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TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME OTHER CHLORINATED AGENTS

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International Agency for Research on Cancer

World Health Organization

TETRACHLOROETHYLENE

Tetrachloroethylene was considered by previous IARC Working Groups in 1979, 1987, and 1995 (IARC, 1979, 1987, 1995). New data have since become available and these have been taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

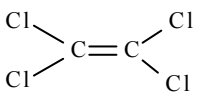
Chem. Abstr. Serv. Reg. No.: 127-18-4

Chem. Abstr. Name: Tetrachloroethene

IUPAC Systematic Name: Tetrachloroethylene

Synonyms: Ethylene tetrachloride; PCE; 'per'; PER; PERC; 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

Description: Colourless, nonflammable liquid; ethereal odour (O'Neil *et al.*, 2006)

Boiling-point: 121 °C (O'Neil *et al.*, 2006)

Melting-point: –22 °C (O'Neil *et al.*, 2006)

Density: 1.6230 at 20 °C/relative to H_2O at 4 °C (O'Neil *et al.*, 2006)

Spectroscopy data: Infrared (prism [5422]; grating [469]), ultraviolet [1485] and mass [1053] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

Solubility: Slightly soluble (0.206 g/L at 25 °C; HSDB, 2012); miscible with alcohol, ether, chloroform, benzene (O'Neil *et al.*, 2006); soluble in ethanol, diethyl ether and benzene (Haynes, 2012)

Volatility: Vapour pressure, 1 kPa at 10 °C (Haynes, 2012)

Stability: Photo-oxidized in air with sunlight (half-time, about 12 hours), giving phosgene and trichloroacetyl chloride (EPA, 1982; Hickman, 1993)

Reactivity: Incompatible with chemically active metals such as barium, lithium and beryllium, and with sodium hydroxide, potash and strong oxidizers (NIOSH, 1994)

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

Conversion factor: mg/m^3 = 6.78 × ppm, calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa).

1.1.4 Technical products and impurities

Tetrachloroethylene is available commercially in several grades, including a vapour degreasing grade, a dry-cleaning grade, an industrial grade for use in formulations, a high-purity low-residue grade, a spectrophotometric grade, and a grade specifically formulated for use as a transformer fluid (IARC, 1995; ATSDR, 1997a). It typically has a purity of 95% or more for dry-cleaning and industrial grades, 99% or more for more refined grades, and 99.995% for isomerization and fluorocarbon grades. The various grades differ in the amount and type of stabilizers added to prevent decomposition (ATSDR, 1997a).

Trade names for tetrachloroethylene include Ankilostin, Antisol 1, Didakene, Dow-per, Dilatin PT, Fedal-Un, Nema, Perawin, Perchlor, Perclene, Percosolv, Perklone, PerSec, Tetlen, Tetracap, Tetraleno, Tetralex, Tetravec, Tetroguer and Tetropil (IARC, 1995; Doherty, 2000a; EPA, 2013).

1.1.5 Analysis

Several methods for the analysis of tetrachloroethylene in air, solids, liquids, water, and food were reviewed by WHO (1984), EPA (1985), Greenberg *et al.* (1992) and Demeestere *et al.* (2007). Selected methods for the analysis of tetrachloroethylene in various matrices are presented in Table 1.1.

1.2 Production and use

1.2.1 Production process

(a) Manufacturing processes

Tetrachloroethylene was first prepared in 1821 by Michael Faraday using thermal decomposition of hexachloroethane (Doherty, 2000a). For many years, the most important process for producing tetrachloroethylene was from acetylene via trichloroethylene, but because of the increasing price of acetylene feedstock in the 1970s, newer processes involving direct chlorination or oxychlorination of other hydrocarbons were introduced (ATSDR, 1997a).

(b) Production volume

Production of tetrachloroethylene in Japan, western Europe and the USA reached its peak in the 1980s (Linak *et al.*, 1992). In 1992, annual capacity was 10 000 tonnes in Austria, 30 000 tonnes in Belgium, 62 000 tonnes in France, 100 000 tonnes each in Germany and in Italy, 21 000 tonnes in Spain, 130 000 tonnes in the United Kingdom of Great Britain and Northern Ireland, 96 000 tonnes in Japan and 223 000 tonnes in the USA (Linak *et al.*, 1992). In 2007, the USA was the largest consumer of tetrachloroethylene (43% of demand), followed by western Europe (19%), China (10%) and Japan (9%) (Glauser & Ishikawa, 2008).

1.2.2 Use

In the 1950s, about 80% of tetrachloroethylene was used in dry-cleaning, and 15% in metal-cleaning and vapour degreasing (Doherty, 2000a). By the 1980s, the pattern was changing as a result of the establishment of environmental regulations and improved technology, and about 50% of tetrachloroethylene was used for dry-cleaning, 28% for chemical intermediates (mostly for production of fluorocarbons), and 10–15% for metal cleaning and degreasing

Table 1.1 Methods for the analysis of tetrachloroethylene

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Air collected in specially-prepared canister; desorb	GC/MS	NR	EPA (1999a)
		GC/ECD	NR	
		GC/FID	NR	
		GC/PID	NR	
	Analyte collected on sorbent tube; thermally desorb to GC from cold trap	GC/MS	NR	EPA (1999b)
		GC/ECD	NR	
		GC/FID	NR	
		GC/PID	NR	
Water	Purge with inert gas and trap; desorb to GC	GC/PID	0.05 µg/L	EPA (1988, 1995a)
		GC/HECD	0.04 µg/L	
	Purge with inert gas and trap; desorb to GC	GC/PID	0.01 µg/L	EPA (1988)
	Purge with inert gas and trap; desorb to GC	GC/MS	0.05 µg/L	EPA (1988, 1995b)
	Extract with methyl-*t*-butyl ether or pentane	GC/ECD	0.002 µg/L	EPA (1995c)
Liquid and solid wastes	Purge with inert gas and trap	GC/PID	0.05 µg/L	EPA (1996a)
		GC/HECD	0.04 µg/L	
	Purge with inert gas and trap; and various other methods	GC/MS	5 µg/kg (soil/ sediment)	EPA (1996b)
			500 µg/kg (wastes)	
			5 µg/L (groundwater)	
Blood	Purge with inert gas and trap on Tenax	GC/MS	0.022 ppb	Ashley *et al.* (1992)

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

(Linak *et al.*, 1992; Doherty, 2000a). The relative proportions used for dry-cleaning and chemical production have continued to shift, with more than 50% being used as intermediates and 15% for dry-cleaning in the 1990s (ATSDR, 1997a). Currently the most common use of tetrachloroethylene is as a feedstock for producing fluorocarbons (Glauser & Ishikawa, 2008).

(a) Dry-cleaning industry

Since the 1950s, tetrachloroethylene has been the most commonly used dry-cleaning solvent (Doherty, 2000a). Tetrachloroethylene is ideally suited for dry-cleaning as it is nonflammable and a good degreaser that does not saturate the fabric fibres, thus avoiding swelling and shrinking of the fabric (Linak *et al.*, 1992; NICNAS, 2001).

By the 1960s, almost all dry-cleaning facilities in the USA used tetrachloroethylene, and this continued until the 1990s (Doherty, 2000a). In 2007, tetrachloroethylene was used by about 70% of dry-cleaners in the USA (State Coalition for Remediation of Drycleaners, 2009). It is currently used by two thirds of dry-cleaners in Denmark, and 90% of dry-cleaners in France (ECSA, 2012).

Technological changes in dry-cleaning machines are well documented for the USA (Earnest, 2002), Europe (von Grote *et al.*, 2003; Johansen *et al.*, 2005), and Australia (NICNAS, 2001). Before the 1960s, most machines were transfer types for which the clothes (which had been immersed in tetrachloroethylene) were moved manually from the washer to the dryer.

In the 1960s, dry-to-dry machines were invented that did not require manual transfer. In addition, the newer machines were equipped with carbon absorbers and did not vent into the atmosphere. Improvements in recycling dry-cleaning solvents in closed machines have meant that more than 95% of tetrachloroethylene is recovered in these modern machines. However, in practice, the replacement of the transfer machines took about two decades. In a study in New Jersey communities in 1984, dry-to-dry machines were present in 75% of the facilities included (Garetano & Gochfeld, 2000).

Alternatives for tetrachloroethylene have been developed, including 1-bromopropane, carbon dioxide, hydrocarbon solvents, and propylene glycol ether in response to restrictions on the use of tetrachloroethylene in the dry-cleaning industry (California EPA, 2008).

(b) Metal-degreasing in the automotive and metal industries

Tetrachloroethylene is used as a degreasing agent in vapour and liquid forms. It dissolves many organic compounds (including pitches and waxes) and inorganic compounds, and can be used to clean metal parts. Tetrachloroethylene is used as a solvent in aerosol products for cleaning tyres, brakes, engines, carburettors and wire; in 2004, such uses accounted for 12% of the total use of tetrachloroethylene in the USA (TURI, 2006). These aerosol automotive products may be used by the public, as well as by professionals.

Tetrachloroethylene has been used in cleaning products for electrical equipment; these products can be applied by spraying, brushing or dipping (NICNAS, 2001).

(c) Other industrial applications

(i) Chemical intermediates

Currently the most common use of tetrachloroethylene is as a feedstock for the production of chlorofluorocarbons and hydrofluorocarbons. Under the Montreal Protocol on Substances that Deplete the Ozone Layer of the 1990s, production of chlorofluorocarbons is being phased out by 2030 due to their contribution to ozone depletion (Doherty, 2000a).

(ii) Textile industry

In textile processing, tetrachloroethylene is used as a solvent to remove oils from fabrics after knitting and weaving operations, and as a carrier solvent for scouring, sizing and desizing, and for fabric finishes and water repellents. Tetrachloroethylene is able to dissolve fats, greases, waxes, and oils without harming natural or synthetic fibres (IARC, 1995).

(iii) Printing industry

Flexographic printing is a method that is similar to letterpress printing, but uses flexible plates. Tetrachloroethylene is used to clean unpolymerized coatings from the flexible film. The cleaning is performed in automated enclosed machinery (NICNAS, 2001). Tetrachloroethylene has also been used in printing inks (EPA, 2013).

(iv) Miscellaneous

There are several other uses of tetrachloroethylene (NICNAS, 2001), including for testing in the coal industry; as a source of chlorine in the catalytic reforming process in petroleum refineries; to clean prints and negatives of cinema film; in typewriter correction fluid; in carpet stain-removal products; and as an antihelminthic agent (O'Neil *et al.*, 2006).

1.3 Occurrence and exposure

1.3.1 Natural occurrence

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

1.3.2 Environmental occurrence

Tetrachloroethylene is a volatile organic compound that is widely distributed in the environment due to industrial emissions. Potential environmental exposure to tetrachloroethylene in air, rainwater, surface water, and drinking-water has been reviewed (ATSDR, 1997a). The partitioning tendency of tetrachloroethylene in the environment has been calculated as follows: air, 99.7%; water, 0.3%; soil, < 0.01%; sediment, < 0.01% (Boutonnet *et al.*, 1998).

(a) Air

Measurement data from remote North American sites indicate that background concentrations of tetrachloroethylene have decreased since 1995 by more than 5% per year (McCarthy *et al.*, 2006).

Table 1.2 presents some recent data on concentrations of tetrachloroethylene in air, measured worldwide in remote, rural, suburban, and urban sites, and in indoor air near dry-cleaning shops.

(b) Water

Tetrachloroethylene occurs at low concentrations in drinking-water supplies and frequently occurs as a contaminant of groundwater, owing to its widespread use and physical characteristics. Table 1.3 presents recent measurements of concentrations of tetrachloroethylene in surface waters, groundwater and drinking-water.

(c) Food

As a part of the Total Diet Study in the USA, 20 samples of 70 different foods purchased in supermarkets or restaurants were analysed for tetrachloroethylene during 1996–2000. Tetrachloroethylene was found at low concentrations (up to 102 µg/kg) in 29 out of 70 food items (Fleming-Jones & Smith, 2003).

In a survey of 35 samples of whole milk from Las Vegas, NV, USA, tetrachloroethylene was found at a mean concentration of 0.09 µg/L (range, < 0.01–0.39) (Hiatt & Pia, 2004).

The average concentration of tetrachloroethylene in 4 out of 17 samples of brown grease from food-preparation facility grease traps was 2771.1 µg/L (range, 31.5–8510 µg/L) (Ward, 2012).

1.3.3 Occupational exposure

The National Occupational Exposure Survey conducted between 1981 and 1983 by the United States National Institute for Occupational Safety and Health (NIOSH, 2013) estimated that about 688 000 workers in a wide range of industries, notably dry-cleaning, textiles, metals, automotive, printing and cleaning, were potentially exposed to tetrachloroethylene in the USA at that time. This estimate was based on a survey of products used in companies in 1981–1983 and did not involve actual measurements.

The European CAREX project estimated the number of exposed workers in 15 countries of the European Union (EU-15) to be approximately 820 000 in the early 1990s. Most exposures occurred in dry-cleaning shops (Kauppinen *et al.*, 2000). An update of CAREX for Italy by Mirabelli & Kauppinen (2005) showed a negligible increase in the number of workers exposed, from 102 500 to 106 300, for 1990–1993 and 2001, respectively (excluding jobs flagged as low-level or low confidence).

The number of exposed individuals in Germany in the dry-cleaning industry only was estimated to total almost 25 700 in 1975, decreasing considerably to about 5900 in 2001. This was mainly due to a reduction in the number of garments being dry-cleaned and, to a lesser extent, the replacement of tetrachloroethylene by nonchlorinated solvents. Merging of smaller shops into larger facilities also decreased the number of dry-cleaning machines by 77% (von Grote *et al.*, 2006).

