were calculated on the basis of both national and local mortality rates. There were 48 deaths, giving a standardized mortality ratio (SMR) of 0.56 (95% confidence interval [CI], 0.42–0.75), and 11 cancer deaths, giving an SMR of 0.76 (0.38–1.4), both in comparison with local rates. Three deaths from leukaemia and aleukaemia gave a significant SMR of 4.9 (1.0–14.4); however, the leukaemias were all of different types and occurred in men with different employment histories.

In the study of Blair *et al.* (1990), described in the monograph on dry cleaning on p. 48, there were increased SMRs for cancers at all sites (SMR, 1.2; 95% CI, 1.0–1.3; 294 deaths) and for cancers of the oesophagus (2.1; 1.1–3.6; 13 deaths), cervix (1.7; 1.0–2.0; 21 deaths) and urinary bladder (1.7; 0.7–3.3; 8 deaths). Specific exposures could not be accounted for, but the mortality rates were similar for those entering before and after 1960, when use of tetrachloroethylene became predominant.

In a study described in the monograph on trichloroethylene (p. 97), Spirtas *et al.* (1991) also evaluated exposure to other specified chemicals, including tetrachloroethylene. These analyses showed two deaths from multiple myeloma ([0.12 expected] SMR, 17) in women and four deaths from non-Hodgkin's lymphoma [SMR, 3.2; 95% CI, 0.87–8.1] in men and women exposed to tetrachloroethylene. Data for other cancer sites were not provided.

In a study described in the monograph on trichloroethylene (p. 96), Anttila *et al.* (1995) also included 849 persons in Finland who had been biologically monitored for occupational exposure to tetrachloroethylene. The median measured level of tetrachloroethylene in blood during 1974–83 was 0.7 μmol/L [116 μg/L] in men and 0.4 μmol/L [66 μg/L] in women. A total of 31 cancer cases were observed (standardized incidence ratio [SIR], 0.90; 95% CI, 0.61–1.3), but significant excess risks were not seen for cancer at any site. There were two cases of cervical cancer (3.2;

0.39–12) and three cases of non-Hodgkin's lymphoma (3.8; 0.77–11). The observed numbers were not provided for several sites of potential interest, such as the oesophagus and urinary bladder.

In the study of Ruder *et al.* (1994), described in the monograph on dry cleaning (p. 49), in the subcohort of 625 workers employed only in shops where tetrachloroethylene was the primary solvent used, an excess was seen for cancer of the oesophagus (SMR, 2.6; 95% CI, 0.72–6.8; four deaths); no excess was seen for cancers of the intestine (1.0; 0.32–2.3; five deaths), urinary bladder (no case [1.0 expected]), pancreas (0.73; 0.09–2.6; two deaths) or female genital organs (1.6; 0.68–3.1; eight deaths).

These studies are summarized in Table 10.

2.3 Case–control studies

2.3.1 Cancer of the liver and bile duct

Bond *et al.* (1990) conducted a case–control study nested in a cohort of 21 437 hourly workers employed at a chemical company in Midland City and Bay City, MI, United States. Among the 6259 men who had died in 1940–82, 44 had cancer of the liver or bile duct mentioned on their death certificates (11 primary liver cancer, 14 cancer of the gall-bladder or bile ducts, 19 cancer of the liver not specified as primary or secondary). A random sample of 1888 men was chosen to serve as controls. Company records were searched for potential exposure to 11 chemical agents. Exposure to tetrachloroethylene was recorded for six cases, giving an odds ratio of 1.8 (95% CI, 0.8–4.3).

Hardell *et al.* (1984) (in a study described in detail in the monograph on trichloroethylene, p. 101) studied 98 patients with liver cancer and 200 matched controls in the Umeå region of Sweden. One patient and no control reported exposure to tetrachloroethylene.

2.3.2 Malignant lymphoma

Hardell *et al.* (1981) (in a study described in detail in the monograph on trichloroethylene, p. 101) studied 169 patients with malignant lymphoma and 338 controls in the Umeå region of Sweden. One patient and no control reported exposure to tetrachloroethylene.

2.3.3 Brain tumours

In a study described in detail in the monograph on trichloroethylene (p. 102), Heineman *et al.* (1994) studied white men in the United States with astrocytic brain tumours. A total of 111 of these 300 men had job titles that were compatible with exposure to tetrachloroethylene (odds ratio, 1.2; 95% CI, 0.8–1.6). None of the risk estimates for subgroups reached statistical significance.

2.3.4 Renal-cell carcinoma

In the study of Sharpe *et al.* (1989) (described in the monograph on trichloroethylene, p. 101) in Montréal, Canada, 10 of 164 patients and three of 161 controls had been exposed to

Table 10. Summary of data from cohort studies of exposure to tetrachloroethylene

Cancer site	Studies in which subjects were exposed predominantly to tetrachloroethylene						Studies in which subjects had mixed exposures, including tetrachloroethylene								
	Anttila *et al.* (1995) 292 men and 557 women monitored for exposure (Finland, 1974–92)			Ruder *et al.* (1994) 625 men and women employed in dry cleaning (USA, 1960–90)			Blair *et al.* (1990) 5365 men and women employed in dry cleaning (USA, 1948–78)			Olsen *et al.* (1989) 2610 white men employed at a chemical company (USA, 1956–80)			Spirtas *et al.* (1991) 14 457 men and women employed in aircraft maintenance (subcohort exposed to tetrachloroethylene) (USA, 1953–82)		
	SIR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR[a]	95% CI	Obs	SMR	95% CI	Obs
All cancers	0.90	0.61–1.3	31	1.0	0.76–1.3	54	1.2	1.0–1.3	294	0.76	0.38–1.4	11	NR		
Oesophagus	NR			2.6	0.72–6.8	4	2.1	1.1–3.6	13	NR			NR		
Stomach	NR			–		0	0.8	0.4–1.4	11	NR			NR		
Colon	NR			1.0	0.32–2.3	5	1.0	0.6–1.4	25	NR			NR		
Cervix	3.2	0.39–12	2	1.6[b]	0.68–3.1	8	1.7	1.0–2.0	21	NR			NR		
Kidney	1.8	0.22–6.6	2	1.2	0.03–6.5	1	0.5	0.1–1.8	2	NR			NR		
Urinary bladder	NR			–	[1.0 expected]	0	1.7	0.7–3.3	8	NR			NR		
Brain and nervous system	1.2	0.14–4.2	2	NR			0.2	0.0–1.2	1	3.2	0.67–9.4	3	NR		
Lymphohaemato-poietic system	1.4	0.28–4.0	3	0.49	0.06–1.8	2	1.2	0.8–1.8	24	NR			NR		
Non-Hodgkin's lymphoma	3.8[c]	0.77–11	3	NR			1.7	0.7–3.4	7	NR			[3.2][a]	[0.87–8.1]	4
Leukaemias	NR			NR			0.9	0.4–1.8	7	4.9	1.0–14	3	NR		

SIR, standardized incidence ratio; CI, confidence interval; Obs, number of cases or deaths observed; SMR, standardized mortality ratio; NR, not reported

[a]In comparison with local mortality rates

[b]Female genital organs

[c]Includes ICD 202

degreasing solvents (odds ratio, 3.4; 95% CI, 0.92–13). The agents most widely used were reported to be tetrachloroethylene, 1,1,1-trichloroethane, trichloroethylene and dichloromethane.

2.3.5 Multiple sites

In the study of Siemiatycki (1991), described in the monograph on trichloroethylene (p. 103), the estimated prevalence of exposure to tetrachloroethylene was 1%. The odds ratio for prostatic cancer was 1.8 ([95% CI, 0.8–4.1]; nine cases) for any exposure and 3.2 ([1.1–9.3]; eight cases) for 'substantial' exposure.

2.4 Studies of drinking-water

The reservations expressed in the monograph on trichloroethylene (p. 103) with regard to the relevance of some of the studies on drinking-water for evaluating carcinogenicity apply equally to tetrachloroethylene, especially in view of the fact that some people may have been exposed to high concentrations of both of these compounds and perhaps others.

Aschengrau *et al.* (1993) studied residents of the five Upper Cape towns in Massachusetts, United States, in whom cancers of the urinary bladder and kidney and leukaemia had been diagnosed in 1983–86. During the late 1970s, tetrachloroethylene had leached into drinking-water from the inner vinyl lining of water distribution pipes (see p. 173); the concentrations at sites of low use (with slow water flow, such as in dead-end sites in the distribution system) had been 1600–7750 μg/L, and that at sites of medium and high use was 1.5–80 μg/L. Population controls were selected for living persons under the age of 65 by random-digit dialling, for living persons over the age of 65 from the Medicare files and for deceased persons from the death lists. Residential history was collected by personal interview, and relative exposure to tetrachloroethylene in drinking-water was estimated. The final study groups included 61 people with cancer of the urinary bladder and 852 controls, 35 patients with cancer of the kidney and 777 controls and 34 people with leukaemia and 737 controls. Odds ratios of 4.0 (95% CI, 0.65–25; based on four exposed cases) and 8.3 (1.5–45; two exposed cases) were found for urinary bladder cancer and leukaemia, respectively, in people with estimated exposure to tetrachloroethylene-contaminated drinking-water at above the 90th percentile. The estimates were controlled for potential confounding factors. None of the patients with cancer of the kidney had been exposed to tetrachloroethylene at this level.

Isacson *et al.* (1985) tabulated cancer incidence data in Iowa, United States, in 1969–81 by two groups of areas, with levels of < 0.3 μg/L and ≥ 0.3 μg/L tetrachloroethylene in groundwater. There were virtually no differences in the incidence rates of cancers of the urinary bladder, breast, colon, lung, prostate or rectum between the two groups of areas.

In a study described in detail in the monograph on trichloroethylene (p. 103; Lagakos *et al.*, 1986), the occurrence of childhood leukaemia in a community in Massachusetts, United States, was significantly related to consumption of water from two wells that had been contaminated with chlorinated organic chemicals, including tetrachloroethylene. The level of tetrachloroethylene measured in 1979 was 21 ppb [μg/L].

In a study described in detail in the monograph on trichloroethylene (p. 104; Cohn *et al.*, 1994), the highest level of tetrachloroethylene in groundwater was 14 μg/L; 11 towns had levels

> 5 μg/L. When these towns were compared with towns where no tetrachloroethylene was detected in drinking-water, a slight increase in the incidence of leukaemia was noted among women (odds ratio, 1.2; 95% CI, 0.9–1.5) but not among men (0.8; 0.7–1.1). The odds ratio for the incidence of non-Hodgkin's lymphoma in women was 1.1 (0.9–1.3) and that in men was 1.1 (0.9–1.4).

Vartiainen *et al.* (1993) (in a study described in detail in the monograph on trichloroethylene, p. 104) studied cancer incidence in two Finnish villages where the groundwater was contaminated with trichloroethylene and tetrachloroethylene. The average urinary excretion of tetrachloroethylene was 0.19 and 0.10 μg per day for inhabitants of the two exposed villages and 0.11 and 0.09 μg per day for two groups of controls.With the possible exception of non-Hodgkin's lymphoma, which occurred in marginal excess of one of the villages (SIR, 1.4, 95% CI, 1.0–2.0; 31 cases) but not in the other (0.6; 0.3–1.1; 14 cases), neither overall cancer incidence nor the incidence of liver cancer or lymphohaematopoietic cancers was increased for inhabitants of the two villages.

3. Studies of Cancer in Experimental Animals[1]

3.1 Oral administration

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F1 mice, five weeks of age, were administered tetrachloroethylene (USP grade; purity, > 99%) in corn oil by gavage on five days per week for 78 weeks. The time-weighted average doses of tetrachloroethylene were 536 and 1072 mg/kg bw per day for males and 386 and 772 mg/kg bw per day for females. The treatment period was followed by a 12-week observation period. Groups of 20 vehicle controls and 20 untreated controls of each sex were included. Mortality was significantly increased in animals treated with tetrachloroethylene in comparison with controls. The numbers of survivors at the end of the study were 11/20 untreated control males, 10/20 vehicle control males, 19/50 low-dose males and 10/48 high-dose males; and 11/20 untreated control females, 18/20 vehicle control females, 11/50 low-dose females and 7/49 high-dose females. All animals were submitted to a complete necropsy and histopathological evaluation. Significantly increased incidences (Fisher exact test) of hepatocellular carcinomas were seen in all treated groups: in males, the rates were 2/17 untreated controls, 2/20 vehicle controls, 32/49 ($p < 0.001$) animals at the low dose and 27/48 ($p < 0.001$) at the high dose; in females, the rates were 2/20 untreated controls, 0/20 vehicle controls, 19/48 ($p < 0.001$) at the low dose and 19/48 ($p < 0.001$) at the high dose (United States National Cancer Institute, 1977).

[1] The Working Group was aware of a study in progress in which rats were exposed to tetrachloroethylene by inhalation (IARC, 1994b).

3.1.2 Rat

Groups of 50 male and 50 female Osborne-Mendel rats, seven weeks of age, were administered two doses of tetrachloroethylene (purity, > 99%) in corn oil by gavage on five days per week for 78 weeks. The time-weighted average doses of tetrachloroethylene were 471 and 941 mg/kg bw per day for males and 474 and 949 mg/kg bw per day for females. The treatment period was followed by a 32-week observation period. Groups of 20 vehicle controls and 20 untreated controls of each sex were included. Mortality was significantly increased in treated animals in comparison with controls. The numbers of survivors at the end of the study were 5/20 untreated control males, 2/20 vehicle control males, 6/50 low-dose males and 2/50 high-dose males; and 12/20 untreated control females, 8/20 vehicle control females, 17/50 at the low dose and 14/50 at the high dose. All animals were submitted to a complete necropsy. There was no difference in tumour incidence between control and treated animals. Toxic nephropathy occurred in 88 and 94% of treated males and in 50 and 80% of treated females but not in controls (United States National Cancer Institute, 1977). [The Working Group noted that the high mortality precluded an evaluation of carcinogenicity.]

3.2 Inhalation

3.2.1 Mouse

Groups of 49 or 50 male and 49 or 50 female B6C3F1 mice, eight to nine weeks of age, were exposed to air containing tetrachloroethylene (purity, 99.9%) at concentrations of 0, 100 or 200 ppm (0, 680 or 1360 mg/m^3) for 6 h per day on five days per week for 103 weeks. Survival was significantly reduced ($p < 0.05$) among exposed male mice and among females at the high dose: the numbers of survivors at the end of the study were 46/49 control males, 25/50 at the low and 32/50 at the high dose; and 36/49 control females, 31/50 at the low and 19/50 at the high dose. All animals were submitted to a complete necropsy and histopathological evaluation. Exposure-related increases in the incidences of liver neoplasms were seen in all treated animals. In males, the incidences of hepatocellular adenomas were 12/49 controls, 8/49 at the low dose and 19/50 ($p = 0.012$, incidental tumour test) at the high dose; the incidences of hepatocellular carcinomas were 7/49 controls, 25/49 ($p = 0.016$) at the low dose and 26/50 ($p = 0.001$) at the high dose; and the combined incidences of hepatocellular adenomas or carcinomas were 17/49 controls, 31/49 ($p = 0.026$) at the low dose and 41/50 ($p < 0.001$) at the high dose. In females, the incidences of hepatocellular carcinomas were 1/48 controls, 13/50 ($p < 0.001$) at the low dose and 36/50 ($p < 0.001$) at the high dose; and the combined incidences of hepatocellular adenomas or carcinomas were 4/48 controls, 17/50 ($p < 0.001$) at the low dose and 38/50 ($p < 0.001$) at the high dose. Degeneration and necrosis of the liver in treated mice were also related to exposure. In males, degeneration was seen in 2/49 controls, 8/49 animals at the low dose and 14/50 at the high dose; necrosis was seen in 1/49 controls, 6/49 at the low dose and 15/50 at the high dose. In females, degeneration was seen in 1/49 controls, 2/50 at the low dose and 13/50 at the high dose; necrosis was seen in 3/48 controls, 5/40 at the low dose and 9/50 at the high dose (Mennear *et al.*, 1986; United States National Toxicology Program, 1986).

3.2.2 Rat

In a study reported as an abstract, groups of 96 male and 96 female weanling Sprague-Dawley rats were exposed to air containing 300 or 600 ppm (2030 or 4070 mg/m^3) tetrachloroethylene (purity, 99.9%) for 6 h per day on five days per week for 12 months. The exposure period was followed by an observation period that extended through the rats' lifetime (up to 19 additional months). The control groups consisted of 192 male and 192 female rats. Slightly higher mortality was reported among males exposed to the dose of 600 ppm. All rats were submitted to necropsy and histopathological examination. No dose-related increase in tumour incidence was seen in exposed rats in comparison with controls (Rampy *et al.*, 1977). [The Working Group noted that the duration of exposure was too short to adequately evaluate the carcinogenicity of tetrachloroethylene.]

Groups of 50 male and 50 female Fischer 344/N rats, eight to nine weeks of age, were exposed to air containing tetrachloroethylene (purity, 99.9%) at concentrations of 0, 200 or 400 ppm (0, 1360 or 2720 mg/m^3) for 6 h per day on five days per week for up to 103 weeks. Survival of male rats exposed to the high dose was significantly lower ($p < 0.05$) than that of controls; the numbers of survivors at the end of the study were 23 male controls, 19 males at the low dose and 11 at the high dose; and 23 female controls, 21 at the low dose and 24 at the high dose. All animals were submitted to a complete necropsy and histopathological evaluation. Dose-related increases (life-table test) in the incidence of mononuclear-cell leukaemia were seen in animals of each sex; the incidences were 28/50 control males, 37/50 ($p = 0.046$) at the low dose and 37/50 ($p = 0.004$) at the high dose; 18/50 control females, 30/50 ($p = 0.023$) at the low dose and 29/50 ($p = 0.053$) at the high dose. On the basis of life-table analysis (with adjustment for survival), the incidences of advanced (stage 3) mononuclear-cell leukaemia were increased in animals of each sex: 20/50 control males, 24/50 at the low dose and 27/50 ($p = 0.022$) at the high dose; 10/50 control females, 18/50 at the low dose and 21/50 ($p = 0.029$) at the high dose. The historical incidence of mononuclear-cell leukaemia in rats at the same laboratory was 47% in males and 29% in females. Uncommonly occurring renal tubular-cell adenomas or adenocarcinomas were found in male rats; adenomas were seen in 1/49 controls, 3/49 at the low dose and 2/50 at the high dose; adenocarcinomas occurred in 0/49 controls, 0/49 at the low dose and 2/50 at the high dose (not statistically significant even when combined). The incidence of renal tubular-cell hyperplasia was also increased in treated males, with 0/49 controls, 3/49 at the low dose and 5/50 at the high dose; karyomegaly was found in 1/49 control males, 37/49 at the low dose and 45/50 at the high dose and in 0/50 control females, 8/49 at the low dose and 20/50 at the high dose (Mennear *et al.*, 1986; United States National Toxicology Program, 1986).

3.3 Intraperitoneal injection

Mouse: In a screening assay based on the increased multiplicity and incidence of lung tumours in a strain of mice highly susceptible to development of this neoplasm, groups of 20 strain A/St male mice, six to eight week of age, were given intraperitoneal injections of tetrachloroethylene [purity unspecified] in tricaprylin three times a week at doses of 80 mg/kg bw (14 injections) or 200 or 400 mg/kg bw (24 injections). Twenty-four weeks after the first injection, the mice were killed and their lungs were examined under a dissecting microscope.

Tetrachloroethylene did not increase the incidence of pulmonary adenomas in treated mice in comparison with vehicle control mice (Theiss *et al.*, 1977).