Table 1.4 presents exposure to tetrachloroethylene in the dry-cleaning industry by country and

Table 1.2 Concentrations of tetrachloroethylene in air

Location	Concentration (μg/m³)		Comments	Reference
	Mean	Range		
Outdoor air				
Remote				
Antarctica	NR	0.032–0.075	Five remote sites	Zoccolillo *et al.* (2009)
Atlantic Ocean	NR	NR–30 ppt	Background tropospheric levels	Class & Ballschmiter (1986)
North America	0.022	0.015–0.029	Remote background concentration	McCarthy *et al.* (2006)
Urban and rural				
Canada	0.19	0.015–2.44	Near 74 homes	Zhu *et al.* (2005)
North Rhine – Westphalia, Germany	NR	0.03–7.33	Over four seasons at two sites	Begerow *et al.* (1996)
Italy	NR	0.109–0.719	Twelve rural sites	Zoccolillo *et al.* (2009)
	NR	0.461–4.314	Four urban & suburban sites	
Leipzig, Germany	0.01	NR	At seven sites	Gokhale *et al.* (2008)
Shizuoka Prefecture, Japan	0.11[a]	0.05–0.32	Near 25 homes	Ohura *et al.* (2006)
Hyogo Prefecture, Japan	NR	0.07–0.28	At six sites	Okada *et al.* (2012)
Tarragona, Spain	0.67	NR–1.0	Near large industrial complex	Ramírez *et al.* (2012)
Endicott, NY, USA	NR	0.1–24	Above contaminated soil	Forand *et al.* (2012)
Minneapolis, MN, USA	0.8	0.2–1.7	Near 284 households	Adgate *et al.* (2004)
Five cities, USA	NR	0.858–4.34	24-hour air concentration	Rappaport & Kupper (2004)
Dallas, TX, USA	[2.2]	[1.4–13]	Ambient air near gas wells	Rich (2011)
Minnesota, USA	0.44	< 0.21–25.08	25 sites in state (1991–1998)	Pratt *et al.* (2000)
Seattle, WA, USA	0.21	NR	Ambient air at six sites	Wu *et al.* (2011)
Indoor air				
Ottawa, ON, Canada	1.15	0.015–9.23	In 75 homes	Zhu *et al.* (2005)
France	1.3[b]	0.4–72	In 490 homes	Billionnet *et al.* (2011)
North Rhine-Westphalia, Germany	NR	0.10–50.04	Over four seasons at two sites	Begerow *et al.* (1996)
Leipzig, Germany	0.33	NR	In homes	Gokhale *et al.* (2008)
Shizuoka Prefecture, Japan	0.16[a]	0.06–0.34	In 25 homes	Ohura *et al.* (2006)
Minneapolis, MN, USA	3.5	0.5–5.2	In 284 homes	Adgate *et al.* (2004)
New Jersey, USA	NR	< 1.4–540	Urban and suburban homes	Weisel *et al.* (2008)
Near dry-cleaning shops				
France	NR	20–2900	Indoor air	Chiappini *et al.* (2009)
Mulheim, Germany	1360[b]	< 10–> 10 000[c]	Indoor air	Altmann *et al.* (1995)
New York, NY, USA	35	3–5000	Indoor air	McDermott *et al.* (2005)
New York, NY, USA	2150	1800–2400	Indoor air	Schreiber *et al.* (2002)
New York, NY, USA	340[a]	127–700	Indoor air	New York State Department of Health (2010)

[a] Geometric mean
[b] Median
[c] Read from graph
ppt, parts per trillion

Table 1.3 Concentrations of tetrachloroethylene in water

Country	Location	Concentration µg/L		Comments	Reference
		Mean	Range		
Ground and surface water					
China	Eastern China	NR	NR–35.6	Groundwater at five sites	Bi *et al.* (2012)
Croatia	Sašnak	16.28	9.08–21.35	Groundwater samples, 1995–1996	Vedrina-Dragojević & Dragojević (1997)
Europe	Southern North Sea	0.023	NR–0.280[a]	Ten locations, 1998–2000	Huybrechts *et al.* (2005)
Greece	Northern Greece	NR	< 0.02–0.19	Surface water	Kostopoulou *et al.* (2000)
Taiwan, China	Country-wide	NR	2–21	Groundwater near eight contaminated sites	Fan *et al.* (2009)
	Taoyuan City	520	0.1–5228	Groundwater near contaminated site	Lee *et al.* (2002)
USA	Bush River, MD	NR	30–90	Contaminated surface water near Aberdeen Proving Grounds	Burton *et al.* (2002)
	Minnesota	NR	1–120	Groundwater near hazardous waste disposal sites	Sabel & Clark (1984)
	Cape Cod, MA	NR	1.5–7750	Leaching into drinking-water from pipes	Janulewicz *et al.* (2008)
	Camp Lejune, NC	NR	NR–1580 ppb	Contaminated groundwater	Sonnenfeld *et al.* (2001)
	Country-wide	NR	0.02–4800	5000 groundwater samples, 1985–2002	Moran *et al.* (2007)
Drinking-water					
USA	Camp Lejune, NC	153	2–400	*Drinking-water*	NRC (2009)

NR, not reported; ppb, parts per billion

time period. Gold *et al.* (2008) reported average personal exposures of 59 ppm for dry-cleaning workers in the USA in 1936–2001. Lynge *et al.* (2011) provided insight into temporal trends in exposure to tetrachloroethylene in Nordic countries over a 60-year period. In the mid-1970s, personal exposures were reported as a median concentration of about 20 ppm, and this decreased to about 3 ppm in 2000. Stationary measurements indicated concentrations up to 100 ppm in the 1950s and 1960s (see Fig. 1.1). Recent studies in Egypt and the Islamic Republic of Iran showed that high exposures in dry-cleaning still occur, with concentrations of 100 ppm in air reported in both countries (Azimi Pirsaraei *et al.*, 2009; Emara *et al.*, 2010; Rastkari *et al.*, 2011).

Exposure to tetrachloroethylene in other industries and occupations (mainly degreasing, particularly in the metal and plastics industries) is summarized in Table 1.5, presented by industry and country. Gold *et al.* (2008) reported average concentrations for personally measured exposure among workers degreasing metal and plastics in the USA to be 95 ppm during 1944–2001. In these industries, exposure levels have decreased by two orders of magnitude over a 60-year period.

Concentrations of tetrachloroethylene in blood among workers in dry-cleaning and other industries are summarized in Table 1.6. For studies on biological monitoring of urine for trichloroacetic acid, a metabolite of tetrachloroethylene,

Table 1.4 Exposures to tetrachloroethylene in dry-cleaning shops

Country (year)	No. of plants	Job/task/industry	No. of samples	Air concentration				Reference
				Mean		Range		
				ppm	mg/m³	ppm	mg/m³	
Europe								
Belgium	6	Dry-cleaning	26 subjects (P) TWA	20.8	141	8.9–37.5	60–254	Lauwerys *et al.* (1983)
Finland (1982–85)	6	Dry-cleaning	10 (S) TWA	13	88	3–29	20–197	Rantala *et al.* (1992)
Finland	6 shops 3 industrial	Dry-cleaning operators shops		4.1	28	NR	NR	Räisänen *et al.* (2001)
		Operators, industrial		4.6	32	NR	NR	
		Pressers, shops		1.1	7.7	NR	NR	
		Presser, industrial		0.5	3.4	NR	NR	
		Customer-service shops	6 (P) TWA	0.1	0.8	NR	NR	
Europe; Nordic countries (1947–2001)		Dry-cleaning (total)	609 (S)	11.92		NR		Lynge *et al.* (2011)
			687 (P)	7.27		NR		
		Dry-cleaner	461 (P)	7.50		NR		
		Shop assistant	104 (P)	6.25		NR		
France	26	Dry-cleaning	> 100 per shop	NR	NR	0–100	0–678	Davezies *et al.* (1983)
France (1989–1990)	36	Dry-cleaning operator	5–10 per shop[a]	17.3	117.3	NR–100	NR–678	Anon (1991)
Germany		Dry-cleaning	19 workers		62 (end of wk)		16–672	Pannier *et al.* (1986)
			55 (P)		43 (following Monday)		NR	
Germany		Dry-cleaners	101 workers (P) TWA		205		NR	Seeber (1989)
Germany (1987, 1989)	15	Dry-cleaning	75 (S)		45% > 50		3.1–331	Gulyas & Hemmerling (1990)
					33% > 100		NR	
					9% > 200		NR	
Germany (1993–1994)	21	Dry-cleaning operator	100		7.4		< 0.02–27	Klein & Kurz (1994)
Italy	47	Dry-cleaning	143 workers	11.3	77	1–80.8	7–548	Missere *et al.* (1988)
Italy (1992–93)	28	Dry-cleaning	60 workers[b]					Aggazzotti *et al.* (1994)
			(P) TWA		NR		2.6–221.5	
			(S)		36		0.19–308	

Table 1.4 (continued)

Country (year)	No. of plants	Job/task/industry	No. of samples	Air concentration				Reference
				Mean		Range		
				ppm	mg/m³	ppm	mg/m³	
Italy	12	Dry-cleaning	(P) TWA Group A (19 workers) Group B (14 workers)	 4.35 0.66		 0.21–23.4 0.01–6.2		Gobba *et al.* (1997)
Italy	7	Dry-cleaning shops	26 workers		44.2		5.6–224.6	Gobba *et al.* (2003)
Netherlands (1976)	1	Dry-cleaning	48 (5 workers)	6.7	45	3.7–25.9	25–176	van der Tuin & Hoevers (1977a)
Netherlands (1977)	1	Dry-cleaning	86 (10 workers)	41.3	280	11–101	75–685	van der Tuin & Hoevers (1977b)
Netherlands (1978)	1	Dry-cleaning	80 (9 workers)	59.7	405	10.0–250	68–1695	van der Tuin (1979)
Netherlands	4	Dry-cleaning, industrial	82 workers		7.9 (extrapolated from biomonitoring values)		1–221	Verplanke *et al.* (1999)
Norway	1	Dry-cleaning shop Offshore	13 (P) long-term 4 (P) short-term		6.7 69		4.2–11 28–177	Steinsvåg *et al.* (2007)
Switzerland	10	Dry-cleaning	49 workers (P) 1 wk	18.5	125			Boillat *et al.* (1986)
United Kingdom	90	Dry-cleaning shops	333 (P)	74% < 30 88% < 50 97% < 100	203 339 678			Shipman & Whim (1980)
	41	Dry-cleaning factories	160 (P)	53% < 30 76% < 50 93% < 100	203 339 678			
United Kingdom (1990–91)	81	Dry-cleaning operator	405 (P) TWA	22.5	153	0–360	0–2441	Edmondson & Palin (1993)

Table 1.4 (continued)

Country (year)	No. of plants	Job/task/industry	No. of samples	Air concentration				Reference
				Mean		Range		
				ppm	mg/m³	ppm	mg/m³	
Middle East and Asia								
Egypt		Dry-cleaning shops	40 workers (S)	< 140		NR		Emara *et al.* (2010)
Islamic Republic of Iran	69	Dry-cleaning shops	179 workers					Azimi Pirsaraei *et al.* (2009)
		Machine operator	71 workers (P)	11.5		0.6 –81		
		Presser	63 workers (P)	9.6		0.6 –132.3		
		Clerk	45 workers (P)	7.2		0.6–51		
Islamic Republic of Iran		Dry-cleaning shops	30 workers					Rastkari *et al.* (2011)
			10 (8 kg machines) (P)		31.04		NR	
			10 (12 kg machines) (P)		50.87		NR	
			10 (18 kg machines) (P)		120.99		NR	
Japan	3	Dry-cleaning	56 workers TWA	20	136	3.8–94.4	26–640	Cai *et al.* (1991)
Republic of Korea	8	Dry-cleaning shops	8 (S)		4.2		NR	Jo &Kim. (2001)
North America								
USA		Dry-cleaners, commercial	19 (S) (12 workers)	91.5	621	31–270	210–1831	Kerr (1972)
		Dry-cleaners, coin-operated	11 (S) (4 workers)	125	848	87–264	590–1790	
USA		Dry-cleaning area	3 (S)	33	222	21–48	142–325	Eddleston & Polakoff (1974)
		Spotter and dry cleaners	4 (P)	62	420	10–171	68–1160	
USA		Dry-cleaners	96 (P)	41	278	5–125	34–848	Center for Chemical Hazard Assessment (1985)
USA (1975)		5 machine operators	(S)	37.2	252	12.2–62.2	83–422	Tuttle *et al.* (1977)
		2 pressers		11.4	77	4.6–18.3	31–124	
		5 counters		1.3	9	0.4–2.3	3–16	
		7 miscellaneous		3	20	0.9–5.1	6–35	
		5 machine operators	(P)	20.5	139	2.3–38.7	16–262	
		2 pressers		4.48	30	4.1–4.9	28–33	
		5 counters		0.95	6.4	0.3–1.6	2–11	
		7 miscellaneous		2	14	0–4.3	0–29	

Table 1.4 (continued)