3.4 Topical application

Mouse: In a study of two-stage carcinogenesis on mouse skin, single doses of 163 mg tetrachloroethylene [purity unspecified] in 0.2 ml of acetone were applied to the dorsal skin of 30 female ICR:Ha Swiss mice aged six to eight weeks; 14 days later, topical applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 5 µg in 0.2 ml of acetone, three times per week) were begun, for at least 61 weeks. Seven skin papillomas were found in 4/30 treated mice, and six papillomas were found in 6/90 TPA-treated controls. Trichloroethylene was also administered in 0.2 ml of acetone by repeated topical application (three times per week) to groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, for at least 63 weeks at doses of 18 or 54 mg per mouse. One papilloma occurred in a mouse treated with the lower dose; no skin tumours were observed among controls or mice given the higher dose (Van Duuren *et al.*, 1979).

3.5 Carcinogenicity of metabolites

Carcinogenicity studies on a known metabolite, trichloroacetic acid, are summarized in a separate monograph in this volume.

Mouse: Tetrachloroethylene oxide, a presumed metabolite of tetrachloroethylene, was administered to groups of 30 female ICR/Ha Swiss mice, six to eight weeks of age, by repeated skin application for 66 weeks (7.5 mg/mouse three times weekly) or by a subcutaneous injection of 500 µg/mouse in 0.05 ml of trioctanoin once a week for up to 80 weeks. The incidence of tumours at the site of application was not increased (Van Duuren *et al.*, 1983).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

The toxicokinetics of tetrachloroethylene in humans has been reviewed (Hake & Stewart, 1977; Reichert, 1983).

The mean blood concentration of tetrachloroethylene in a group of 590 nonoccupationally exposed people in the United States was 0.19 ppb [µg/L] (Ashley *et al.*, 1994).

Exposure of nine men and 41 women employed in dry cleaning shops to concentrations of tetrachloroethylene ranging from traces to 85 ppm [576 mg/m^3] (4-h samples randomly collected over the working week) led to blood concentrations of 9–900 µg/L (samples collected during the working day). The median values were 14.8 ppm [100 mg/m^3] in air and 143 µg/L in blood (Mutti *et al.*, 1992).

The kinetics and metabolism of tetrachloroethylene have been reported in a large number of studies of volunteers. Pulmonary uptake of tetrachloroethylene is rapid, but complete tissue equilibrium is achieved only after several hours. In six male volunteers (mean body weight, 77 kg; range, 67–86), the estimated uptake of tetrachloroethylene after exposure to 72 ppm [488 mg/m^3] for 4 h at rest was 455 mg (range, 370–530). Uptake from an atmosphere containing 144 ppm [976 mg/m^3] was 945 mg (range, 670–1210), i.e. 2.08-fold higher, at rest and 1318 mg (range 1060–1510) when the 4 h exposure was combined with a work load of 100 W for two half-hour periods [3.6 kJ]. The alveolar retention at rest at the end of the exposure was calculated to be about 60% (Monster *et al.*, 1979).

The human blood:air partition coefficients range from 10.3 to 14.0 (Hattis *et al.*, 1990; Gearhart *et al.*, 1993).

Excretion of tetrachloroethylene in breath is proportional to the level of exposure (Fernandez *et al.*, 1976; Solet & Robins, 1991). Several studies have indicated slow elimination of tetrachloroethylene by exhalation; for example, tetrachloroethylene was still detectable at a concentration of about 1 ppm [~ 6.78 mg/m^3] 162 h after exposure to 496 and 992 mg/m^3 for 4 h. More than 80% of the estimated uptake was recovered in breath (Monster *et al.*, 1979). Terminal half-lives of 34–55 h were reported for exhalation of tetrachloroethylene (Stewart *et al.*, 1961b, 1970). Unchanged compound is excreted by exhalation at three different rate constants, with half-lives of 12–16 h, 30–40 h and about 55 h (Monster *et al.*, 1979). Only a minor amount (< 2 %) of the retained tetrachloroethylene is recovered as identified metabolites, which include trichloroacetic acid and trichloroethanol (Ikeda *et al.*, 1972; Ikeda & Imamura, 1973; Ikeda, 1977; Monster *et al.*, 1979; Ohtsuki *et al.*, 1983). In these studies, 20–40% of the tetrachloroethylene was not recovered. None of the other metabolites identified in animals has yet been confirmed in humans. As is seen with trichloroethylene, trichloroacetic acid is slowly cleared over the course of several days, with an estimated half-life of 144 h (Ikeda & Imamura, 1973). Urinary recoveries of trichloroacetic acid indicate that biotransformation of tetrachloroethylene in humans is no longer linear after exposure by inhalation to > 100 ppm [> 678 mg/m^3] (Ohtsuki *et al.*, 1983). Conjugation of tetrachloroethylene with glutathione was not detectable in either cytosolic or microsomal fractions of human liver from seven donors (Green *et al.*, 1990).

4.1.2 Experimental systems

The absorption of tetrachloroethylene has been studied in rodents after inhalation, oral administration and skin contact.

The level of tetrachloroethylene in the blood of adult male Sprague-Dawley rats reached a maximum 1 h after oral ingestion and was maximal immediately after the end of a 6-h inhalation period. The peak blood levels were 10 μg/ml immediately after exposure to 573 ppm [3885 mg/m^3] for 6 h and 40 μg/ml 1 h after oral administration of 500 mg/kg bw. Blood levels declined following first-order kinetics, with a single half-life of about 7 h and an elimination rate constant (K_e) of about 0.10/h (Pegg *et al.*, 1979). The mean blood:air partition coefficients in a number of mouse strains range from 16.9 to 24.4 (Hattis *et al.*, 1990; Gearhart *et al.*, 1993).

Percutaneous absorption of ^{14}C-tetrachloroethylene from dilute aqueous solutions (10–100 ppb [μg/L]) was studied in hairless guinea-pigs exposed in an air-tight glass chamber

containing no headspace for 70 min (the head of each sedated animal protruded through a latex diaphragm). Uptake of tetrachloroethylene, as determined by the reduction in radioactivity in the aqueous phase and the amount of radiolabel in the urine and faeces of the animals, was fairly rapid and amounted to 25–30% of the tetrachloroethylene present (Bogen *et al.*, 1992).

Unanaesthetized male Sprague-Dawley rats were exposed to 50 or 500 ppm [339 or 3390 mg/m^3] tetrachloroethylene for 2 h through a one-way breathing valve. The tetrachloroethylene concentrations in exhaled breath increased to a steady-state level within 20 min and were directly proportional to the inhaled concentrations. Blood levels increased throughout the exposure period at both concentrations. The maximal blood concentrations were about 1.2 µg/ml in the group exposed to the lower concentration and 20 µg/ml at the higher level (Dallas *et al.*, 1994a).

Toxicokinetic parameters were estimated in male Sprague-Dawley rats after either inhalation of 500 ppm [3390 mg/m^3] tetrachloroethylene for 2 h or intravenous injection of 10 mg/kg bw. The tissue concentrations (area under the concentration–time curve, based upon measurements from 1 min to 72 h) and maximal tissue concentrations were higher after the inhalation regime, and the tissue concentrations were at least five times higher in fat than in any other tissue examined. Tetrachloroethylene was found throughout the body. The half-lives in all tissues varied around 430 min after both exposure regimes (Dallas *et al.*, 1994b).

Toxicokinetic parameters were compared in male Sprague-Dawley rats and male beagle dogs after oral administration of 10 mg/kg bw tetrachloroethylene. Neither the tissue concentrations (area under the concentration–time curve, based on measurements from 1 min to 72 h) nor the maximal tissue concentrations were appreciably different in the two species, although maximal concentrations occurred earlier in rats. Tetrachloroethylene had much longer half-lives in tissue and blood of dogs than rats; the values in blood were 384 ± 145 min in four rats and 865 ± 385 min in three dogs, while the values for other tissues were about 400 min in rats and 2000 min in dogs (Dallas *et al.*, 1994c).

The metabolism of tetrachloroethylene was studied in male B6C3F1 mice individually housed in 0.7-L closed exposure chambers for 8 h. The starting concentrations were 200, 1000 and 3500 ppm [1356, 6780 and 23 730 mg/m^3]. The maximal metabolic velocity (V_{max}) was 0.2 mg/h per kg, the Michaelis-Menten constant (K_m) was 2.0 mg/L and the first-order metabolic rate was 2.0 g/kg. Dermal absorption was also rapid, and peak concentrations of tetrachloroethylene were reached in blood 30 min after application (Gearhart *et al.*, 1993). Less than 5% of the administered radioactivity was recovered in the animals 72 h after oral administration of 500 mg/kg bw tetrachloro[1,2-C^{14}]ethylene by gavage or after exposure by inhalation to 600 ppm [4068 mg/m^3] for 6 h (Pegg *et al.*, 1979).

Elimination of tetrachloroethylene and its metabolites by the main routes is dependent on dose. In general, mice have a greater capacity than rats to biotransform tetrachloroethylene. After single oral doses of 500 and 800 mg/kg bw ^{14}C-tetrachloroethylene, male B6C3F1 and female NMRI mice excreted 10.3 and 7.1% of the recovered radiolabel in urine within 72 h; 94.6 and 96.0% of the administered radiolabel was recovered (Schumann *et al.*, 1980; Dekant *et al.*, 1986). After male Sprague-Dawley rats were given oral doses of 1 and 500 mg/kg bw, 16.5 and 4.6% of the radiolabel was recovered in urine within 72 h; 71.5 and 89.9% of the recovered radiolabel was found in expired tetrachloroethylene, and 2.5 and 0.5%, respectively, was expired

as carbon dioxide; 103 and 91% of the administered radiolabel was recovered (Pegg *et al.*, 1979). After female Wistar rats were given 800 mg/kg bw orally, 2.3% of the recovered radiolabel was found in urine; 98.9% of the administered dose was recovered (Dekant *et al.*, 1986). After male and female Fischer 344 rats and B6C3F1 mice were exposed once for 6 h to 400 ppm [2712 mg/m^3] tetrachloroethylene, the peak blood levels of the major metabolite, trichloroacetic acid, were 13 times higher in mice than in rats. Comparisons of tissue concentrations, measured as the area under the concentration–time curve, showed that the mice had been exposed to 6.7 times more trichloroacetic acid than the rats (Odum *et al.*, 1988).