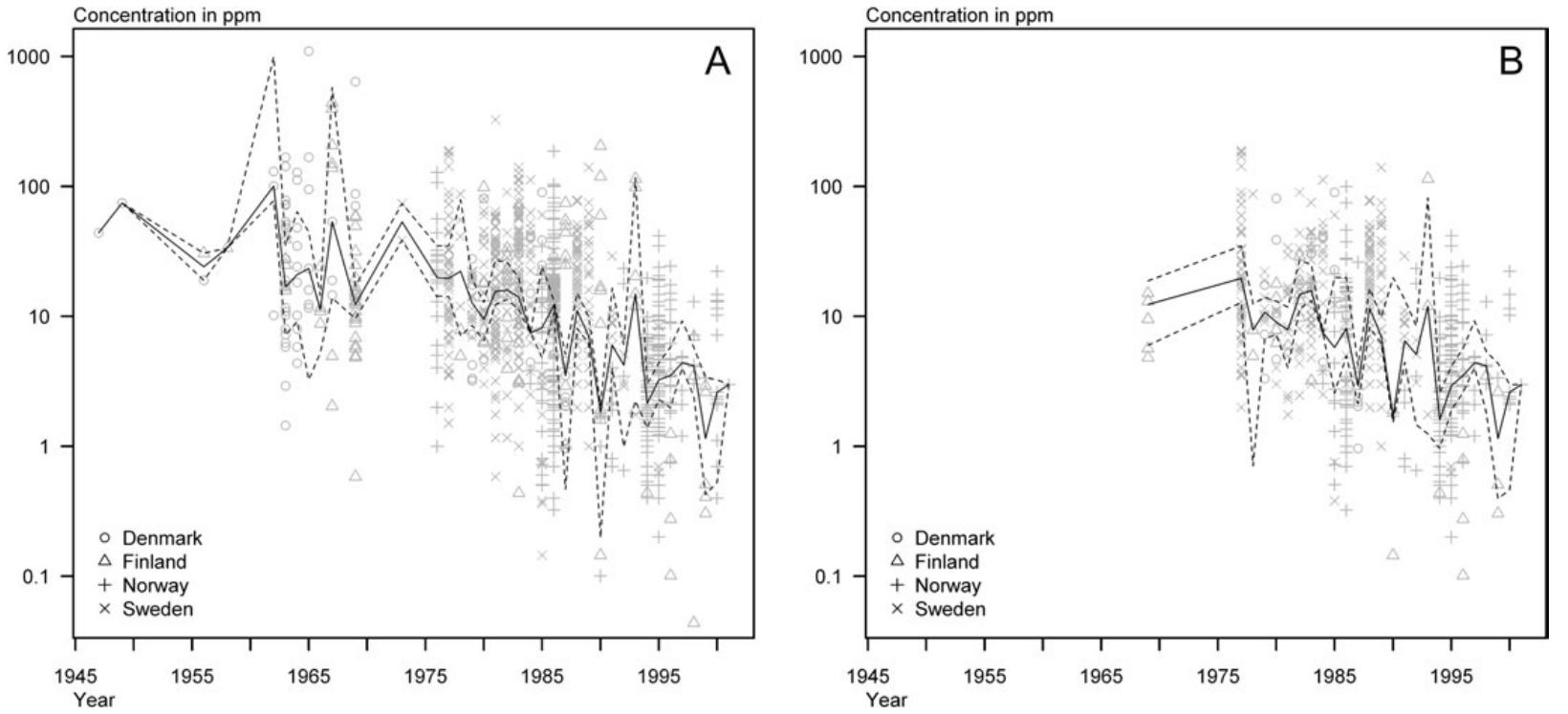
Country (year)	No. of plants	Job/task/industry	No. of samples	Air concentration				Reference
				Mean		Range		
				ppm	mg/m³	ppm	mg/m³	
USA (1977–79)	44	Machine operator	45 (P) TWA	31[c] 22[d]	210[c] 149[d]	4.0–149	27–1010	Ludwig (1981), Ludwig *et al.* (1983)
	35	Presser	52 (P) TWA	5.7[c] 3.3[d]	39[c] 22[d]	0.1–37	0.7–251	
	12	Seamstress	12 (P) TWA	6.6[c] 3[d]	45[c] 20[d]	0.6–29	4–197	
	31	Counter area	31 (P) TWA	5.9[c] 3.1[d]	40[c] 21[d]	0.3–26	2–176	
	39	Machine operator during transfer	134 (P) 5-min peak	76[c] 44[d]	515[c] 298[d]	3.3–366	22–2482	
	30	Machine operator during transfer	49 (P) 15-min peak	55[c] 33[d]	373[c] 224[d]	1–269	7–1824	
USA	44	Washer to dryer transfer	175 (S)	95.8	650	1.0–775	7–5255	NIOSH (1981)
		Counter area	39 (S)	4.8	33	0.3–26.4	2–179	
		Dry-cleaning area	36 (S)	32.8	222	0.5–177	3.4–1200	
		Washer area	25 (S)	22	169	2.0–91	14–617	
		Pressing area	26 (S)	6	41	0.2–40	1.4–271	
		Spotting area	14 (S)	12.3	83.4	0.9–35	6.1–237	
USA (1982)	17	Transfer	(P) TWA	86.6	587	28.5–302.7	193–2053	Materna (1985)
			(P) 5-min peak	135.9	921	11.3–533.8	77–3620	
	3	Dry-to-dry	(P) TWA	28.2	191	3.0–75.9	20–515	
USA (1984)	1	Dry-cleaning (transfer process)	2 (P) TWA	54.5	370	45–64	305–434	Pryor (1985)
			10 (P) 15-min ceiling	306	2075	68–597	461–4049	
USA (1985)	1	Dry-cleaning (dry-to-dry process)	4 (S) TWA		119		79–135	Burr & Todd (1986)

Table 1.4 (continued)

Country (year)	No. of plants	Job/task/industry	No. of samples	Air concentration				Reference
				Mean		Range		
				ppm	mg/m³	ppm	mg/m³	
USA (1980s)		Transfer				NR	NR	International Fabricare Institute (1987)
	471	Machine operator	TWA	49.8	338			
	43	Counter person, etc.		16.7	113			
	57	Spotter, finisher		18.1	123			
		Dry-to-dry						
	157	Machine operator		23.2	157			
	16	Counter person, etc.		10.8	73			
	24	Spotter, finisher		12.1	82			
USA		Dry-cleaning	34 workers (P)		7.9		0.002–55	Eskenazi *et al.* (1991)
USA	10	Operator/presser in dry-cleaning (transfer and dry-to-dry)	60 (P) (13 workers)	10	68	0.17–58.24	1.2–395	Petreas *et al.* (1992)
USA	4		35 (P) (18 workers)	3.15		NR		McKernan *et al.* (2008)
USA (1936–2001)		Dry-cleaning, all job titles	1395 (P)	59		0–4636		Gold *et al.* (2008)
			481 (S)	54		0–1648		
		Operator transfer	441 (P)	150		0–1000		
		Operator (dry-to-dry)	149 (P)	19		0.3–257		
		Spotter	72 (P)	6.6		0.01–39		
		Presser/seamstress	179 (P)	5.6		0.1–52		
		Counter clerk	92 (P)	3.4		0–15		
USA	7		18 workers	3.8		NR		Tucker *et al.* (2011)

[a] Worst-case sampling (highest exposed worker)
[b] Six to eight spot samples taken at each plant
[c] Arithmetic mean
[d] Geometric mean
min, minute; NR, not reported; P, personal air sample; S, stationary air sample; TWA, time-weighted average

Fig. 1.1 Air concentrations of tetrachloroethylene in dry-cleaning shops in the Nordic countries



A All measurements, 1947–2001
B Personal measurements, 1969–2001
The straight and dotted lines represent the median and 95% confidence intervals, respectively.
From Lynge *et al.* (2011), by permission of Oxford University Press

Table 1.5 Exposures to tetrachloroethylene in industries and occupations other than those associated with dry-cleaning

Country, time Period	No. of plants	Job, task or industry	No. of samples	Air concentration [mg/m³]		Reference
				Mean	Range	
Poland	1	Repair rubber belts in brown coal mining	13 (P)	0.6	0.1–5.5	Gromiec *et al.* (2002)
Republic of Korea	90	Solvent workshops in 90 factories	173 (P)	[27.2] (GM)	[2.2]–[5629]	Moon *et al.* (2001)
USA	60	Degreasing (11 non-condensing machines)	68	[1498]	[163–5966]	Morse & Goldberg (1943)
	8	Degreasing	14	[1220] (work in)	[170–2102]	Crowley *et al.* (1945)
			24	[3282] (work out)	[542–12 204]	
	1	Degreasing, auto industry	Short-term	NR	[1573–2610]	Coler & Rossmiller (1953)
	1	Degreasing, printing plates	4 (S)	78	25–99.3	Pryor (1977)
			2 (P)	57	28–86.4	
	1	Degreasing, medical equipment	3 (S)	[106]	[48–197]	Tharr & Donahue (1980)
	1	Degreasing	6 (P)	[271]	[34–1180]	Burgess (1981)
	1	Degreasing, foundry	1 (P)	86.1	NR	Hartle & Aw (1984)
			3 (S)	130.3	40.9–250	
	1	Cutlery manufacture, blade degreasing	2 (P)	[115]	[104–126]	Center for Chemical Hazard Assessment (1985)
	1	Electroplating	5 (P)	[753]	[557–1253]	Daniels & Kramkowski (1986)
	1	Plating, degreasing	1 (P)	11	NR	Abundo *et al.* (1994)
			1 (S)	2	NR	
	NR	Degreasing metal and plastics	206 (P)	95 ppm	0–1800	Gold *et al.* (2008)
			49 (S)	2.3 ppm	0.1–37	
	1	Polyether urethane foam, car industry	3 (S)	2.1	0.4–4.2	White & Wegman (1978)
			9 (P)	4.2	< 0.05–8.0	
	1	Urethane foam	3 (S)	0.6	0.344–0.714	Costello (1979)
	1	Protective coatings	11	[2.7]	[ND–27]	Burroughs (1980)
	1	Filling aerosol cans with carburettor cleaner	30 (S)	[311]	[31–1248]	Hervin *et al.* (1972)
			30 (P)	[403]	[104–1010]	
	1	Coal-testing laboratory	1 (P)	[1010]	NR	Jankovic (1980)
			Several (S)	NR	[746–1315]	
	1	Automotive brake manufacture	11 (P)	103	10–350	Hervin & Lucas (1973)
			11 (S)	145	10–350	

Table 1.5 (continued)

Country, time Period	No. of plants	Job, task or industry	No. of samples	Air concentration [mg/m³]		Reference
				Mean	Range	
USA (cont.)	1	Specialty packaging	4 (P)	[4]	[1.4–5.4]	Hanley (1993)
			5 (S)	[15]	[1.8–41]	
	1	Rubber moulding	15 (P)	[17.6]	[ND–36]	Cook & Parker (1994)
			1 (S)	[8]	NR	
	14	Motion-picture film processing	119 (P)	189	2.7–1606	Mosely (1980)
			51 (S)	111	2.2–965	
	1	Spray painting	9 (P)	21.4	4.4–50	Hartle & Aw (1983)
	1	Automotive parts, fasteners	2 (S)	1.3	1.1–1.5	Ahrenholz & Anderson (1982)
	1	Motion-picture film processing	4 (S)	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 (S)	0.29	< 0.01–0.88	
	1	Taxidermy	9 (P)	403	< 0.01–1546	Gunter & Lybarger (1979)

NR, not reported; ND, not detected; P, personal air sample (breathing zone); S, stationary air sample

Table 1.6 Biomonitoring of occupational exposure to tetrachloroethylene

Country Year of study	Job/Task	Number of subjects	Air concentrations Mean (range)	Blood concentrations Mean (range)	Reference
Finland 1974–83	Various	3976	NA	Men, 0.12 mg/L Women, 0.07 mg/L	Anttila *et al.* (1995a)
Germany 1992	Dry-cleaners	12	NR	NR (0.20–3.10) mg/L	Popp *et al.* (1992)
Italy	Dry-cleaners	26	44.2 (5.6–224.6) mg/m^3	725.6 (96.8–3303) µg/L	Gobba *et al.* (2003)
Republic of Korea 1993	Metal degreasers	13	22.4 (0–61) ppm	0.85 (0.2–2.5) mg/L	Jang *et al.* (1993)
USA 2008	Dry-cleaners (4 facilities)	18 women	3.15 ppm	0.07 mg/L pre-shift	McKernan *et al.* (2008)

NA, not applicable; NR, not reported

the reader is referred to the *Monograph* on trichloroacetic acid in this Volume.

1.3.4 Exposure of the general population

Exposure to tetrachloroethylene has been measured in several populations not exposed occupationally, primarily in Germany and the USA (Table 1.7). While concentrations are generally low, living near a dry-cleaning facility considerably increases the level of exposure (Altmann *et al.*, 1995; Schreiber *et al.*, 2002; Storm *et al.*, 2011).

In a study of breast milk in the USA, tetrachloroethylene was detected in seven out of eight samples analysed (Pellizzari *et al.*, 1982).

1.4 Regulations and guidelines

Tetrachloroethylene has been registered on the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) of the European Commission (ECHA, 2013). Allowable time-weighted averages range from 70 mg/m^3 in Denmark and Sweden, to 345 mg/m^3 in some other European countries (Table 1.8). The European Union recommendation for an occupational exposure limit (OEL) according to the Scientific Committee on Occupational Exposure Limits (SCOEL) is 20 ppm for workers (European Commission, 2009). The American Conference of Governmental Industrial Hygienists (ACGIH, 2002) has established a threshold limit value (TLV) of 25 ppm and biological exposure indices (BEIs) of 5 ppm in end-exhaled air collected before the last shift of the working week, 0.5 mg/L in blood collected before the last shift of the working week, and 3.5 mg/L as trichloroacetic acid in urine collected at the end of the working week.

The state of California, USA, has started to phase out the use of tetrachloroethylene for dry-cleaning, and any new uses have been banned as from 2008, while use in pre-existing machines is to be discontinued by 2023 (California EPA, 2008). No information on bans in any other countries was available to the Working Group.

2. Cancer in Humans

In the previous evaluation by the *IARC Monographs* IARC (1995), the Working Group concluded that tetrachloroethylene was *probably carcinogenic to humans* (Group 2A) based on *limited* evidence in humans and *sufficient*

Table 1.7 Population exposures to tetrachlorethylene

Country Year of study	Subjects	No. of subjects	Age (years)	Blood concentrations			Personal air sample	Reference
				Mean	Range	Measurable %		
Croatia	General population	38	26–62	0.07 µg/L	0–2.54 µg/L	82%	–	Skender *et al.* (1993)
Germany	No known occupational exposure	39	23–52	0.4 µg/L median	< 0.1–3.7µg/L	95%	–	Hajimiragha *et al.* (1986)
Germany	Living above dry-cleaners	29	6–76	106 µg/L	< 6.5–1330 µg/L	–	–	Popp *et al.* (1992)
Germany	Living above dry-cleaners	19	NR	17.8 µg/L	NR	NR	NR	Altmann *et al.* (1995)
Germany		191	Children (5–7 yr)	0.02 µg/L	< 0.004–0.131	NR	NR	Begerow *et al.* (1996)
		223	Adult women	0.05 µg/L	0.01–6.34			
	Not near dry-cleaners	86 urban		0.05 µg/L	0.01–0.80			
		127 rural		0.04 µg/L	0.01–0.05			
	Near dry-cleaners	5 urban		0.33 µg/L	0.09–6.34			
		4 rural		0.45 µg/L	0.15–2.41			
USA	NHANES III	590	20–59	0.19 ppb	ND–0.62 ppb	–	–	Ashley *et al.* (1994)
USA	NHEXAS	147	Adult	0.21 µg/L	NR	39%	–	Clayton *et al.* (1999)
USA	Living near dry-cleaners	10	NR	6.43 µg/L (afternoon)	1.1–18	NR	948 µg/m^3 (daytime)	Schreiber *et al.* (2002)
			NR	4.87 µg/L (morning)	1.1–7	NR	420 µg/m^3 (overnight)	
USA		73	Children	NR	NR	NR	3.7 µg/m^3	Adgate *et al.* (2004)
USA, 1981–87	Bayonne	139	Adults	NR	NR	NR	7.8	Rappaport & Kupper (2004)
	Elizabeth	191					8.9	
	Greensboro	24					3.1	
	Devils Lake	23					5.2	
	Los Angeles	179					7.1	

Table 1.7 (continued)

Country Year of study	Subjects	No. of subjects	Age (years)	Blood concentrations			Personal air sample	Reference
				Mean	Range	Measurable %		
USA	SHIELD	113	6–10	0.03 µg/L	NR	37–62%	–	Sexton *et al.* (2005)
USA	Live near dry-cleaners; indoor air	11	Adult	1.28 µg/L	–	–	–	Storm *et al.* (2011)
		7	Child	0.51 µg/L				
	> 100 µg/m³	39	Adult	0.13 µg/L				
	Live near dry-cleaners; indoor air	28	Child	0.11 µg/L				
	< 100 µg/m³	39	Adult	0.05 µg/L				
	Not living near dry-cleaners	32	Child	0.03 µg/L				
USA	NHANES	2940	12–59	NR	LOD–0.17 µg/L	–	–	CDC (2013)

LOD, limit of detection; NR, not reported

Table 1.8 Regulations and guidelines for tetrachlorethylene

Country or region	TWA concentration (mg/m³)	Carcinogenicity[a]
Australia	340	–
Austria	345	–
Belgium	172	–
Canada, Quebec	170	–
Denmark	70	–
Europe GHS	–	H351
European classification	–	R40
France	138	–
Germany AGS	138	–
Germany TRGS	–	K3
Germany MAK	–	3B
New Zealand	335	–
Singapore	170	–
Spain	172	–
Sweden	70	–
Switzerland	345	–
USA OSHA	170	A3
ACGIH	25	–
NTP	–	Reasonably anticipated
United Kingdom	345	–

[a] Carcinogenicity: H351, suspected of causing cancer; R 40, limited evidence of a carcinogenic effect; K3, substances which possibly are carcinogenic for humans and thus give cause for concern; 3B, substances which are proved/possibly carcinogenic and therefore give reason for concern; Group C, possible human carcinogen; A3, confirmed animal carcinogen with unknown relevance to humans
ACGIH, American Conference of Governmental Industrial Hygienists; EPA, Environmental Protection Agency; GHS, Global Harmonization System; MAK, maximum occupational concentrations; NTP, National Toxicology Program; OSHA, Occupational Safety and Health Administration; TRGS, Technical rules for hazardous substances; TWA, 8-hour time-weighted average
From GESTIS (2012)

evidence in experimental animals. In studies in humans, associations occurred with cancers of the oesophagus, cervix, and with non-Hodgkin lymphoma, but confounding could not be entirely excluded. No consistent pattern of elevated risk was observed for cancer of the kidney.

A substantial body of literature on the epidemiology of cancer and exposure to tetrachloroethylene was available to the Working Group and included both cohort and case–control studies. The two designs complement each other in that cohort designs typically provide a narrower range of occupations for exposure assessment than do case–control designs, while case–control studies are able to control for some important potential confounders. While many cancers have been evaluated, there has been a focus on lymphatic and haematopoietic cancers, and tumours of the urinary tract. Exposure assessments range from simple job-title determinations to quantitative assessments. While tetrachloroethylene has been used in several occupations, including vehicle repair, other mechanics, printers, and electricians, it is particularly associated with dry-cleaning (see Section 1). In many workplaces where tetrachloroethylene is used, other chlorinated solvents can also be found. There is some overlap between exposures to tetrachloroethylene and trichloroethylene in studies evaluated for this *Monograph*; this complicated the interpretation of study findings, but it should be remembered that nearly all workplaces have multiple exposures.

The Working Group did not consider in its evaluation several studies that reported results only for "laundry and dry-cleaning workers" combined (Malker & Weiner, 1984; McLaughlin *et al.*, 1987; Lynge & Thygesen, 1990; Minder & Beer-Porizek, 1992; Lynge *et al.*, 1995; Andersen *et al.*, 1999; Travier *et al.*, 2002; Pukkala *et al.*, 2009). Similarly, studies based on occupations coded on death certificates that combined laundry and dry-cleaning workers (Katz & Jowett, 1981; Duh & Asal, 1984; Nakamura, 1985; Walker *et al.*, 1997) were also considered to be uninformative with regard to tetrachloroethylene exposure. Launderers typically handle soap and other chemical cleaning agents, while persons engaged in dry-cleaning work have used different types of chlorinated solvents, mainly tetrachloroethylene, supplemented with trichloroethylene and fluorocarbons (Andersen *et al.*, 1999). Since the exposure assessment was not specific to tetrachloroethylene, this would consequently result in a dilution of the magnitude of any observed effect.

2.1 Cohort studies

Most of the studies of cohorts exposed to tetrachloroethylene focused on dry-cleaning and related occupations. However, a few cohorts of non-dry-cleaning workers are discussed in Section 2.1.2. In addition to studies that characterized exposure by employment in occupation or industry categories combining "laundry and dry-cleaning," the Working Group also excluded studies of exposure to mixed solvents without further distinction.

2.1.1 Dry-cleaning workers

Tetrachloroethylene became the most commonly used dry-cleaning solvent in the 1950s, replacing carbon tetrachloride, which was considered to be more toxic, and trichloroethylene, which was harsher on fabrics (Ludwig, 1981; IARC, 1995; Doherty, 2000a, b). Large studies of cohorts of dry-cleaning workers have been conducted in Europe and the USA. Because of the large number of small shops with a few employees each and the high turnover in this industry, the United States National Cancer Institute (NCI) cohort was assembled through union records (Blair *et al.*, 1979; Blair *et al.*, 1990, 2003), as was the NIOSH cohort (Brown & Kaplan, 1987; Ruder *et al.*, 1994, 2001; Calvert *et al.*, 2011), while most of the European studies, with the exception of Anttila *et al.* (1995a, b), Lynge *et al.* (2006) and Seldén & Ahlborg (2011), used census records linked to cancer-registry or mortality data. None of the cohort studies of dry-cleaning workers assessed exposure to tetrachloroethylene directly. Table 2.1 presents the most recent results of cohort studies on eight cancer sites of interest: cancers of the lung, kidney, bladder, liver, breast, cervix, oesophagus, and lympohaematopoietic system (Hodgkin disease, non-Hodgkin lymphoma, multiple myeloma, and leukaemia).

The NCI cohort study enrolled members of a union of dry-cleaning workers in Missouri, USA, which had 11 062 members between 1945 and 1978, of whom 5790 had held membership for 1 year or more. After exclusion of 425 members for whom information on race, sex, or date of birth was unavailable, the analysis was restricted to 5365 members who were followed from entry to the union or on 1 January 1948 (whichever came later) until 1 January 1979: follow-up was extended to 31 December 1993 for the most recent update and included 5369 members (Blair *et al.*, 2003). The cohort provided 146 082 years of follow-up until 1993 and expected numbers of deaths were calculated from national rates. The mortality rate was as expected for all causes combined (standardized mortality rate [SMR], 1.0; 95% CI, 1.0–1.1; 2351 deaths), but slightly higher than expected for cancer (SMR, 1.2; 95% CI, 1.1–1.3; 590 deaths). Excesses were found for cancers of the oesophagus (SMR, 2.2; 95%

Table 2.1 Cohort studies of occupational exposure to tetrachloroethylene

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bond *et al.* (1990), Michigan, USA 1940–82	44 (liver cancer deaths)	Employees from chemical plant; company work records	Liver, gallbladder or bile ducts (ICDA-8 155–156 and 197.8)	Exposed to tetrachloroethylene	6	1.8 (0.8–4.3)	Age
Anttila *et al.* (1995a) Finland 1967–92	849	All workers biologically monitored for tetrachloroethylene in blood. Median: women, 0.4 µmol/L; men, 0.7 µmol/L	Kidney	Exposed to tetrachloroethylene	2	1.82 (0.22–6.56)	SIR. Occupation not specified "tetrachloroethylene was used in dry-cleaning, and to a small extent also in degreasing and in the graphic industry"
			Lymphohaematopoietic tissues (200–204)		3	1.38 (0.28–4.02)	
			Non-Hodgkin lymphoma (200, 202)		3	3.76 (0.77–11.0)	
			Multiple myeloma (203)		0	–	
			Cervix uteri (171)		2	3.20 (0.39–11.6)	
			Lung, bronchus (162.0–162.1)		5	1.92 (0.62–4.48)	
Boice *et al.* (1999), California, USA 1960–66	2631	Aircraft-manufacturing workers. JEM without quantitative estimate of intensity, 1987–1988, 8-h TWA, tetrachlorethylene concentration (atmospheric monitoring): 3 ppm [mean] and 9.5 ppm [median]	Oesophagus (150)	Routine exposure to tetrachlorethylene	6	1.47 (0.54–3.21)	SMR. Employed ≥ 1 year from 1960 onwards; 30% exposed to tetrachlorethylene and probably other solvents also
			Cervix uteri (180)		0	0.47 expected cases	
			Kidney (189.0–189.2)		2	0.69 (0.08–2.47)	
			Bladder and other urinary tract (188, 189.3–189.9)		2	0.70 (0.09–2.53)	
			NHL (200, 202)		8	1.70 (0.73–3.34)	
			Hodgkin disease (201)		0	0.63 expected cases	
			Bronchus, trachea, and lung (162)		46	1.08 (0.79–1.44)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Blair *et al.* (2003) Missouri, USA 1948–93	5369	Dry-cleaning workers: occupational history from union records	Kidney (189)	Overall	8	1.0 (0.4–2.0)	SMR adjusted for age at death, year of death, race, and sex. Reference was population of USA.
				Little/no exposure	1	0.3 (< 0.1–1.6)	
				Medium/high exposure	7	1.5 (0.6–3.1)	
			Bladder (188)	Overall	12	1.3 (0.7–2.4)	
				Little/no exposure	5	1.4 (0.4–3.2)	
				Medium/high exposure	7	1.5 (0.6–3.1)	
			Liver (155)	Overall	10	0.8 (0.4–1.5)	
			Breast (174)	Overall	68	1.0 (0.8–1.3)	
				Little/no exposure	30	0.8 (0.6–1.2)	
				Medium/high exposure	29	1.2 (0.8–1.7)	
			Lymphatic, haematopoietic	Overall	39	1.0 (0.7–1.3)	
				Little/no exposure	18	1.0 (0.6–1.5)	
				Medium/high exposure	17	0.9 (0.5–1.4)	
			NHL (200, 202)	Overall	12	0.9 (0.5–1.6)	
			Hodgkin disease (201)	Overall	5	2.0 (0.6–4.6)	
			Multiple myeloma (203)	Overall	7	0.8 (0.3–1.6)	
			Leukaemia (204–207)	Overall	12	0.8 (0.4–1.4)	
			Oesophagus (150)	Overall	26	2.2 (1.5–3.3)	
				Little/no exposure	7	2.1 (0.9–4.4)	
				Medium/high exposure	16	2.2 (1.2–3.5)	
			Cervix (180)	Overall	27	1.6 (1.0–2.3)	
				Little/no exposure	12	1.5 (0.8–2.7	
				Medium/high exposure	11	1.4 (0.7–1.7)	
		Overall	Lung		125	1.4 (1.1–1.6)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Lynge *et al.* (2006) Denmark, Finland, Norway, Sweden 1970–2001	46 768 (695 dry-cleaner and other exposed; 183 other in dry-cleaning; 2420 unexposed)	Laundry and dry-cleaning workers identified from the 1970 censuses in Denmark, Norway, Sweden, and Finland; duration of employment assessed through pension scheme data (Denmark, Finland) and biography of dry-cleaning shop owners & yellow pages of telephone books (Denmark)	Bladder cancer (excluding *in situ*)	Dry-cleaning workers	93	1.44 (1.07–1.93)	RR adjusted for matching criteria and, where relevant, for smoking and alcohol use. Case–control study nested in Nordic cohort; three controls per case randomly selected from cohort matched on country, sex, age, calendar period at diagnosis time.
Radican *et al.* (2008) USA 1973–2000	14 455 (851 ever exposed to tetrachloroethylene)	Aircraft-maintenance workers from Hill Air Force Base, Utah; employed > 1 yr; 1952–1956, JEM (intensity), internal referent (workers with no chemical exposures)	Lymphatic & haematopoietic (men)	Any exposure to TETRA	14	1.92 (1.00–3.69)	Age, race HR for mortality. Lung cancer mortality not reported.
			NHL (men)		5	2.32 (0.75–7.15)	
			NHL (women)		2	2.35 (0.52–10.71)	
			Multiple myeloma (men)		3	1.71 (0.42–6.91)	
			Multiple myeloma (women)		2	7.84 (1.43–43.06)	
			Lung		NR	–	
			Non-malignant respiratory diseases (men)		46	1.83 (1.28–2.60)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Calvert *et al.* (2011) California, Illinois, Michigan, New York, USA 1940–2004	1704	Dry-cleaners: occupational history from union records	Kidney (189)	Overall	5	1.1 (0.4–2.7)	SMR. Reference was population of USA. All employed in plant using tetrachloroethylene at least 1 year by 1960
				TETRA only	2	1.4 (0.2–4.9)	618 workers exposed to tetrachloroethylene only
			Bladder (188)	Overall	10	1.8 (0.9–3.3)	
				TETRA only	0		
				Employed < 5 years; < 20 years since first employed	0		*P* by employment duration, 0.12
				Employed ≥ 5 years; < 20 years since first employed	0	–	
				Employed < 5 years; ≥ 20 years since first employed	1	0.5 (0.03–2.5)	
				Employed ≥ 5 years; ≥ 20 years since first employed	9	4.1 (2.1–7.1)	
			Liver, biliary tract (155, 156)	Overall	1	0.1 (0.0–0.7)	
				TETRA only	0	–	
			Breast (174)	Overall	28	1.1 (0.7–1.5)	
				TETRA only	10	1.1 (0.5–1.9)	
			Lymphatic, haematopoietic	Overall	19	0.9 (0.5–1.4)	
				TETRA only	11	1.5 (0.8–2.7)	
			NHL (200, 202)	Overall	11	1.6 (0.8–2.8)	
				TETRA only	6	2.5 (0.9–5.4)	
			Oesophagus (150)	Overall	16	2.4 (1.4–4.0)	
				TETRA only	6	2.7 (0.98–5.8)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Calvert et al. (2011) California, Illinois, Michigan, New York, USA 1940–2004 (cont.)				Employed < 5 years; < 20 years since 1st employed	0	–	*P* by employment duration, 0.09
				Employed ≥ 5 years; < 20 years since first employed	0	–	
				Employed < 5 years; ≥ 20 years since first employed	5	2.2 (0.9–4.5)	
				Employed ≥ 5 years; ≥ 20 years since first employed	11	4.8 (2.7–7.9)	
			Cervix (180)	Overall	13	1.8 (0.98–3.1)	
				TETRA only	5	2.1 (0.7–4.9)	
				Employed < 5 years; < 20 years since first employed	2	0.8 (0.2–2.7)	*P* by employment duration, 0.66
				Employed ≥ 5 years; < 20 years since first employed	4	2.6 (0.9–6.0)	
				Employed < 5 years; ≥ 20 years since first employed	4	2.8 (0.9–6.3)	
				Employed ≥ 5 years; ≥ 20 years since first employed	3	2.1 (0.6–5.4)	
		Overall	Lung		77	1.3 (1.0–1.6)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Seldén & Ahlborg (2011) Sweden 1985–2006	9440	Questionnaire mailed to all "washing establishments" on company workers for past 11 years, production volumes, washing techniques, chemicals used (1973–1983): TETRA group = subgroup of dry-cleaners and laundries with a proportion of dry-cleaning with tetrachloroethylene only	Liver, gallbladder (155)	TETRA group (men)	8	2.14 (0.92–4.21)	SIR; cancer incidence study; no information on exposure at the company or individual level was available, but estimates of the proportion of tetrachloroethylene and other detergents employed (as reported by the companies over the period of interest) were used as proxy; response rate, 38%; no data on workers from nonresponding companies.
				Employed < 1 year	0	0	
				1–4 years	3	3.19 (0.66–9.31)	
				5–11 years	5	2.06 (0.67–4.80)	
			Breast (174)	TETRA group (women)	140	0.85 (0.72–1.00)	
			Hodgkin disease (201)	TETRA group (men)	3	3.22 (0.66–9.40)	
			Non-Hodgkin lymphoma (200, 202)	TETRA group [men & women]	[33]	[1.42 (0.98–2.0)]	
				employed < 1 year	[10]	[3.28 (1.57–6.03)]	
				1–4 years	[7]	[1.03 (0.41–2.12)]	
				5–11 years	[16]	[1.20 (0.69–1.95)]	
			Oesophagus (150)	TETRA group (women)	3	1.25 (0.26–3.65)	
			Cervix (171)	TETRA group (women)	16	1.19 (0.64–1.93)	
				Employed < 1 year	1	0.32 (0.01–1.78)	
				1–4 years	8	1.72 (0.74–3.40)	
				5–11 years	7	1.24 (0.50–2.56)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Seldén & Ahlborg (2011) Sweden 1985–2006 (cont.)			Lung (162)	TETRA group (men)	23	1.30 (0.82–1.94)	
				TETRA group (women)	35	1.09 (0.76–1.51)	
			Liver	Dry cleaner	11	0.76 (0.38–1.52)	
			Cervix	Dry cleaner	36	0.98 (0.65–1.47)	
			Kidney	Dry cleaner	29	0.67 (0.43–1.05)	