After exposure to 10 ppm [67.8 mg/m^3] tetrachloroethylene for 6 h, male B6C3F1 mice excreted 62.5% of the recovered radiolabel in urine and 7.9% as ^{14}C-carbon dioxide over 72 h; only 12% was excreted as unchanged tetrachloroethylene in expired air (Schumann *et al.*, 1980). Male Sprague-Dawley rats exposed to 9.1 ppm [61.7 mg/m^3] or 573 ppm [3885 mg/m^3] tetrachloro[1,2-^{14}C]ethylene for 6 h expired 68.1 and 88.0% as unchanged tetrachloroethylene and 3.6 and 0.7% as ^{14}C-carbon dioxide over 72 h; 18.7 and 6.0%, respectively, were recovered in urine over the same time (Pegg *et al.*, 1979).

The biotransformation of tetrachloroethylene in male Sprague-Dawley rats and B6C3F1 mice is a saturable process, and saturation occurs at higher doses in mice than rats. Furthermore, mice metabolized 8.5 and 1.6 times more tetrachloroethylene per kilogram of body weight after inhalation of 10 ppm [67.8 mg/m^3] or a single oral dose of 500 mg/kg bw. The higher rate of metabolism in mice is paralleled by greater irreversible binding of tetrachloroethylene metabolites to hepatic macromolecules than in rats after inhalation of 10 or 600 ppm [67.8 or 4068 mg/m^3] or a single oral dose of 500 mg/kg bw (Schumann *et al.*, 1980).

Other studies also showed that mice have a greater capacity for the biotransformation of tetrachloroethylene than rats (standardized for body weight), the magnitude of which depends on the dose and route of administration. Male and female DD mice excreted 3.9 times more trichloroacetic acid after inhalation of 200 ppm (1380 mg/m^3) tetrachloroethylene for 8 h than male Wistar rats; and after intraperitoneal injection of 2.78 mmol/kg [461 mg/kg] bw tetrachloroethylene to the same strains of animals, mice excreted 4.3 times more trichloroacetic acid than rats (Ikeda & Ohtsuji, 1972). After exposure of Wistar rats, Sprague-Dawley rats and B6C3F1 mice to 60 ppm [407 mg/m^3] tetrachloroethylene by inhalation, biotransformation to urinary trichloroacetic acid was 2.7 times higher in mice than in rats (Bolt & Link, 1980).

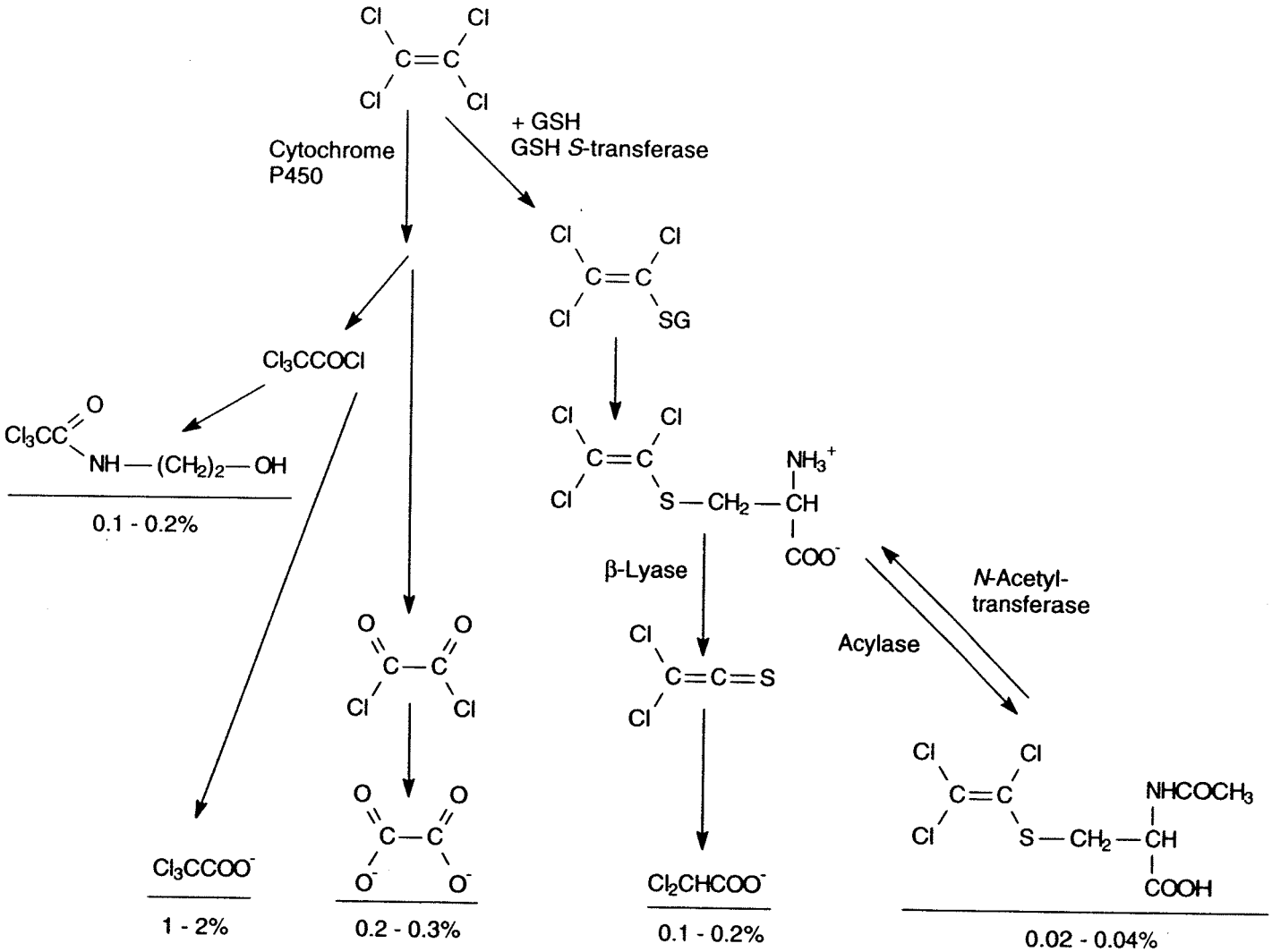
Several excretory metabolites have been identified in rodents (see Figure 1). In most studies, trichloroacetic acid was reported to be the major metabolite, representing about 50% of the radiolabel in urine (Yllner, 1961; Daniel, 1963; Dekant *et al.*, 1986). Oxalic acid, trichloroethanol and *N*-trichloroacetyl-2-aminoethanol are derived from the oxidative biotransformation of tetrachloroethylene and further reactions of trichloroacetyl chloride with water and phospholipids, respectively (Pegg *et al.*, 1979; Dekant *et al.*, 1986). *N*-Acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine is the end-product of the conjugation of tetrachloroethylene with glutathione and represents a minor metabolite in urine (< 2% of the radioactivity in urine pooled over 72 h after administration of 800 mg/kg bw tetrachloroethylene). The concentrations of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine in pooled urine samples from five Fischer 344 rats and five B6C3F1 mice, one, seven and 14 days after exposure to atmospheres of 400 ppm [2760 mg/m^3] tetrachloroethylene for 6 h per day for up to 14 days, were 0.75, 2.04 and

0.55 μg/ml in male rats; 1.30, 0.90 and 1.04 μg/ml in female rats; 0, 0.07 and 0.20 μg/ml in male mice; and 0, 0 and 0.15 μg/ml in female mice. The concentrations of this metabolite in the urine of male Fischer 344 rats given 1500 mg/kg bw per day by gavage were 23.0 μg/ml after one day, 41.1 μg/ml after 17 days and 32.7 μg/ml after 42 days (Green *et al.*, 1990). Dichloroacetic acid, which was found to represent no more than 5.1% of the administered radioactivity in urine pooled over 72 h after administration of 800 mg/kg bw tetrachloroethylene, has been suggested to be the end-product of renal processing of *S*-(1,2,2-trichlorovinyl)glutathione by the mercapturic pathway and cleavage by cysteine conjugate β-lyase, followed by hydrolysis of the thioketene intermediate (Dekant *et al.*, 1988, 1991).

N^{ε}-(Trichloroacetyl)-L-lysine residues are formed in liver proteins of rats treated with tetrachloroethylene. Western blot analysis of renal fractions from rats treated with either ^{14}C-tetrachloroethylene or *S*-(1,2,2-trichlorovinyl)-L-cysteine also suggested the presence of modified proteins in mitochondria and cytosol, but not in microsomes. The modified proteins that were separated after each of these treatments had identical relative molecular masses. Incubation of rat renal mitochondria with *S*-(1,2,2-trichlorovinyl)-L-cysteine *in vitro* resulted in the formation of N^{ε}-(dichloroacetyl)-L-lysine. This residue was quantified in kidney mitochondria and liver microsomes (which are the fractions in each organ with the largest quantities of rabbit anti-trifluoroacetyl serum cross-reactive material), 24 h after treatment of male rats with 1000 mg/kg bw tetrachloroethylene: 12 nmol/mg protein were found in kidney and only 46 pmol/mg in liver. N^{ε}-(Dichloroacetyl)-L-lysine is probably formed by the reaction of dithioketene with lysine in proteins after cleavage of *S*-(1,2,2-trichlorovinyl)-L-cysteine by β-lyase (Birner *et al.*, 1994).