HR, hazard ratio; JEM, job-exposure matrix; NHL, non-Hodgkin lymphoma; NR, not reported; TETRA, tetrachloroethylene; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCE, trichloroethylene; TWA, time-weighted average

CI, 1.5–3.3; 26 deaths), lung (SMR, 1.4; 95% CI, 1.1–1.6; 125 deaths), cervix uteri (SMR, 1.6; 95% CI, 1.0–2.3; 27 deaths) and bladder (SMR, 1.3; 95% CI, 0.7–2.4; 12 deaths), and for Hodgkin disease (SMR, 2.0; 95% CI, 0.6–4.6; five deaths). There was no excess of cancer of the liver or of the kidney (see Table 2.1). The risk of cancer of the oesophagus was highest for African-American men (SMR, 3.1; 95% CI, 1.9–5.0; 18 deaths). Exposure assessment was based on the published literature, applied to the job titles in the union records. The relative risk for cancer of the oesophagus for all cohort members was not related to the estimated exposure level; for those with little or no exposure it was 2.1; for those with medium or high exposure it was 2.2. There were 18 deaths from lymphatic and haematopoietic malignancies among those with little or no exposure (SMR, 1.0) and 17 (SMR, 0.9) among those with medium or high exposure. When mortality was compared by year of joining the union (before or after 1960, when tetrachloroethylene became the predominant solvent used), there was no difference at most sites except bladder, for which the SMR for those joining the union before 1960 was 1.1 (95% CI, 0.5–2.0, nine deaths), and for those joining after 1960 the SMR was 2.9 (95% CI, 0.6–9.5, three deaths). [The size of the cohort and the extended follow-up made this a valuable study. There was little evidence of an exposure–response effect, but the Working Group noted that the higher mortality for cancer of the bladder after the introduction of tetrachloroethylene supported the involvement of an occupational rather than a lifestyle risk factor. The Working Group also noted, however, that mortality from cancer of the oesophagus was in excess, possibly supporting an effect of smoking.]

The NIOSH cohort included 1704 unionized dry-cleaning workers from four cities in California, Illinois, Michigan and New York, USA. The inclusion criteria were: employment for at least 1 year before 1960 in a shop where tetrachloroethylene was the primary solvent used, and no known exposure to carbon tetrachloride. A survey in 1977–79 (Brown & Kaplan, 1987) showed geometric mean, time-weighted average concentrations of tetrachloroethylene in the range of 3–22 ppm (20.3–149 mg/m^3); other solvents used for spot cleaning were not detected in the samples. Visits were made to many of the facilities that were still operating, and data on solvent use and solvent levels were collected (Ludwig, 1981). These monitoring data, and the job-title information available for about one third of the NIOSH cohort, were not used to create a job-exposure matrix for the NIOSH study, but were used to verify exposure to tetrachloroethylene and other solvents used in dry-cleaning, and to exclude workers who had been exposed to carbon tetrachloride or trichloroethylene.

In the analyses, two subcohorts were defined: people employed only in shops where tetrachloroethylene was the primary solvent used, and people whose work also involved exposure to other solvents. The most recent update added mortality follow-up until 31 December 2004, accounted for 94% of the women and 97% of the men, and generated 63 426 person-years at risk, but did not extend employment follow-up (Calvert *et al.*, 2011). The mean duration of employment in dry-cleaning shops until 31 December 1990 was 6.4 years for those exposed only to tetrachloroethylene and 11.4 years for those also exposed to other solvents; the latter group had a mean duration of 6.0 years of exposure to tetrachloroethylene. Expected numbers of deaths were calculated from the national death rates. There were 1255 deaths (SMR, 1.0; 95% CI, 1.0–1.1) and 322 cancer deaths (SMR, 1.2; 95% CI, 1.1–1.4). The SMRs were significantly increased for cancers of the oesophagus (SMR, 2.4; 95% CI, 1.4–4.0; 16 deaths), tongue (SMR, 4.5; 95% CI, 1.5–10; five deaths), and trachea, bronchus and lung (SMR, 1.3; 95% CI, 1.0–1.6; 77 deaths). Mortality from cancer of the pancreas was elevated (SMR, 1.5; 95% CI, 1.0–2.3; 22 deaths). When the analysis was restricted to workers with a 20-year latency

since first employment and with a duration of employment > 5 years, the SMRs were increased for cancers at all sites combined (SMR, 1.3; 95% CI, 1.2–1.5; 130 deaths) and, notably, for cancers of the oesophagus (SMR, 4.8; 95% CI, 2.7–8; 11 deaths) and urinary bladder (SMR, 4.1; 95% CI, 2.1–7; nine deaths). There were also three cancers of the tongue (SMR, 3.5; 95% CI, 0.73–10). Only one death from cancer of the liver and biliary tract was found (with 7.7 expected). The SMR for chronic obstructive pulmonary disease was 1.2 (95% CI, 0.8–1.6; 33 deaths). [In this study, exposure to tetrachloroethylene and other solvents was verified (until the end of work-history collection in 1978). The elevated SMRs for all cancers and oesophageal and bladder cancers for those who had worked 5 years or more support an exposure–response effect. However, because two thirds of the workers were exposed to solvents other than tetrachloroethylene, and there were no deaths from cancer of the bladder among workers exposed to tetrachloroethylene only, the possible contribution of exposure to other solvents must be considered. In addition, the cancer sites with excess mortality are all known to be associated with consumption of tobacco, and the elevated SMR for chronic obstructive pulmonary disease indicated that consumption of tobacco could play a role in the excess mortality at these sites. The excesses for cancers of the bladder and oesophagus, however, appear to be accounted for entirely by consumption of tobacco, given the relatively small increase in mortality from cancer of the lung.]

In a case–control study nested within the Nordic population (Lynge *et al.*, 2006), the authors evaluated incident cases of selected cancers (bladder, oesophagus, gastric cardia, pancreas, cervix, kidney, liver, and non-Hodgkin lymphoma) reported in the respective national registers from 1997 to 2001. Three controls for each case (six for esophageal cancer) were randomly selected from the cohort and were frequency-matched by country, sex, 5-year age group, and date of case diagnosis by 5-year calendar period. The cohort focused on 46 768 laundry and dry-cleaning workers registered in the 1970 census in Denmark, Finland, Norway, and Sweden, because tetrachloroethylene was by far the most commonly used dry-cleaning solvent in these countries before and during the study period. Dry-cleaning workers were defined as "persons stated to be dry-cleaners, owners of dry-cleaning shops, and other persons employed in dry-cleaning shops with < 10 workers." The last category was included because of the shared work tasks and physical proximity to equipment in small shops. Census and registry data were supplemented with implied exposure status (working as a dry-cleaner or in a dry-cleaning shop), based on original texts from the census forms (Denmark and Norway), interviews (Norway and Sweden), and pension-scheme data (Denmark and Finland) for cases and controls.

There was a statistically significant excess incidence of cancer of the bladder among dry-cleaners (relative risk [RR], 1.4; 95% CI, 1.1–1.9; 93 cases) and the risk of pancreatic cancer was also elevated (RR, 1.27; 95% CI, 0.90–1.80; 57 cases). There were no statistically significant excesses of cancer at any of the other sites. For those working in dry-cleaning for 10 years or more, there were elevated risks of cancers of the bladder (RR, 1.6; 95% CI, 1.1–2.3; 53 cases), pancreas (RR, 1.2; 95% CI, 0.7–2.0; 23 cases) and cervix (RR, 1.2; 95% CI, 0.6–2.2; 16 cases) and no increases in risk of cancer of the oesophagus, gastric cardia, kidney, liver, or of non-Hodgkin lymphoma (Lynge *et al.*, 2006). [Tests for trend by increasing duration of employment were not presented.] [Table 2.1 presents results for those definitely known to be dry-cleaners only. The unexposed comparison group comprised laundry workers, rather than the general population used for comparison in cohorts from studies in the USA, to indirectly adjust for tobacco smoking habits.]

Seldén & Ahlborg (2011) assembled a cohort of 10 389 dry-cleaning and laundry workers in

Sweden in 1984, based on a questionnaire mailed to all "washing establishments" (response rate, 38%) about workers, production volume, and chemicals used. Data on cancer incidence were obtained by matching to the national cancer register for 1985–2006. Use of tetrachloroethylene in dry-cleaning was reported by 61% of the cohort members (6356 out of 10 389). Among those who were exposed to tetrachloroethylene through dry-cleaning work, there was an increase in incidence of cancer among men only (standardized incidence ratio [SIR], 1.11; 95% CI, 0.97–1.26), with excesses of non-Hodgkin lymphoma (SIR, 2.0; 95% CI, 1.1–3.3; 15 cases) and cancers of the liver (SIR, 2.1; 95% CI, 0.9–4.2; eight cases) and lung (SIR, 1.3; 95% CI, 0.8–1.9; 23 cases). There was no significant excess of cancer of the bladder. [The study population may overlap with that of Lynge *et al.* (2006). Despite the large number of study participants and the identification of those exposed to tetrachloroethylene, the lack of quantitative data on exposure and the low response rate for the questionnaire were limitations of this study.]

A cohort of 3974 workers in Finland who were biomonitored for occupational exposure to halogenated hydrocarbons, including tetrachloroethylene, during 1974–1983 was followed for cancer incidence from 1967 to 1992 (Anttila *et al.*, 1995a, b). These workers were exposed to tetrachloroethylene in dry-cleaning, and to a small extent also in degreasing and in the graphics industry. Among workers exposed to tetrachloroethylene, there was no overall increased risk of cancer (SIR, 0.9; 95% CI, 0.6–1.3; 31 cases), but there were indications of an increased risk of non-Hodgkin lymphoma (SIR, 3.8; 95% CI, 0.8–11.0; three cases) and cancers of the pancreas (SIR, 3.1; 95% CI, 0.6–9.0; three cases), cervix (SIR, 3.2; 95% CI, 0.4–12.0; two cases), and lung (SIR, 1.92; 95% CI, 0.62–4.48; five cases) [based on a small number of cases].

2.1.2 Workers in other industries

Bond *et al.* (1990) conducted a case–control study that was nested within a cohort of workers in a chemical plant in Michigan, USA (see Section 2.2.7). The risk estimate for cancer of the liver and biliary tracts associated with exposure to tetrachloroethylene, assessed via company work records, was 1.8 (95% CI, 0.8–4.3).

Boice *et al.* (1999) studied aircraft-manufacturing workers exposed to tetrachloroethylene and trichloroethylene in or after 1960 and followed for vital status until 1996. Exposure was assessed by industrial hygiene walk-through inspections of factories to become familiar with the manufacturing processes and patterns of use of chemicals; interviews with over 50 long-term employees (retired and active); review of existing industrial hygiene files, job descriptions going back to the 1940s, and other historical documents; and detailed job histories from the work history cards of factory workers. In 2681 workers exposed to tetrachloroethylene, overall cancer mortality was not elevated (SMR, 0.90; 95% CI, 0.82–0.98; 476 exposed cases), and for those workers with > 5 years of exposure, the relative risk was 0.74 (95% CI, 0.6–0.9; 123 deaths; *P* for trend, 0.01) compared with no exposure. For non-Hodgkin lymphoma, exposure was associated with increased risk without exposure–response relationship; for workers with > 5 years exposure, the relative risk was 1.4 (95% CI, 0.7–3.0; 10 deaths; *P* for trend, > 0.20) compared with no exposure. [Workers were exposed to multiple solvents so any increased risks may not have been attributable to tetrachloroethylene.]

A study of mortality in aircraft-maintenance workers (Radican *et al.*, 2008) is discussed in more detail in the *Monograph* on trichloroethylene in this volume, because tetrachloroethylene was not the major or only solvent exposure. The following cancer outcomes were assessed in relation to exposure to tetrachloroethylene: cancer of the breast (one exposed case), non-Hodgkin

lymphoma (hazard ratio [HR] in men, 2.3, 95% CI, 0.8–7.2, five exposed cases; HR in women, 2.4; 95% CI, 0.5–10.7; two exposed cases), and multiple myeloma (HR in men, 1.7, 95% CI, 0.4–6.9; three exposed cases; HR in women, 7.8; 95% CI, 1.4–43.1; two exposed cases), accounting for age, race, and sex.

2.2 Case–control studies

The association between occupational exposure to tetrachloroethylene and various cancers has been evaluated in numerous case–control studies. While a few studies assessed tetrachloroethylene specifically, the majority of studies assessed occupations and industries with potential exposure to tetrachloroethylene, such as dry-cleaning and aircraft workers. As discussed in Section 2.1, studies that assessed exposure to mixed solvents without distinguishing further, or that assessed the combined occupational category of "laundry and dry-cleaning workers" were excluded from this review (i.e. United States National Bladder Cancer Study by Silverman *et al.*, 1989, 1990). No study further subdivided exposures by job tasks that would likely incur higher exposure (i.e. among dry-cleaning workers, no distinction was made between machine operators, who handle tetrachloroethylene-soaked garments, and other workers). One research group assessed the risk for several cancers associated with environmental exposure to tetrachloroethylene (Aschengrau *et al.*, 1993, 1998, 2003; Vieira *et al.*, 2005; Gallagher *et al.*, 2011; Paulu *et al.*, 1999).

2.2.1 Cancer of the bladder

The results of case–control studies of cancer of the bladder are presented in Table 2.2. All these studies adjusted for smoking.

The only study to report risk of cancer associated with residential exposure to tetrachloroethylene in drinking-water was carried out in Massachusetts, USA (Aschengrau *et al.*, 1993). Living and deceased cases diagnosed in 1983–1986 were identified from the state cancer registry. Population controls from the same geographical area and matched by vital status and age group were selected by random-digit dialling, death registrations, or health insurance rolls, if aged > 65 years. Information about occupational history, water consumption, bathing habits, exposure to specific chemicals, and potential confounding factors was obtained by telephone or in-person interviews with subjects or their next of kin. Semiquantitative estimates of exposures to tetrachloroethylene were developed using an algorithm based on residence and water-system design. Multivariable logistic regression models were adjusted for sex, age at diagnosis or index year, vital status at interview, educational level, and occupational exposure to benzene and other solvents. The analysis included 61 cases of cancer of the bladder and 852 controls. The adjusted odds ratio was 1.39 (95% CI, 0.67–2.91) for any exposure to tetrachloroethylene, and 4.03 (95% CI, 0.65–25.10) for exposure above the 90th percentile of the semiquantitative estimates. The number of exposed cases was too small to allow analysis to account for latency. [This study included estimates of specific exposure to tetracholorethylene, and adjustment for an array of risk factors. However, interpretation was hampered by the small number of exposed cases.]

The NCI conducted the National Bladder Cancer Study, a case–control study of 2982 incident cases and 5782 controls carried out over 18 months, starting in 1977, in 10 areas of the USA (Hartge *et al.*, 1984). As part of this study, Schoenberg *et al.* (1984) studied risk of cancer of the bladder according to occupation in white men in New Jersey, USA. Information on incident cases and age-stratified population controls selected by random-digit dialling was collected by interviewing in person to collect information about smoking, occupational

Table 2.2 Case-control studies of cancer of the bladder and exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population	Exposure Assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Aschengrau *et al.* (1993) USA, Massachusetts: 1983–89	61 852	Population	Telephone/in-person interviews with subjects or next of kin on occupational history, water consumption, bathing habits, exposure to specific chemicals and potentially confounding factors; tetrachloroethylene-contaminated water estimated from exposure model	Any exposure to tetrachloroethylene	13	1.39 (0.67–2.91)	Sex, age at diagnosis, vital status at interview, education, cigarette smoking, urinary-tract infection and past occupational exposure Tetrachloroethylene is not the only compound to which the population was residentially exposed
				Took mostly baths		1.99 (0.40–10.01)	
				High exposure to tetrachloroethylene	4	4.03 (0.65–25.10)	RDD > 90th percentile
Schoenberg *et al.* (1984) USA, New Jersey: 1978–79	658 1258	Age-stratified population controls	Caucasian men, age 21–84 yr, in-person interview with questionnaire, industry and job title surrogate exposure metric	White men, ever dry-cleaning workers	7	1.3 (0.5–3.6)	Age, cigarette smoking Study population overlaps with the US National Bladder Cancer Study and had the same method of exposure assessment. Launderers may be included in the same exposure category as dry-cleaners.
Steineck *et al.* (1990) Sweden, Stockholm: 1985–87	254 287	Population	Men, birth years, 1911–1945, living in County of Stockholm 1985–1987, mailed questionnaire, occupational title as surrogate,	Male dry-cleaning workers	2	1.2 (0.2–9.2)	OR adjusted for birth year and smoking, exposure after 1981 excluded
Burns & Swanson (1991) USA, Michigan	2160 3979	Hospital	Men and women, age 40–84 yr, telephone interview, longest period (usual) employed in occupation or industry	Usual occupation as dry-cleaning workers	8	1.9 (0.7–4.9)	OR adjusted for cigarette smoking, race, sex, and age at diagnosis Rectal or colon cancer controls; possible overlap with Swanson & Burns (1995)

Table 2.2 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population	Exposure Assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Swanson & Burns (1995) USA, Michigan	627 1972 (all sites)	Population	Age 40–84 yr; phone interview (occupation, smoking)	Women whose usual occupation is dry-cleaning worker	6	2.0 (0.7–6.2)	Adjusted for age at interview, race, and cigarette smoking Possible overlap with Burns &Swanson (1991)
Pesch *et al.* (2000a) Germany, 5 regions: 1991–95	704 2650	Population controls (case age ± 5 yr, same sex)	Hospital record study, in-person interview (case in hospital, control at home), tetrachloethylene JEM	JEM, men, medium exposure	162	1.1 (0.9–1.3)	Age, smoking, study centre
				JEM, women, medium exposure	21	1.8 (1.0–3.0)	Age, smoking, study centre
				JEM, men, high exposure	172	1.2 (1.0–1.5)	Age, smoking, study centre
				JEM, women, high exposure	15	1.0 (0.6–1.9)	Age, smoking, study centre
				JEM, men, substantial exposure	71	1.4 (1.0–1.9)	Age, smoking, study centre
				JEM, women, substantial exposure	3	0.7 (0.2–2.5)	Age, smoking, study centre
				JTEM, men, medium exposure	37	1.0 (0.7–1.5)	Age, smoking, study centre No JTEM data for women
				JTEM, men, high exposure	47	1.2 (0.8–1.7)	Age, smoking, study centre
				JTEM men, substantial exposure	22	1.8 (1.1–3.1)	Age, smoking, study centre
Gaertner *et al.* (2004) Canada, 7 Provinces: 1994–97	535 men 1430 men	Population	Occupational title reported on mailed questionnaire	Male dry-cleaners	4	1.24 (0.23–6.64)	Age, province, race, smoking status, consumption of fruit, fried food, coffee, past occupational exposure
Colt *et al.* (2011) USA, Maine, New Hampshire, Vermont: 2001–04	263 371	Population	Aged 30–79 yr, occupational histories through interview coded by occupation (SOC 7658) and industry (SIC 721)	Women in dry-cleaning plants, except rug	6	2.2 (0.4–11.9)	Age, race, Hispanic ethnicity, state, smoking status, and employment in a high-risk occupation Controls frequency-matched by age (within 5 yr), state, and sex

Table 2.2 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population	Exposure Assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Colt et al. (2011) USA, Maine, New Hampshire, Vermont: 2001–04 (cont.)	895 1031	Population	Aged 30–79 yr, occupational histories through interview coded by occupation (SOC 7658) and industry (SIC 721)	Men in dry-cleaning plants, except rug	4	0.9 (0.2–3.8)	Age, race, Hispanic ethnicity, state, smoking status, and employment in a high-risk occupation
Christensen *et al.* (2013) Montreal, Canada	484 533	Population	Occupational exposures derived using subject-reported job history and expert assessment	Men–any exposure to tetrachloroethylene Men–substantial tetrachloroethylene exposure	2 2	0.5 (0.1–3.0) 0.9 (0.1–7.3)	Age, census tract median income, educational attainment (years), ethnicity (French Canadian vs others), questionnaire respondent (self vs proxy), smoking (cigarettes-years), coffee intake, aromatic amines An update of Siemiatycki *et al.* (1994)

JEM, job-exposure matrix; JTEM, job-task exposure matrix; OR, odds ratio; RDD, relative delivered dose; vs, versus

history and exposures. The analysis included 658 cases and 1258 controls. The adjusted odds ratio for dry-cleaning workers was 1.33 (95% CI, 0.50–3.58; seven cases). [It is likely that all the analyses of the National Bladder Cancer Study used the same strategies for exposure assessment, and therefore the "dry-cleaning workers" group may have included launderers.].

In a study of men with urothelial cancer diagnosed in Stockholm, Sweden, in 1985–7, which included 254 cases and 287 referents, there was no increase in risk of urothelial cancer among men who reported working in dry-cleaning (RR, 1.2; 95% CI, 0.2–9.2; two cases) (Steineck *et al.*, 1990).

A case-referent study of cancer of the bladder in Detroit, Michigan, USA, included 2160 cases of cancer of the bladder that were compared with 3979 cases of colorectal cancer identified from a surveillance programme (Burns & Swanson, 1991). The odds ratio for dry-cleaning workers, adjusted for smoking, race, sex, and age, was 1.9 (95% CI, 0.7–4.9; eight cases). Using the same source of data, cases of cancer of the bladder in women diagnosed in 1984–91 were compared with 1972 population controls for "usual occupation" and "ever employed" (Swanson & Burns, 1995). Having a "usual occupation" of dry-cleaning worker was associated with an adjusted (for age, race, and smoking) odds ratio of 2.0 (95% CI, 0.7–6.2; six cases). [The Working Group noted that there may have been some overlap between the cases included in these two studies].

Pesch and colleagues (Pesch *et al.*, 2000a) carried out a study of urothelial carcinoma (bladder, ureter, and renal pelvis) in which exposure to tetrachloroethylene was evaluated using exposure matrices for job title or job task. Analyses with a job-exposure matrix reported relative risks for medium (men: 1.1, 95% CI, 0.9–1.3; women: 1.8, 95% CI, 1.0–3.0), high (men: 1.2, 95% CI, 1.0–1.5; women: 1.0, 95% CI, 0.6–1.9), and substantial (men: 1.4, 95% CI, 1.0–1.9; women: 0.7, 95% CI, 0.2–2.5) exposure. Analyses with a job-task exposure matrix reported relative risks for medium (1.0, 95% CI, 0.7–1.5), high (1.2, 95% CI, 0.8–1.7), and substantial exposure (1.8, 95% CI, 1.1–3.1), for men only.

Risk factors for cancer of the bladder in seven provinces of Canada were examined for 887 cases (535 men) diagnosed in 1994–97 compared with 2847 frequency-matched controls (1430 men) surveyed in 1996 (Gaertner *et al.*, 2004). Among men, the odds ratio for employment as a dry-cleaning worker was 1.24 (95% CI, 0.23–6.64; four cases), adjusted for age, province, race, smoking, and nutritional factors. Data were not reported for women.

A study of cancer of the bladder in Maine, New Hampshire, and Vermont, USA, compared the occupations of 1158 people with cancer of the bladder newly diagnosed in 2001–4 and 1402 population controls. The odds ratio for workers in dry-cleaning plants was 0.86 (95% CI, 0.19–3.81; four cases) for men and 2.19 (95% CI, 0.41–11.85; six cases) for women after adjusting for several covariates, including smoking and occupation with a high risk of bladder cancer (Colt *et al.*, 2011).

Christensen *et al.* (2013) conducted a study of occupational risk factors for selected cancers in men aged 35–70 years in metropolitan Montreal, Canada. In an analysis of 484 cases of cancer of the bladder and 533 population controls, odds ratios were 0.5 (95% CI, 0.1–3.0; two cases) for any exposure to tetrachloroethylene, and 0.9 (95% CI, 0.1–7.3; two cases) for substantial exposure to tetrachloroethylene, after adjusting for smoking and other covariates (Christensen *et al.*, 2013).

2.2.2 Cancer of the upper aerodigestive tract

See Table 2.3.

Two case–control studies evaluated cancer of the upper aerodigestive tract and exposure to tetrachloroethylene, or employment as a dry-cleaner, through personal interviews.

Vaughan *et al.* (1997) reported odds ratios > 1 (not statistically significant) and dose–response or duration–response patterns for laryngeal cancer, although there were few exposed cases. Christensen *et al.* (2013) classified study subjects by degree of occupational exposure to tetrachloroethylene; none of the oesophageal cancer cases were exposed to tetrachloroethylene. [The study by Christensen *et al.* (2013) is an update of the study by Siemiatycki (1991).]

2.2.3 Lymphatic and haematopoietic cancers

See Table 2.4.

Associations between haematopoietic cancers and occupational exposure to tetrachloroethylene have been evaluated in several case–control studies.

In a study in residents exposed to drinking-water contaminated by tetrachloroethylene in Cape Cod, Massachusetts, USA [described in Section 2.2.1] (Aschengrau *et al.*, 1993), the odds ratio for leukaemia was 8.33 (95% CI, 1.53–45.29; two exposed cases) for people with estimated exposure above the 90th percentile. [There were few exposed cases and exposure to tetrachloroethylene was derived from a model.]

Occupational exposure to dry-cleaning fluids was assessed in a case–control study in the state of New York, USA (Kato *et al.*, 2005). The study included incident cases of non-Hodgkin lymphoma in women aged 20–79 years diagnosed between October 1995 and September 1998; 722 were eligible and 376 were included. Population controls (aged < 65 years, from driving-licence records; aged > 65 years, from healthcare records) were selected (1498 eligible, 463 included). Exposure data were collected via telephone interview. For the seven cases in people exposed to dry-cleaning fluids (not further specified), the odds ratio was 1.59 (95% CI, 0.49–5.13), after adjusting for several covariates.