In studies of the biotransformation of tetrachloroethylene in rat and mouse liver microsomes, trichloroacetic acid was identified as an end-product (Costa & Ivanetich, 1980). As with trichloroethylene, an epoxide has been proposed as an intermediate, and its rearrangement is postulated to result in trichloroacetyl chloride (Bonse & Henschler, 1976; Henschler & Bonse, 1977). Consideration of the mechanism of cytochrome P450-mediated olefin oxidation, however, suggests that trichloroacetyl chloride may also be formed in the absence of the epoxide (Guengerich & Macdonald, 1984). Tetrachlorooxirane may react with water to give oxalic acid; trichloroacetyl chloride is hydrolysed to trichloroacetic acid or may react in small amounts with proteins and phospholipids (Costa & Ivanetich, 1980; Dekant *et al.*, 1987). The rates of oxidation of tetrachloroethylene seen in mouse liver microsomes were significantly higher than those seen in rat liver microsomes. Both cytosolic and microsomal glutathione *S*-transferases catalysed the formation of *S*-(1,2,2-trichlorovinyl)glutathione from tetrachloroethylene (Dekant *et al.*, 1987; Green *et al.*, 1990). Conjugation in rat liver fractions occurred at a higher rate in the cytosol (18.2 pmol/min per mg protein) than in microsomes (6.4 pmol/min per mg protein), and the conjugation rate in mouse liver cytosol was only 3.4 pmol/min mg protein. The kinetic constants for kidney cytosolic β-lyase in mice, rats and humans were measured using *S*-(1,2,2-trichlorovinyl)-L-cysteine (which cleaves cysteine conjugates to give pyruvate and ammonia) as the substrate: the K_m values were about 5.1 mmol/L for mice, 1.0 mmol/L for rats and 2.6 mmol/L for humans; and the V_{max} values were about 1.4 nmol/min per mg for mice, 3.8 nmol/min per mg for rats and 0.6 nmol/min per mg for humans (Green *et al.*, 1990).

Figure 1. Metabolism of tetrachloroethylene in rats



From Dekant *et al.* (1986)
Identified urinary metabolites are underlined; percentages are those of an oral dose of 800 mg/kg bw excreted as individual metabolites.

4.1.3 Comparison of humans and animals

In one study, the blood:air partition coefficient for mice (21.5) was about twice the human value (11.6). The reason for this significant species difference is not known (Gearhart *et al.*, 1993).

Toxicokinetic modelling of the uptake and elimination of tetrachloroethylene showed that human metabolic parameters could be predicted by scaling rat metabolic parameters for tetrachloroethylene as a function of body weight (Ward *et al.*, 1988). Trichloroacetic acid and trichloroethanol have been reported as urinary metabolites of tetrachloroethylene in both humans and experimental animals. A comparison of the enzyme kinetics of hepatic conjugation of tetra-

chloroethylene with glutathione and cleavage of the cysteine *S*-conjugate by β-lyase suggested that this pathway may not be relevant for humans. Human kidney contains β-lyase activity, but biosynthesis of glutathione conjugates, a prerequisite for β-lyase activation, could not be demonstrated (Green *et al.*, 1990).

4.2 Toxic effects

4.2.1 Humans

Acute exposure to tetrachloroethylene by inhalation results in central nervous system depression. Liver and kidney toxicity have been reported as effects of acute exposures to very high doses (Reichert, 1983). In dry cleaners chronically exposed to tetrachloroethylene, increased levels of markers of early renal damage and/or dysfunction were attributed to the exposure (Mutti *et al.*, 1992).

4.2.2 Experimental systems

The acute toxicity of tetrachloroethylene is low. LD_{50} values of 6000–8571 mg/kg bw have been reported in mice after oral administration, and values of 2400–13 000 mg/kg bw have been reported in rats (Dybing & Dybing, 1946; Witey & Hall, 1975). In rats, the 6-h LC_{50} was 4100 ppm [27 798 mg/m^3] and the 8-h LC_{50} was 5000 ppm [33 900 mg/m^3]; in mice, the 4-h LC_{50} was 5200 ppm [35 256 mg/m^3] and the 6-h LC_{50} was 2978 ppm [20 191 mg/m^3]. Histopathological examination of mice 24 h after intraperitoneal injection of 4600 mg/kg bw showed minimal hepatic damage (Klaassen & Plaa, 1966). After injection of 3800 mg/kg bw, the kidneys of mice showed swelling of the proximal convoluted tubules on histological examination (Plaa & Larson, 1965).

After subchronic exposure, the major target for the toxicity of tetrachloroethylene is the liver in mice and the kidney in rats. Male and female Sprague Dawley rats that received theoretical doses of 14, 400 or 1400 mg/kg bw tetrachloroethylene per day for 90 consecutive days in their drinking-water had higher liver: and kidney:body weight ratios at the higher doses (Hayes *et al.*, 1986). In male and female Fischer 344 rats dosed orally with 1000 mg/kg bw tetrachloroethylene daily for 10 days, protein droplet accumulation in the P2 segment of the proximal tubule and increased cell replication rates were observed in males but not in females. The tritiated thymidine-labelling index was increased by two- to threefold in male rats. The cells of the P2 segment have short microvilli, relatively few, small apical vacuoles and varying amounts of protein droplets. In untreated female Fischer 344 rats, these protein droplets were rare and very small, whereas they were clearly visible in about 25% of control males. Immunohistochemical staining for $\alpha_{2\mu}$-globulin showed it to be present in these droplets, and its quantity increased when the droplets were larger and more frequent (Goldsworthy *et al.*, 1988); however, no data are available on the binding of tetrachloroethylene or its metabolites to $\alpha_{2\mu}$-globulin.

Male Swiss mice dosed by gavage with 20–2000 mg/kg bw per day of tetrachloroethylene for six weeks showed dose-related increases in their liver:body weight ratio at 100 mg/kg bw per day or more and histological effects and elevated alanine transaminase activity at 200 mg/kg bw

per day or more (Buben & O'Flaherty, 1985). Mice also developed histopathological hepatic changes after an 11-day treatment with daily oral doses as low as 100 mg/kg bw tetrachloroethylene (Schumann *et al.*, 1980). In male and female B6C3F1 mice exposed to 200 or 400 ppm [1356 or 2712 mg/m^3] tetrachloroethylene for 6 h for 14, 21 or 28 consecutive days, a two- to threefold increase in the number of peroxisomes and in the activity of peroxisomal enzymes was seen in liver. Peroxisome proliferation was more marked in male than in female mice but was not seen in Fischer 344 rats of either sex after identical treatment (Odum *et al.*, 1988).

Administration by gavage of 1000 mg/kg bw tetrachloroethylene in corn oil daily for 10 days to male Fischer 344 rats and male B6C3F1 mice resulted in peroxisome proliferation in the livers of animals of both species but in the kidneys only of mice, although the latter response was marginal (Goldsworthy & Popp, 1987).

In studies to determine the doses that could be administered chronically by inhalation to male and female Fischer 344 rats, it was found that a dose of 1750 ppm [11 865 mg/m^3] for 6 h per day for 14 days killed about one-half of the animals, whereas 875 ppm [5933 mg/m^3] was not lethal (United States National Toxicology Program, 1986). Four of 10 male and 7/20 female rats exposed to 1600 ppm [10 848 mg/m^3] for 13 weeks died before the end of the study. The incidence and severity of hepatic congestion was dose-related, this effect clearly persisting at 400 ppm [2712 mg/m^3]. In the subsequent two-year study, no remarkable treatment-related pathological effects were seen in the liver at either of the doses used (200 and 400 ppm [1356 and 2712 mg/m^3]); however, the frequency of renal enlargement and cytomegaly was increased in both males and females, particularly (but not only) in the proximal convoluted tubules and the inner half of the cortex. The incidences of karyomegaly and tubular hyperplasia are given in section 3.2.2 (p. 184).

In parallel studies with male and female B6C3F1 mice, the highest dose used during 14 days of exposure to 1750 ppm [11 865 mg/m^3], 6 h per day, was not lethal, and there was only a slight deficit in body weight gain (United States National Toxicology Program, 1986). In the 13-week study, 2/10 male and 4/10 female mice exposed to 1600 ppm [10 848 mg/m^3] died before the end of the observation period. Liver lesions (leukocyte infiltration, centrilobular necrosis and biliary stasis) were seen in males and females at 400, 800 and 1600 ppm [2712, 5424 and 10 848 mg/m^3], and karyomegaly was seen in renal tubular epithelial cells of all animals exposed to > 200 ppm [> 1356 mg/m^3]. In the subsequent two-year study, dose-related increases were observed in the prevalence of liver degeneration (both sexes), hepatocellular necrosis (both sexes) and nuclear inclusions (males only). Dose-related increases were also observed in the prevalence of renal tubular epithelial cell karyomegaly (both sexes), casts (both sexes) and nephrosis (females only).

Tetrachloroethylene has been reported to inhibit the activity of natural cytotoxic cells from liver and spleen of mice and rats after exposure *in vitro*, while only natural killer and natural P-815 killer cell activities were inhibited in rat cells (Schlichting *et al.*, 1992). Administration *in vivo* did not affect subsequently isolated immune cells. Tetrachloroethylene also inhibited the activity of natural immune cells isolated from human liver (Wright *et al.*, 1994). Direct inhibition of immune function may increase the possibility of tumour development in affected organs.

4.3 Reproductive and prenatal effects

4.3.1 Humans

(a) Endocrine and gonadal effects

The semen quality of 34 dry cleaners was compared with that of 48 laundry workers who were members of the Laundry and Dry Cleaners Union in the San Francisco Bay area and Greater Los Angeles, CA, United States (Eskenazi *et al.*, 1991a). The sperm concentrations and the overall percentage of abnormal forms were similar in the two groups. The sperm heads of dry cleaners had significantly more round forms, fewer narrow forms and showed greater amplitude of lateral head displacement and less linearity in the sperm swimming paths. These subtle effects on sperm quality were related to the concentration of tetrachloroethylene in expired air; it was not established whether these changes affected fertility.

(b) Fertility

Taskinen *et al.* (1989) conducted a nested case–control study of 120 cases of spontaneous abortion and 251 controls on the basis of a file of 6000 Finnish workers who had been biologically monitored for exposure to solvents. Information about their marriages and their wives' pregnancies and spontaneous abortions were obtained from national registries; data on paternal occupational exposure to solvents were collected by means of a questionnaire sent to workers and covered the period of spermatogenesis. The likelihood of exposure was defined in three categories: unexposed, potentially exposed (i.e. use of solvents was possible but no exposure was reported or measured) and probably exposed (i.e. exposure was measured or reported). No association was found between paternal occupational exposure to tetrachloroethylene and spontaneous abortion (crude odds ratio, 0.5; 95% CI, 0.2–1.5).