In a case–control study of several haematological malignancies in 12 areas of Italy, incident cases in people aged 20–74 years diagnosed in 1991–1993 were recruited (Miligi *et al.*, 2006; Costantini *et al.*, 2008). The cases included diagnoses of non-Hodgkin lymphoma, including chronic lymphocytic leukaemia (821 men, 607 women); and Hodgkin lymphoma (159 men, 145 women), leukaemia (345 men, 241 women), and multiple myeloma (129 men, 134 women). Controls were randomly selected from the general population. Data on occupational history were collected by person-to-person interviews, and exposures assessed by experts. Age-adjusted Mantel–Haenszel odds ratios were calculated, or odds ratios were calculated with multiple logistic regression taking potential confounders into account. Fourteen cases of non-Hodgkin lymphoma had medium/high exposure to tetrachloroethylene (OR, 1.2; 95% CI, 0.6–2.5) (Miligi *et al.*, 2006). For leukaemia, seven cases had medium/high exposure to tetrachloroethylene (OR, 1.0; 95% CI, 0.4–2.7) (Costantini *et al.*, 2008).

A case–control study in six regions in Germany included 710 incident cases of malignant lymphoma in people aged 18–80 years and an equal number of population controls. Controls were identified from the population register, and recruitment continued until one participating control had been identified for each participating case. Face-to-face interviews were conducted. An industrial physician estimated cumulative exposure to tetrachloroethylene (intensity × frequency × years). The odds ratios associated with levels of exposure to tetrachloroethylene were 1.1 (95% CI, 0.5–2.3; 16 cases) for low exposure; 1.0 (95% CI, 0.5–2.2; 14 cases) for medium exposure; and 3.4 (95% CI, 0.7–17.3; six cases) for high exposure (Seidler *et al.*, 2007).

Gold *et al.* (2011) conducted a case–control study in the Seattle-Puget Sound region of Washington and the Detroit metropolitan area of Michigan, USA, between 1 January 2000 and 31 March 2002. The analysis included 181 incident cases of multiple myeloma in people aged

Table 2.3 Case–control studies of cancers of the upper aerodigestive tract and exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Vaughan *et al.* (1997), Washington (USA), 1983–87 and 1987–90	491 oral cavity and pharynx, 235 larynx, 404 oesophagus and gastric cardia 724 controls	Population	Personal interview		Duration of employment in dry-cleaning industry			Age, sex, education, study period, alcohol consumption, cigarette smoking
				Oral cavity	Never (< 6 mo)	484	1.0 (ref)	
					Ever (≥ 6 mo)	7	1.2 (0.3–4.6)	
					1–9 yr	6	1.4 (0.3–5.7)	
					≥ 10 yr	1	0.4 (0.0–31.6)	
					Exposure to tetrachloroethylene			
					Possible	7	1.2 (0.3–4.6)	
					Probable	4	1.5 (0.2–9.5)	
					1–29 ppm-yr	3	1.0 (0.1–7.0)	
					≥ 30 ppm-yr	4	1.4 (0.2–8.7)	
					Duration of employment in dry-cleaning industry			
				Larynx	Never (< 6 mo)	230	1.0 (ref)	
					Ever (≥ 6 mo)	5	2.7 (0.6–10.9)	
					1–9 yr	3	1.9 (0.3–10.8)	
					≥ 10 yr	2	5.5 (0.4–75.0)	
					Exposure to tetrachloroethylene			
					Possible	4	2.3 (0.5–10.2)	
					Probable	1	0.9 (0.1–12.9)	
					1–29 ppm-yr	2	2.0 (0.2–17.9)	
					≥ 30 ppm-yr	2	2.5 (0.3–19.1)	
					Duration of employment in dry-cleaning industry			
				Oesophagus (SCC)	Never (< 6 mo)	107	1.0 (ref)	
					Ever (≥ 6 m)	2	3.6 (0.5–27.0)	
					1–9 yr	2	4.6 (0.5–39.4)	

Table 2.3 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Vaughan et al. (1997), Washington (USA), 1983–87 and 1987–90 (cont.)					≥ 10 yr	0	–	
					Exposure to tetrachloroethylene			
					Possible	2	3.6 (0.5–27.0)	
					Probable	2	6.4 (0.6–68.9)	
					1–29 ppm-yr	2	11.9 (1.1–124)	
					≥ 30 ppm-yr	0	–	
					Duration of employment in dry-cleaning industry			
				Oesophagus (ADC)	Never (< 6 mo)	293	1.0 (ref)	
					Ever (≥ 6 mo)	2	1.1 (0.2–5.7)	
					1–9 yr	1	0.8 (0.1–7.7)	
					≥ 10 yr	1	1.7 (0.1–26.5)	
					Exposure to tetrachloroethylene			
					Possible	2	1.1 (0.2–5.7)	
					Probable	1	0.9 (0.1–10.0)	
					1–29 ppm-yr	1	2.0 (0.2–21.7)	
					≥ 30 ppm-yr	1	0.7 (0.1–6.8)	
Christensen *et al.* (2013), Montreal (Canada) 1979–85	99 533	Population	Personal interview + expert assessment	Oesophagus (ICD-9 150)	Tetrachloroethylene exposure	0	–	

ADC, adenocarcinoma; mo, month; SCC, squamous cell carcinoma; yr, year

Table 2.4 Case–control studies of haematopoietic cancers and exposure to tetrachloroethylene

Reference, study location, period	Total cases Total controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Convariates Comments
Kato *et al.* (2005), New York State, USA, 1995–98	376 female NHL patients 463 selected from driver licence/health care records	Telephone interview	Exposed to dry-cleaning fluid	7	1.59 (0.49–5.13)	Age at index date, family history of hematologic cancer, college education, surrogate status, year of interview, body mass index 10 years before interview, average frequency of use of pain-relieving drugs, total number of episodes of systemic antibiotic use, total number of uses of household pesticide products, duration of work involving pesticide exposures
Miligi *et al.* (2006); Costantini *et al.* (2008)	1135 NHL+chronic lymphocytic leukaemia patients 1246 population controls	Interview	Expert-assessed exposure to TETRA:			Sex, age, education, area Costantini *et al.* (2001), Miligi *et al.* (1999, 2006) derive from the same data set
			Very low/low	18	0.6 (0.3–1.2)	
			Medium/high	14	1.2 (0.6–2.5)	
	586 with leukaemia 1278 population controls	Interview	Expert assessed exposure to TETRA:	6	0.6 (0.2–1.6)	Sex, age, education, area
			Very low/low			
			Medium/high exposure	7	1.0 (0.4–2.7)	
Seidler *et al.* (2007), Germany	710 lymphoma patients 710 population controls	Interview	Expert-assessed TETRA exposure			Smoking and alcohol; Controls were matched on region, sex and age
			Low (> 0 to ≤ 9.1)	16	1.1 (0.5–2.3)	
			Medium (> 9.1 to ≤ 78.8)	14	1.0 (0.5–2.2)	
			High (> 78.8)	6	3.4 (0.7–17.3)	
Gold *et al.* (2011), Seattle-Puget Sound/Detroit, USA, 2000–02	181 with multiple myeloma 481 controls identified by random-digit dialling/Medicare records	Interview	Job-exposure-matrix for TETRA	29	1.4 (0.9–2.4)	Age, race, study site, gender and years of education
			Highest category of cumulative exposure	14	2.5 (1.1–5.4)	

Table 2.4 (continued)

Reference, study location, period	Total cases Total controls	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Convariates Comments
Christensen *et al.* (2013) Montreal, Canada, 1979–85	215 hospitalized NHL patients	Personal interview + expert assessment				Age, census tract median income, educational attainment (years), ethnicity (French Canadian vs others), questionnaire respondent (self vs proxy), smoking
	533 population controls		Any TETRA exposure	3	2.2 (0.5–10)	Update of Siemiatycki (1991)
			Substantial TETRA exposure	2	2.6 (0.4–19)	
	2341 cancer controls		Any exposure	3	1.7 (0.5–6.2)	
			Substantial exposure	2	1.7 (0.3–8.5)	

NHL, non-Hodgkin lymphoma; TETRA, tetrachloroethylene

35–74 years and 481 population controls selected by random-digit dialling (aged < 65 years) and from Medicare files (aged ≥ 65 years). In-person interviews were conducted with recording of occupational history and a job-exposure matrix for solvents was applied. Twenty-nine cases had ever been exposed to tetrachloroethylene (OR, 1.4; 95% CI, 0.9–2.4). A significant trend (P = 0.04) was observed with cumulative exposure level (intensity × frequency × years summed over all exposed jobs): in the highest exposure category, the odds ratio was 2.5 (95% CI, 1.1–5.4). In a further analysis excluding jobs for which the exposure assessor had low confidence the odds ratio was 1.5 (95% CI, 0.8–2.9) for ever exposure and 3.3 (95% CI, 1.2–9.5) in the highest category (Gold *et al.*, 2011). [The Working Group noted that only half of the identified cases participated in the study.]

Cases in men aged 35–70 years diagnosed in Montreal, Canada, between September 1979 to June 1985 were included in a case–control study by Christensen *et al.* (2013) based on the population studied previously by Siemiatycki (1991). In total, 215 cases of non-Hodgkin lymphoma were recruited and 2341 cases of other cancers, and a population sample served as controls. Personal interviews were conducted and exposure was assessed by expert evaluation. Exposure to tetrachloroethylene was associated with an odds ratio of 1.7 (95% CI, 0.5–6.2; three exposed cases) when combining cancer and population controls, using proportional weighting.

2.2.4 Cancer of the kidney

See Table 2.5.

Seven case–control studies have examined risk of cancer of the kidney associated with occupations involving exposure to tetrachloroethylene, particularly dry-cleaning. All studies except one conducted personal interviews with study subjects.

The study by Delahunt *et al.* (1995) was based on cancer-registry data and exposure assessment relied on occupational data recorded in the cancer registry. Two studies applied job-exposure matrices and classified subjects by degree of exposure to tetrachloroethylene (Dosemeci *et al.*, 1999; Pesch *et al.*, 2000b). In one study, a team of chemists and industrial hygienists translated job titles into potential exposures (Christensen *et al.*, 2013). In one study, subjects were classified according to occupational exposure to dry-cleaning solvents (Mandel *et al.*, 1995). In the remaining studies, subjects were classified by job title (Asal *et al.*, 1988; Delahunt *et al.*, 1995; Karami *et al.*, 2012). All studies reported positive associations for men, or for women, or both, although statistical significance was only reached in three studies (Delahunt *et al.*, 1995; Mandel *et al.*, 1995; Pesch *et al.*, 2000b), and one of them reported only crude risk estimates (Delahunt *et al.*, 1995). Among the three studies that evaluated dose–response or duration–response trends (Mandel *et al.*, 1995; Pesch *et al.*, 2000b; Karami *et al.*, 2012), only Karami *et al.* (2012) reported monotonic positive trends. Two studies reported protective (non-significant) associations among women (Dosemeci *et al.*, 1999; Pesch *et al.*, 2000b) and one study among men (Asal *et al.*, 1988). [The study by Christensen *et al.* (2013) was based in the same population included in the study by Siemiatycki (1991), with refinements in exposure assessment and case classification.]

Environmental exposure to tetrachloroethylene has been evaluated in a case–control study (Aschengrau *et al.*, 1993, described in Section 2.2.1) which included cancers of the kidney and other sites. None of the 35 kidney cancer cases were classified as exposed to tetrachloroethylene.

2.2.5 Cancer of the breast

Several analyses have been undertaken to evaluate the risk of cancer of the breast among women exposed to drinking-water contaminated with

Table 2.5 Case–control studies of kidney cancer and occupational exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Asal *et al.* (1988), Oklahoma (USA), 1981–84	315 313 (hospital), 336 (population)	Hospital and population	Personal interview	Renal cell carcinoma (ICD not reported)	Dry-cleaning workers, men Dry-cleaning workers, women	3 8	0.7 (0.2–2.3) 2.8 (0.8–9.8)	Age, smoking, weight Response rates not reported; [In Oklahoma petroleum solvents are more often used in dry-cleaning than tetrachloroethylene]
Delahunt *et al.* (1995), New Zealand, 1978–86	710 (men), from the cancer registry 12 756 (men)	Cancer registry, primary tumours from sites other than the urinary tract	Occupational data recorded in the cancer registry. Occupation classified using the New Zealand Standard Classification of Occupations, a modification of the ISCO	Malignant neoplasms of the kidney, excluding the renal pelvis (ICD 189.0)	Dry-cleaning workers	Not reported	1.92 (0.27–13.89)	Unadjusted estimates Occupational code was available for 98.9% cases and for all controls
Mandel *et al.* (1995), Australia, Denmark, Germany, Sweden, USA	1732 2309	Population	Personal interviews	Renal cell adenocarcinoma (ICD-9 189.0)	Dry-cleaning solvents (men) Duration of occupational exposure 1–7 years 8–25 years 26–60 years Dry-cleaning solvents (women)	245 70 98 75 57	1.4 (1.1–1.7) 1.2 (0.9–1.8) 1.7 (1.2–2.4) 1.2 (0.9–1.8) 1.6 (1.0–2.7)	Age, smoking status, body mass index, education and study centre Response rates: 72.3% (cases), 74.7% (controls) Overlaps with Mellemgaard *et al.* (1994) and McCredie & Stewart (1993) The only statistically significant association among women

Table 2.5 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Dosemeci *et al.* (1999) Minnesota (USA), 1988–90	438 687	Population	Personal interview and job-exposure matrix (JEM)	Renal cell carcinoma (ICD not reported)	Tetrachloroethylene exposure, All	50	1.07 (0.7–1.6)	Age, gender (for total), smoking, hypertension and/or use of diuretics and/or anti-hypertension drugs and body mass index Response rates: 87% (cases), 86% (controls)
					Tetrachloroethylene exposure, Men	42	1.12 (0.7–1.7)	
					Tetrachloroethylene exposure, Women	8	0.82 (0.3–2.1)	
Pesch *et al.* (2000b) Germany, 1991–95	935 4298	Population	Interviewer-administered standardized questionnaire, plus job-exposure (JEM) and job task-exposure matrices (JTEM)	Renal cell carcinoma (ICD not reported)	German JEM, Men			Age, study centre, smoking Response rates: 88% (cases), 71% (controls)
					Unexposed and < 30th percentile	not reported	1.0 (ref)	
					Medium (> 30th percentile)	154	1.4 (1.1–1.7)	
					High (> 60–90th percentile)	119	1.1 (0.9–1.4)	
					Substantial (> 90th percentile)	50	1.4 (1.0–2.0)	
					German JEM, Women			
					Unexposed and < 30th percentile	not reported	1.0 (ref)	
					Medium (> 30th percentile)	12	0.7 (0.4–1.3)	
					High (> 60–90th percentile)	19	1.1 (0.7–1.9)	
					Substantial (> 90th percentile)	4	0.7 (0.3–2.2)	
					JTEM, Men			
					Unexposed and < 30th percentile	not reported	1.0 (ref)	
					Medium (> 30th percentile)	44	1.2 (0.9–1.7)	
					High (> 60–90th percentile)	39	1.1 (0.7–1.5)	