The reproductive outcomes of the wives of 17 men exposed to tetrachloroethylene in dry cleaning were compared with those of the wives of 32 laundry workers who were not exposed to dry cleaning fluids. The mean number of pregnancies was 2.1 in both groups, and the rates of spontaneous abortion were not significantly different (11.1% for dry cleaners' wives and 15.2% for laundry workers' wives; odds ratio, 2.5; 95% CI, 0.6–10.9). A small, nonsignificant, trend was seen for an association between the length of time to conception and the concentration of tetrachloroethylene in the husband's expired air (Eskenazi *et al.*, 1991a,b). [Interpretation of these findings is necessarily limited by the small sample size.]

(c) Pregnancy

(i) Spontaneous abortion

Several studies of the reproductive outcomes of women involved in dry cleaning reported specific results in relation to exposure to tetrachloroethylene.

In the nested case–control study conducted in Finland, described in detail in the monograph on dry cleaning (p.), exposure to tetrachloroethylene was assessed as high when tasks included dry cleaning for an average of at least 1 h daily or when the woman reported handling tetrachloroethylene at least once a week. Exposure was considered to be low when tasks included pressing at a dry cleaners or removing spots or when the woman reported handling tetrachloroethylene less than once a week. High exposure to tetrachloroethylene was associated

with an excess risk for spontaneous abortion (odds ratio, 3.4; 95% CI, 1.0–11.2), adjusted for use of other solvents, heavy lifting at work and frequent use of alcohol (Kyyrönen et al., 1989).

In the study of reproductive outcomes among dry cleaning workers in the Nordic countries (Olsen *et al.*, 1990), described in detail in the monograph on dry cleaning (p. 59), the authors noted that CFC-113 was increasingly used in the later years of the study. Women were grouped into three categories of potential exposure to tetrachloroethylene: no exposure, low exposure (women working in dry cleaning but who were not in the high exposure group) and high exposure (women who actually did dry cleaning or spot removal for at least 1 h per day). The combined odds ratios for spontaneous abortion, adjusted for parity, smoking and drinking habits, were 1.17 (95% CI, 0.74–1.85) for the women with low exposure and 2.88 (95% CI, 0.98–8.44) for those with high exposure. [The Working Group noted that 118 of the 159 spontaneous abortions included in the combined study occurred in Finland. The results of the Finnish study are those reported by Kyyrönen *et al.* (1989).]

The study of Bosco *et al.* (1987), described in detail in the monograph on dry cleaning (p. 60), is relevant to tetrachloroethylene. Of the 56 pregnancies occurring during employment as a dry cleaner, five ended in a spontaneous abortion, whereas one of the 46 pregnancies that occurred in women who were not employed ended in a spontaneous abortion ($\chi_2 = 3.05$, $p < 0.10$). The mean concentration of trichloroacetic acid in urine (a marker of exposure to dry cleaning solvents) was higher among cleaners (5.01 μg/L) than among women who only did ironing (1.35 μg/L) and among controls (1.56 μg/L) [standard deviations not reported].

In the study of Lindbohm *et al.* (1990), described in detail in the monograph on trichloroethylene (p. 120), the odds ratios for spontaneous abortion were 0.5 (95% CI, 0.1–2.9) for low exposure to tetrachloroethylene and 2.5 (0.6–10.5) for high exposure. The mean concentration of tetrachloroethylene in the blood samples taken nearest to the pregnancy was higher among six dry cleaning workers (2.11 μmol/L [350 μg/L]) than among seven other workers monitored for exposure to tetrachloroethylene (0.43 μmol/L [71 μg/L]).

In the study in Santa Clara County, CA (United States) (Windham *et al.*, 1991), described in detail in the monograph on trichloroethylene (p. 120), a significant association was found between exposure to tetrachloroethylene and the risk for spontaneous abortion (crude odds ratio, 4.7; 95% CI, 1.1–21.1). The odds ratio increased for women reporting more intense exposure involving skin contact, odour or symptoms (odds ratio, 6.3; $p = 0.04$). Four of the seven women who reported exposure to tetrachloroethylene had also used trichloroethylene. Odds ratios adjusted individually for maternal age, race, education, prior fetal loss, smoking, average number of hours worked and quality of response ranged from 4.2 (adjusted for number of hours worked) to 6.0 (adjusted for age).

(ii) Stillbirths, congenital malformations, low birth weight

Most early studies involved samples that were too small for investigating rare outcomes.

In the study of Kyyrönen *et al.* (1989), 24 cases of malformations in infants of dry cleaning and laundry workers were compared with 93 cases in controls. The odds ratio in relation to exposure to tetrachloroethylene during the first trimester was 0.8 (95% CI, 0.2–3.5), adjusted for exposure to other solvents, alcohol use, smoking habits and the prevalence of febrile disease.

In the Nordic study described above (Olsen *et al.*, 1990), there were 13 stillbirths, 38 cases of congenital malformations and 13 infants with low birth weights (< 1500 g). No association was found with high exposure to tetrachloroethylene (odds ratio, 0.87; 95% CI; 0.20–3.69).

(iii) Lactation and posnatal effects

Bagnell and Ellenberger (1977) reported a case of obstructive jaundice and hepatomegaly in a six-week-old breast-fed infant. Tetrachloroethylene was detected in the mother's milk and blood (see section 1.3.6, p. 175). [The Working Group noted that the levels reported are very unlikely.] After breast-feeding was discontinued, clinical improvement followed rapidly, and serum bilirubin and transaminase and alkaline phosphatase activities returned to normal values.

4.3.2 Experimental systems

Placental transfer of tetrachloroethylene has been demonstrated in rats, suggesting that tetrachloroethylene may be metabolized by the uterus, placenta or fetus, causing accumulation of trichloroacetic acid in the amniotic fluid after maternal inhalation of tetrachloroethylene (Ghantous *et al.*, 1986).

Swiss-Webster mice and Sprague-Dawley rats were exposed by inhalation to tetrachloroethylene (purity > 99%) at 300 ppm [2034 mg/m^3] for 7 h per day on days 6–15 of gestation. The mean body weight of mouse fetuses was significantly reduced in comparison with controls, and delayed ossification of the skull bones was observed. In rats, the resorption rate was significantly increased, from 4% in controls to 9% in the exposed group (Schwetz *et al.*, 1975).

Groups of about 30 Wistar and Sprague-Dawley rats and about 20 New Zealand white rabbits were exposed by inhalation to 500 ppm [3390 mg/m^3] tetrachloroethylene for 6–7 h per day during gestation. No sign of maternal toxicity, fetal toxicity or malformations was observed (Hardin *et al.*, 1981).

Neuromotor function was impaired in newborn Sprague-Dawley rats exposed *in utero* by maternal inhalation of 900 ppm [6102 mg/m^3] tetrachloroethylene for 7 h per day. No significant difference in the performance of behavioural tests was observed between the offspring of dams exposed to 100 ppm [678 mg/m^3] and those of controls (Nelson *et al.*, 1980).

4.4 Genetic and related effects

4.4.1 Humans

Cytogenetic damage in lymphocytes

Of seven male and three female factory workers occupationally exposed to tetrachloroethylene, six were employed in degreasing, with exposure to concentrations of 30–220 ppm [203–1492 mg/m^3] (geometric mean, 92 ppm [624 mg/m^3]) and work histories of 10–18 years (except for one person who had been exposed for only two years); the four others were employed in a support department, had lower exposure (range, 10–40 ppm [67.8–271 mg/m^3], with rare peaks up to 80 ppm [542 mg/m^3]), and had worked for periods of three months to three years. A control group consisted of six men and five women. No increase in the frequency of chromosomal aberrations or sister chromatid exchange and no decrease in mitotic indices or in the frequencies of second- or third-cycle metaphases were seen in cultured peripheral lymphocytes

from the workers. There was, however, a slightly higher frequency than in the controls of peripheral lymphocytes with numerical chromosomal abnormalities (2.5 versus 1.6%; $p < 0.036$). Cultured lymphocytes from the workers responded similarly to those from controls to treatment with mitomycin C with regard to the induction of sister chromatid exchange and chromosomal aberrations (Ikeda *et al.*, 1980). [The Working Group noted that no information was available on the smoking habits of the subjects.]

In the study of Seiji *et al.* (1990), described in detail the monograph on trichloroethylene (p. 123), sister chromatid exchange frequency was studied in dry cleaning workers who had been exposed to tetrachloroethylene and in tetrachloroethylene synthesis workers who were exposed to both tetrachloroethylene and trichloroethylene. An effect was reported in all smoking workers in comparison with nonsmoking controls. [The Working Group noted that the confounding effect of smoking could not be ruled out.]

4.4.2 Experimental systems (see Table 11 and Appendices 1 and 2)

The genetic toxicology of tetrachloroethylene has been reviewed (Fabricant & Chalmers, 1980; Reichert, 1983; WHO, 1984; Vainio *et al.*, 1985; Illing *et al.*, 1987; European Centre for Ecotoxicology and Toxicology of Chemicals, 1990; Jackson *et al.*, 1993). The mechanisms of the genotoxicity of tetrachloroethylene were discussed by Henschler (1987).

(a) DNA binding

Binding of radioactively labelled tetrachloroethylene to calf thymus DNA *in vitro* was reported in one study in the presence of cytosol from mouse and rat kidney, lungs and stomach, microsomes plus cytosol and liver microsomes.

No radioactivity was found in one study in purified hepatic DNA of mice treated *in vivo* with ^{14}C-labelled tetrachloroethylene (detection limit calculated as 10–14.5 alkylations per 10^6 nucleotides). In another study, radioactively labelled tetrachloroethylene bound to DNA and proteins in mouse and rat liver, kidney, lung and stomach *in vivo* (Mazzullo *et al.*, 1987), but the DNA was not purified to constant radioactivity.

(b) Mutation and allied effects

Tetrachloroethylene was not active in the SOS chromotest with *Escherichia coli* and was not mutagenic to bacteria in the absence of metabolic activation. Purified tetrachloroethylene was not mutagenic to *Salmonella typhimurium* or *E. coli* when tested in the presence of a metabolizing system prepared from rat liver microsomes; however, a doubling of revertant frequencies was seen in *S. typhimurium* TA1535 in one study at both doses tested. [The authors considered the finding to be negative.] In another study, purified tetrachloroethylene clearly increased the number of revertants in *S. typhimurium* TA100 in the presence of rat liver glutathione *S*-transferase, glutathione and kidney microsomes. This study was intended to simulate the multistep bioactivation pathway by glutathione conjugation (Vamvakas *et al.*, 1989). The mutagenicity was accompanied by time-dependent formation of *S*-(1,2,2-trichlorovinyl)glutathione, a promutagen activated by kidney microsomes, and did not occur in the absence of glutathione, glutathione *S*-transferase or kidney microsomes. Bile collected from an isolated rat liver system perfused with tetrachloroethylene was clearly mutagenic in the presence

Table 11. Genetic and related effects of tetrachloroethylene

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	–	–	8150	Mersch-Sundermann *et al.* (1989)
PRB, SOS chromotest, *Escherichia coli* PQ37	–	–	0.00	von der Hude *et al.* (1988)
PRB, λ Prophage induction, *Escherichia coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
SAF, *Salmonella typhimurium* BAL13, forward mutation (*ara* test)	–	–	76	Roldán-Arjona *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	660	Bartsch *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Connor *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[c]	–	166 vapour	Shimada *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–[d]	332	Vamvakas *et al.* (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1.3 vapour	DeMarini *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	0	50	Kringstad *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–[c]	(+)	66 vapour	Shimada *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Connor *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA5, *Salmonella typhimurium* UTH8413, reverse mutation	–	–	1000	Connor *et al.* (1985)
SA5, *Salmonella typhimurium* UTH8414, reverse mutation	–	–	1000	Connor *et al.* (1985)
ECK, *Escherichia coli* K12, forward mutation	–	–	150	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*arg*$^+$)	–	–	150	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*gal*$^+$)	–	–	150	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*nad*$^+$)	–	–	150	Greim *et al.* (1975)
SCG, *Saccharomyces cerevisiae* D7, log-phase cultures, gene conversion	+	0	1100	Callen *et al.* (1980)

Table 11 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	–	9960	Bronzetti *et al.* (1983)
SCG, *Saccharomyces cerevisiae* D7, log-phase and stationary cultures, gene conversion	–	–	2440	Koch *et al.* (1988)
SCH, *Saccharomyces cerevisiae* D7, log-phase cultures, mitotic recombination or other genetic alterations (*ade2*)	+	0	1100	Callen *et al.* (1980)
SCH, *Saccharomyces cerevisiae* D7, mitotic recombination	–	–	9960	Bronzetti *et al.* (1983)
SCR, *Saccharomyces cerevisiae* D7, log-phase cultures, reverse mutation	(+)	0	810	Callen *et al.* (1980)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	–	9960	Bronzetti *et al.* (1983)
SCR, *Saccharomyces cerevisiae* D7, log-phase and stationary cultures, reverse mutation	–	–	2440	Koch *et al.* (1988)
SCN, *Saccharomyces cerevisiae* D61.M, growing cells, aneuploidy	(+)	(+)	810	Koch *et al.* (1988)
TSM, *Tradescantia* species, mutation	+	0	7 vapour	Schairer & Sautkulis (1982)
TSI, *Tradescantia* species, micronucleus induction	–	0	600	Sandhu *et al.* (1989)
TSI, *Tradescantia* species, micronucleus induction	(+)	0	2 vapour	Sandhu *et al.* (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive mutation	–		1000 injection	Valencia *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive mutation	–		4000 feeding	Valencia *et al.* (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–[c]	0	166 vapour	Shimada *et al.* (1985)
URP, Unscheduled DNA synthesis, Osborne Mendel rat primary hepatocytes *in vitro*	–	0	0.00	Milman *et al.* (1988)
UIA, Unscheduled DNA synthesis, B6C3F1 mouse primary hepatocytes *in vitro*	–	0	0.00	Milman *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	–	–	245	US National Toxicology Program (1986)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	–	–	164	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster lung (CHL) cells *in vitro*	–	–	500	Sofuni *et al.* (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	–	–	136	Galloway *et al.* (1987)
TRR, Cell transformation, RLV/Fischer rat embryo F1706 cells *in vitro*	+	0	16	Price *et al.* (1978)
TBM, BALB/c-3T3 mouse cells, cell transformation *in vitro*	–	0	250	Tu *et al.* (1985)
HMM, Gene conversion and reverse mutation in *Saccharomyces cerevisiae* D7 recovered from liver, lungs and kidneys of CD-1 mice	–	0	11 000 po × 1	Bronzetti *et al.* (1983)

Table 11 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
HMM, Gene conversion and reverse mutation in *Saccharomyces cerevisiae* D7 recovered from liver, lungs and kidneys of CD-1 mice	0	–	2000 po × 12	Bronzetti *et al.* (1983)
DVA, DNA single-strand breaks (alkaline unwinding) in liver and kidney of male NMRI mice *in vivo*	+[e]		660 ip × 1	Walles (1986)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		88 inh	Ikeda *et al.* (1980)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		88 inh	Ikeda *et al.* (1980)
BID, Binding (covalent) to calf thymus DNA *in vitro*	0	+	9	Mazzullo *et al.* (1987)
BVD, Binding (covalent) to DNA in male B6C3F1 mouse liver *in vivo*	–		1400 inh 6 h	Schumann *et al.* (1980)
BVD, Binding (covalent) to DNA in male B6C3F1 mouse liver *in vivo*	–		500 po × 1	Schumann *et al.* (1980)
BVD, Binding (covalent) to DNA in male BALB/c mouse and Wistar rat liver, kidney, lung and stomach *in vivo*	+		1.3 ip × 1	Mazzullo *et al.* (1987)
BVP, Binding (covalent) to RNA and protein in male BALB/c mouse and Wistar rat liver, kidney, lung and stomach *in vivo*	+		1.3 ip × 1	Mazzullo *et al.* (1987)
***, Enzyme-altered foci in male Osborne Mendel rat liver *in vivo*, promotion protocol, with or without NDEA as an initiator	+		1000, 5 d/week, for 7 weeks	Milman *et al.* (1988)
***, Enzyme-altered foci in male Osborne Mendel rat liver *in vivo*, initiation protocol, phenobarbital as a promoter	–		1000	Milman *et al.* (1988)
Trichloroacetyl chloride				
PRB, λ Prophage induction, *Escherichia coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2.6	DeMarini *et al.* (1994)

NDEA, N-nitrosodiethylamine

[a] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study); 0, not tested

[b] LED, lowest effective dose; HID, highest effective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.00, dose not reported; ip, intraperitoneally; po, orally

[c] Tetrachloroethylene with stabilizers was positive with and without metabolic activation

[d] Weak increase in activity with rat liver S9, rat kidney microsomes and glutathione (GSH); fourfold increase with rat kidney microsomes, GSH and GSH S-transferase

[e] Negative in lung

***, Not included on profile

of rat kidney particulate fractions. In both assay systems, the mutagenicity was reduced by the presence of the γ-glutamyl transpeptidase inhibitor, serine borate, and the β-lyase inhibitor, aminooxoacetic acid, suggesting that the important steps in the metabolic activation of tetrachloroethylene in renal fractions are glutathione *S*-transferase-mediated glutathione conjugation, with subsequent γ-glutamyl-transpeptidase-mediated formation of an *S*-cysteine conjugate and bioactivation of the *S*-cysteine conjugate by β-lyase.

Tetrachloroethylene did not induce gene conversion, mitotic recombination or reverse mutations in yeast in stationary cultures. Both negative and positive findings were reported from studies of cultures in logarithmic growth phase, which stimulates xenobiotic metabolism; and positive results were obtained with tetrachloroethylene containing 0.01% thymol as a stabilizer. In a single study in yeast, tetrachloroethylene (analytical grade) weakly induced aneuploidy in growing cells capable of xenobiotic metabolism.

In single studies with *Tradescantia*, tetrachloroethylene [purity not given] induced mutations, and a 99% pure compound induced a slight increase in the frequency of micronuclei.

In one study with *Drosophila*, tetrachloroethylene did not induce sex-linked recessive lethal mutations.

Highly pure tetrachloroethylene did not induce unscheduled DNA synthesis in rat primary hepatocytes, and tetrachloroethylene did not induce chromosomal aberrations or (in a single study) sister chromatid exchange in Chinese hamster cells *in vitro*. It did not induce gene mutation in mouse lymphoma cells in one study, in the presence or absence of exogenous metabolic activation. In single studies, tetrachloroethylene induced cell transformation in Fischer rat embryo cells but not in mouse BALB/c-3T3 cells in the absence of exogenous metabolic activation.

In a single study, the frequency of gene conversion and reverse mutation was not increased in yeast recovered from the liver, lungs and kidneys of mice after treatment with tetrachloroethylene *in vivo*. In another study, tetrachloroethylene (purity, 99.8%) induced DNA single-strand breaks/alkaline-labile sites in mouse liver and kidney, but not lung, after treatment *in vivo*.

(c) Genetic effects of tetrachloroethylene metabolites

The genetic toxicology of dichloroacetate and trichloroacetate is reviewed in the relevant monographs in this volume.

Trichloroacetyl chloride, a presumed intermediate metabolite of tetrachloroethylene, did not induce λ prophage in *E. coli*, but was mutagenic to *S. typhimurium* TA100.

The minor urinary metabolite *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine was mutagenic to *S. typhimurium* TA100 in the presence of kidney cytosol, which allows deacylation to the corresponding cysteine conjugate (Vamvakas *et al.*, 1987). The presumed intermediate metabolite, *S*-(1,2,2-trichlorovinyl)-L-cysteine, was mutagenic to *S. typhimurium* TA100 in the presence and absence of metabolic activation (Green & Odum, 1985; Dekant *et al.*, 1986). *S*-(1,2,2-Trichlorovinyl)glutathione, the precursor of the cysteine conjugate, was also mutagenic to *S. typhimurium* TA100 in the presence of rat kidney microsomes, which catalyse its degradation to the cysteine conjugate. Both the cysteine and glutathione conjugates induced a low rate of unscheduled DNA synthesis in a cultured porcine kidney cell line (Vamvakas *et al.*, 1989).

(d) Mutations in proto-oncogenes in tumours from tetrachloroethylene-treated animals

A group of 160 male B6C3F1 mice, eight weeks of age, was administered tetrachloroethylene in corn oil by gavage at a dose of 800 mg/kg bw daily on five days per week for up to 76 weeks. There were two concurrent control groups, each consisting of 50 male mice: one was untreated, while the other received corn oil at a dose of 10 ml/kg bw. Ten control mice in each group were killed at 76 weeks, and the remainder were killed at 96, 103 and 134 weeks [numbers not stated]. At death, liver tumours ≥ 0.5 cm diameter were taken for histological examination and for oncogene analysis. At the time of the terminal kill, there were 24 untreated controls, 32 vehicle controls and 112 mice treated with tetrachloroethylene. The numbers of hepatocellular adenomas per mouse in these three groups were 0.9 ± 0.06 (8%), 0.13 ± 0.06 (13%) and 1.43 ± 0.11 (80%). The corresponding numbers of hepatocellular carcinomas were 0.09 ± 0.06 (8%), 0.12 ± 0.06 (12%) and 0.29 ± 0.05 (23%). The authors noted numerous foci of cellular alteration (presumed preneoplastic lesions) in the livers of treated mice but only rare foci in the livers of controls. No neoplasms related to treatment were found at other sites. The frequency of mutations in codon 61 of H-*ras* was significantly *reduced* in 53 hepatocellular tumours from tetrachloroethylene-treated mice in comparison with the 74 combined historical and concurrent controls (24% *versus* 69%). The spectra of these mutations showed a smaller proportion of AAA and a higher proportion of CTA in the tumours from treated mice in comparison with those of controls, but these variations were not statistically significant. Other H-*ras* mutations contributed 4% and K-*ras* mutations contributed 13% to the total in the treated mice, whereas their frequency appeared to be very low in the concurrent controls, and none were seen in the historical controls. The authors interpreted these findings as suggesting that exposure to tetrachloroethylene provides the environment for a selective growth advantage for spontaneous CTA mutations in codon 61 of H-*ras* (Anna *et al.*, 1994).

5. Summary and Evaluation

5.1 Exposure data

Tetrachloroethylene is one of the most important chlorinated solvents worldwide and has been produced commercially since the early 1900s. Most of the tetrachloroethylene produced is used for dry cleaning garments; smaller amounts are used in the production of chlorofluorocarbons and for degreasing metals. About 513 thousand tonnes were used in all applications in western Europe, Japan and the United States in 1990.

Tetrachloroethylene has been detected in air, water, food and animal and human tissues. The greatest exposure occurs via inhalation, and workers in dry cleaning and degreasing are the most heavily exposed. Individuals living or working in the vicinity of such operations have been shown to be exposed to lower concentrations.

5.2 Human carcinogenicity data

Results relevant to assessing the relationship between exposure to tetrachloroethylene and cancer risk are available from five cohort studies. In one study in Finland and one in four states of the United States, exposure was specifically to tetrachloroethylene; biological monitoring was conducted in the Finnish study. In a cohort study in Missouri, United States, in which follow-up was from 1948 to 1978, tetrachloroethylene was the chemical to which predominant exposure had occurred since about 1960. Data for a few cancer sites were reported in two other cohort studies, one in Louisiana and one in Utah, United States, in which exposure was to both tetrachloroethylene and other chemicals. Although data on different levels or duration of exposure were available in some of the cohort studies, the number of observed cases in each category was generally too small to allow adequate statistical power for testing for a dose–response relationship. Data from six relevant case–control studies have also been reported.

In the two cohort studies in which results for oesophageal cancer were reported, namely the four-state United States and Missouri studies, the relative risks were 2.6 and 2.1. Lack of data on smoking or alcohol consumption, both strong risk factors for this cancer, indicates caution in interpreting this observation.

The relative risks for cervical cancer were increased in three cohort studies in which such results were reported; however, potential confounding factors associated with socioeconomic status could not be adjusted for.

Elevated relative risks for non-Hodgkin's lymphoma were observed in all three cohort studies in which such results were reported.

With respect to cancer of the kidney, no consistent pattern of elevated risk was seen in the three cohort studies in which such results were reported. Although a case–control study conducted in Montréal, Canada, showed an odds ratio of 3.4, this was not statistically significant, and the exposure in question was to degreasing solvents and not specifically to tetrachloroethylene. In the cohort study in Missouri, the relative risk for urinary bladder cancer was elevated but not statistically significant; little or no information was available from other studies.

Five studies of people exposed to drinking-water contaminated with tetrachloroethylene have been reported. In four of these, no consistent pattern of risk for any specific cancers was observed. In the fifth study, in Massachusetts, United States, although the increase in the relative risk for leukaemia was significant, the result was based on only two cases. No consistent evidence for an elevated risk for leukaemia was seen in the cohort studies.

In summary, there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma. These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total numbers in the cohort studies combined are relatively small.

5.3 Animal carcinogenicity data

Tetrachloroethylene was tested for carcinogenicity by oral administration in one experiment in mice, and a significant increase in the incidence of hepatocellular carcinomas was observed in animals of each sex. A study in rats treated orally was inadequate for an evaluation of carcino-

genicity. Tetrachloroethylene was tested for carcinogenicity by inhalation in one experiment in mice and in one experiment in rats. The incidence of hepatocellular adenomas and carcinomas was significantly increased in mice of each sex, and the incidence of mononuclear-cell leukaemia was significantly increased in rats of each sex. A nonsignificant increase in the incidence of uncommonly occurring renal-cell adenomas and adenocarcinomas was also observed in male rats. Tetrachloroethylene did not induce skin tumours in mice after administration by topical application in one study.

A presumed metabolite of tetrachloroethylene, tetrachloroethylene oxide, did not increase the incidence of local tumours in mice when given by topical application or subcutaneous injection.

5.4 Other relevant data

Tetrachloroethylene is rapidly absorbed after inhalation and from the gastrointestinal tract, but dermal absorption from the gaseous phase is negligible. The biotransformation of tetrachloroethylene is species- and dose-dependent; mice consistently had a greater capacity to biotransform tetrachloroethylene than rats. Two metabolic pathways have been demonstrated in rodents: cytochrome P450-catalysed oxidation and, as a minor route, glutathione conjugation.

Tetrachloroethylene shows only low acute toxicity in humans and in experimental animals. After repeated administration, the major target organ is the liver in mice and the kidney in rats. Tetrachloroethylene induced peroxisome proliferation in mouse liver after oral administration; a marginal response was observed in mouse kidney and rat liver.

Disturbances of sperm quality and fertility have been observed among dry cleaners exposed to tetrachloroethylene in a few studies of limited size. The results of studies of women exposed to tetrachloroethylene in dry cleaning shops and other settings are generally consistent in showing an increase in the rate of spontaneous abortions; however, other solvents were also present in most of these workplaces. Effects on other reproductive outcomes such as stillbirths, congenital malformations and low birth weight could not be evaluated in these studies.

Tetrachloroethylene can cross the placenta of rats and is metabolized in the placenta or fetus to trichloroacetic acid. Tetrachloroethylene appears to have little toxicity in developing rats and rabbits; high atmospheric concentrations produced delayed fetal development in mice in one study.

The frequencies of gene conversion and gene mutation were not increased in yeast recovered from mice treated with tetrachloroethylene *in vivo*. Tetrachloroethylene increased the frequency of DNA single-strand breakage/alkaline-labile sites in the liver and kidney of mice *in vivo* in one study, but binding to DNA was not demonstrated in mouse liver.

It did not induce gene mutation (in a single study), chromosomal aberrations, sister chromatid exchange (in a single study) or DNA damage in mammalian cells *in vitro*. In single studies, it induced morphological transformation in virus-infected rat embryo cells but not in BALBc/3T3 cells. The only study available showed no induction of gene mutation by tetrachloroethylene in insects. Tetrachloroethylene did not usually induce gene conversion in yeasts; the results with regard to induction of aneuploidy in one study were inconclusive. Tetrachloroethylene did not increase the frequency of mutations in bacteria, except in one study

in which a metabolic activation system consisting of liver and kidney fractions, which favours glutathione conjugation and further activation, was used. The metabolites formed from tetrachloroethylene in rats by minor biotransformation pathways, *S*-1,2,2-trichloroglutathione and derived sulfur conjugates, were genotoxic in bacteria and cultured renal cells.

The frequency of H-*ras* mutations was lower in hepatocellular tumours from tetrachloroethylene-treated mice than in tumours from control animals, whereas the frequency in hepatocellular tumours from trichloroethylene-treated mice was not significantly different from that in controls. The frequency of K-*ras* mutations was higher in liver tumours from tetrachloroethylene-treated mice than in tumours from control animals.

5.5 Evaluation[1]

There is *limited evidence* in humans for the carcinogenicity of tetrachloroethylene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetrachloroethylene.

Overall evaluation[2]

Tetrachloroethylene *is probably carcinogenic to humans (Group 2A).*

In making the overall evaluation, the Working Group considered the following evidence:

(i) Although tetrachloroethylene is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferation and tumour formation in the liver after administration of tetrachloroethylene by inhalation. The spectrum of mutations in proto-oncogenes in liver tumours from mice treated with tetrachloroethylene is different from that in liver tumours from mice treated with trichloroethylene.

(ii) The compound induced leukaemia in rats.

(iii) Several epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma and cervical cancer.

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[1] For definitions of the italicized terms, see Preamble, pp. 22–26.

[2] Dr N.H. Stacey disassociated himself from the overall evaluation.

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