Table 2.5 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Pesch et al. (2000b) Germany, 1991–95 (cont.)					Substantial (> 90th percentile) JTEM, Women	15	1.3 (0.7–2.3)	
					Unexposed and < 30th percentile	not reported	1.0 (ref)	
					Medium (> 30th percentile)	8	2.2 (0.9–5.2)	
					High (> 60–90th percentile)	6	1.5 (0.6–3.8)	
					Substantial (> 90th percentile)	3	2.0 (0.5–7.8)	
Karami *et al.* (2012), Detroit and Chicago (USA), 2003–07	1217 1235	Population	Personal interviews	Kidney (ICD-O C64)	Industry: dry-cleaning plants, except rug			Sex, age at reference date, race, study centre, education level, history of hypertension, smoking status, BMI (5 years before interview), family history of cancer Response rates: 77.5% (cases), 54.4% (controls); controls frequency matched by age group, race, sex, study centre
					never	1169	1.0 (ref)	
					ever	15	2.0 (0.9–4.4)	
					< 5 years	11	1.8 (0.6–5.4)	
					≥ 5 years	4	2.5 (0.4–14.4)	
					P for trend		0.093	

Table 2.5 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Christensen *et al.* (2013), Montreal 1979–85	177 533	Population	Personal interviews	Kidney (ICD-9 189)	Occupational exposure to tetrachloroethylene			Age, census track median income, educational attainment (years), ethnicity (French Canadian versus other), questionnaire respondent (self versus proxy), smoking (cigarette-years), coffee, beer, wine, and spirit intake Only men. Response rates: 82% (all cancer patients, unspecific for kidney), 72% (controls)
					Any exposure	2	1.6 (0.3–9.4)	
					Substantial exposure	2	3.1 (0.4–24)	

tetrachloroethylene in Cape Cod, Massachusetts, USA (Aschengrau *et al.*, 1998, 2003; Vieira *et al.*, 2005; Gallagher *et al.*, 2011). The Working Group focused on the results of the latest re-analysis of these data (Gallagher *et al.*, 2011). Study participants were permanent residents of eight towns in the Cape Cod region. Incident cancers of the breast diagnosed in 1983–1993 were identified from the Massachusetts cancer registry. Controls were demographically similar women living in Cape Cod in 1983–1993, identified by random-digit dialling (age < 65 years), from Medicare files (age ≥ 65 years), or death certificates. Telephone or personal interviews were used to collect residential history and other data. Exposure to tetrachloroethylene was estimated using modelling techniques (manual and automated algorithms). [The automated model redefined many unexposed subjects from the manual model as having low exposure.] The analysis included 930 cases and 1302 controls for the manual assessment, and 920 cases and 1293 controls for the automated assessment. Adjusted for age at diagnosis, vital status at interview, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth/stillbirth, occupational exposure, and study of origin, the odds ratio estimates based on the manual exposure assessment was 1.0 (95% CI, 0.8–1.2). Estimated exposure at > 75th and > 90th percentiles gave adjusted odds ratios of 1.6 (95% CI, 1.1–2.4) and 1.3 (95% CI, 0.7–2.6), respectively. For the automated assessment, the odds ratio was 1.3 (95% CI, 0.9–1.9). [There may be selection bias as only a small proportion of the selected controls could be reached.]

2.2.6 Cancer of the lung

See Table 2.6.

Two case–control studies of cancer of the lung investigated occupational exposure to tetrachloroethylene; both reported increased risks of lung cancer among those exposed to tetrachloroethylene after adjusting for smoking (Brownson *et al.*, 1993; Vizcaya *et al.*, 2013). One case–control study of cancer of the lung assessed residential exposure to tetrachloroethylene through contaminated drinking-water (Paulu *et al.*, 1999). Results showed increased risks for those in the highest categories of exposure.

One of the studies of occupational exposure included cases in nonsmokers (Brownson *et al.*, 1993). Both studies of occupational exposure conducted face-to-face personal interviews. Risks were reported by job title (Brownson *et al.*, 1993) or by degree of exposure to tetrachloroethylene Vizcaya *et al.* (2013). Increased risks of cancer of the lung in female dry-cleaning workers were reported by Brownson *et al.* (1993) (OR, 1.8; 95% CI, 1.1–3.0), adjusted for age, smoking and previous lung disease. For lifetime nonsmokers, the odds ratio was 2.1 (95% CI, 1.2–3.7), adjusted for age and previous lung disease. Increased risk of cancer of the lung associated with exposure to tetrachloroethylene was reported by Vizcaya *et al.* (2013) (OR, 2.54; 95% CI, 1.25–5.26, for any exposure; and OR, 2.4; 95% CI, 0.8–7.7, for substantial exposure). [The study by Vizcaya *et al.* (2013) was a re-evaluation of the Siemiatycki (1991) study, including improved exposure assessment in the same study population.]

Paulu *et al.* (1999) conducted a population-based case–control study to evaluate the risk of cancers of the lung, colon and rectum, brain and pancreas associated with residential exposure to tetrachloroethylene. Cases were incident cancers diagnosed between 1983 and 1986, and resident in the upper Cape towns. Among the selected study subjects, 79.2% of cases of lung cancer, 83.2% of Medicare controls, and 81.1% of next-of-kin for deceased controls were contacted and interviewed. Among controls identified by random-dialling, 73.9% of the eligible and contacted subjects were interviewed. The relative delivered dose of tetrachloroethylene was estimated using a model that took into account residential location, duration of residence, water flow,

Table 2.6 Case–control studies of lung cancer and occupational exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Brownson *et al.* (1993), Missouri (USA), 1986–91	429 (non-smoking women, from the cancer registry) 1021 (non-smoking women)	Population (driver's license and Medicare files)	Interview, occupational and medical history	Lung cancer (ICD not reported)	Dry-cleaning workers (all subjects)	30	1.8 (1.1–3.0)	Age, history of previous lung disease, and active smoking
					Dry-cleaning workers (lifetime nonsmokers)	23	2.1 (1.2–3.7)	Age and history of previous lung disease Response rates: 69% (cases), 73% (controls)
Vizcaya *et al.* (2013), Montreal (Canada). 1980–86 (study 1), 1995–2001 (study 2)	2016 [study 1: 851 (all men), study 2: 430 (women), 735 (men)] 2001 [study 1: 533 (all men), study 2: 570 (women), 898 (men)]	Population	Personal interview	Lung cancer (ICD not reported)	Tetrachloroethylene exposure			Age, smoking habit, educational attainment, socioeconomic status, ethnicity and exposure to eight known carcinogens Response rates: Study 1: 79% (cases), 70% (controls). Study 2: 86% (cases), 70% (controls). Odds ratios are only reported for men
					Any, pooled	23	2.5 (1.2–5.6)	
					Substantial, pooled	10	2.4 (0.8–7.7)	

and pipe characteristics. Adjusted odds ratios for cancer of the lung were moderately elevated among subjects whose exposure level was above the 90th percentile, whether or not a latent period was assumed [ORs and 95% CIs, 3.7 (1.0–11.7), 3.3 (0.6–13.4), 6.2 (1.1–31.6), and 19.3 (2.5–141.7) for 0, 5, 7, and 9 years of latency, respectively]. Results for other cancer sites considered in this study are reported in a subsequent section.

2.2.7 Cancer of the liver

See Table 2.7.

The risk of cancer of the liver associated with occupational exposure to tetrachloroethylene was evaluated in three case–control studies. Two studies included deceased subjects only, while the study by Christensen *et al.* (2013) included both living and deceased subjects. Exposure assessment was based on personal interviews with living study subjects (Christensen *et al.*, 2013), company work history records (Bond *et al.*, 1990) or occupation and kind of business or industry as recorded on the death certificate (Suarez *et al.*, 1989). Subjects were classified by exposure to tetrachloroethylene (Bond *et al.*, 1990; Christensen *et al.*, 2013), or by job title (Suarez *et al.*, 1989). Increased risk of cancer of the liver associated with exposure to tetrachloroethylene was reported by two studies (Bond *et al.*, 1990; Christensen *et al.*, 2013).

2.2.8 Cancer of the brain

See Table 2.8.

Three case–control studies of cancer of the brain evaluated occupational exposure to tetrachloroethylene. None of the studies reported statistically significant increased risks.

Heineman *et al.* (1994) studied white men with astrocytic tumours in the USA. A total of 111 cases had job titles that were compatible with exposure to tetrachloroethylene (OR, 1.2; 95% CI, 0.8–1.6). None of the risk estimates for subgroups of increasing probability, duration or intensity of exposure reached statistical significance. Neta *et al.* (2012) evaluated glioma and meningioma in Arizona, Massachusetts and Pennsylvania in relation to occupational exposure to tetrachloroethylene. Exposure was evaluated through personal interviews, and odds ratios tended to be around 1 and non-statistically significant. These studies are described in more detail in the *Monograph* on trichloroethylene.

Ruder *et al.* (2013) evaluated glioma risk from non-farm occupational exposure (ever/never and estimated cumulative exposure) to tetrachloroethylene among 798 cases and 1175 population-based controls, aged 18–80 years and non-metropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin, United States. Solvent use was estimated based on occupation, industry, and era, using a bibliographic database of published exposure levels and exposure determinants. Unconditional logistic regression was used to calculate odds ratios adjusted for frequency matching variables age group and sex, and age and education. Ever exposure to tetrachloroethylene was associated with reduced risk of glioma (OR, 0.8; 95% CI, 0.6–0.9, 299 cases and 500 controls exposed). Mean estimated cumulative exposure was similar for cases (3.5 ppm-years) and controls (3.1 ppm-years), with OR of glioma of 1.0 (0.9–1.1) for a 1-unit increase in natural-log transformed exposures in ppm–years. In analyses limited to 904 participant blood donors (excluding controls reporting a previous cancer diagnosis) genotyped for glutathione-*S*-transferases *GSTP1, GSTM3*, and *GSTT1*, solvent-exposed individuals with functional *GST* genes that might convert chlorinated solvents crossing the blood-brain barrier into cytotoxic metabolites were not at increased risk of glioma. [Study limitations include the high percentage of proxy case responses and the lack of workplace or serum measurements of solvent levels.]

Brain cancer and non-occupational tetrachloroethylene exposure was evaluated by Paulu

Table 2.7 Case–control studies of liver cancer and occupational exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Suarez *et al.* (1989), Texas (USA) 1969–80,	1742 (cancer deaths), only males 1742	Death certificate records	Occupation and kind of business or industry as recorded on the death certificate	Primary cancer of the liver (ICD 155.0)	Dry-cleaning services	11	0.98 (0.44–2.20)	Age, race, ethnicity [Dry-cleaning solvent in Texas more likely to be Stoddard solvent than PCE];, Controls excluded all neoplasms (ICD 140–239), diseases of the liver and gallbladder (ICD 570–576), infectious hepatitis (ICD 070) and alcoholism (ICD 303)
					Dry-cleaning operators	4	0.55 (0.17–1.75)	
Bond *et al.* (1990), Michigan, USA 1940–82	44 1888 controls		Company work records	Liver, gallbladder or bile ducts (ICDA-8 155–156 and 197.8)	Exposed to tetrachloroethylene	6	1.8 (0.8–4.3)	Age
Christensen *et al.* (2013), Montreal (Canada) 1979–85	48 533	Population	Personal interviews	kidney (ICD-9 189)	Occupational exposure to tetrachloroethylene			Age, census track median income, educational attainment (years), ethnicity (French Canadian versus Other), questionnaire respondent (self versus Proxy), smoking (cigarette-years), beer, wine, and spirit intake Only males. Response rates: 82% (all cancer patients, unspecific for kidney), 72% (controls)
					Any exposure	1	3.3 (0.2–60)	
					Substantial exposure	1	4.4 (0.2–103)	

Table 2.8 Case–control studies of cancer of the brain and exposure to tetrachloroethylene

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Heineman *et al.* (1994), Lousiana (USA) 1978–80 and New Jersey and Philadelphia (USA) 1979–81	654 (from death certificates) 612	Death certificates	Next-of-kin personal interview	Brain or other central nervous system tumour (ICD-9 191, 192, 225, 239.7)	Occupational tetrachloroethylene exposure			Age and study area Response rates: 88% (cases), 83% (controls)
					Ever			
					Any	111	1.2 (0.8–1.6)	
					Low probability, ever	72	1.3 (0.8–1.9)	
					Medium probability, ever	30	0.9 (0.5–1.6)	
					High probability, ever	9	1.2 (0.4–3.5)	
					Exposed 2–20 years			
					Any	71	1.1 (0.7–1.6)	
					Low probability	50	1.1 (0.7–1.8)	
					Medium probability	15	0.9 (0.4–1.9)	
					High probability	6	1.0 (0.3–3.7)	
					Low-medium average intensity	64	1.0 (0.7–1.6)	
					High intensity	7	1.2 (0.4–4.4)	
					Exposed ≥21 years			
					Any	28	1.4 (0.7–2.7)	
					Low probability	14	1.6 (0.6–4.0)	
					Medium probability	11	1.0 (0.4–2.6)	
					High probability	3	∞	
					Low-medium average intensity	25	1.3 (0.7–2.4)	
					High intensity	3	∞	
					Low cumulative exposure			
					Any	33	0.8 (0.5–1.4)	
					Low probability	25	0.8 (0.4–1.5)	
					Medium probability	7	1.0 (0.3–3.1)	
					High probability	1	0.5 (0.0–7.4)	

Table 2.8 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Heineman et al. (1994), Lousiana (USA) 1978–80 and New Jersey and Philadelphia (USA) 1979–81 (cont.)					Medium cumulative exposure			
					Any	45	1.3 (0.8–2.2)	
					Low probability	27	1.6 (0.8–3.1)	
					Medium probability	13	1.0 (0.4–2.4)	
					High probability	5	1.2 (0.3–5.4)	
					High cumulative exposure			
					Any	21	1.5 (0.7–3.2)	
					Low probability	12	1.8 (0.7–5.1)	
					Medium probability	6	0.8 (0.2–2.6)	
					High probability	3	∞	
					Summary measures			
					Low-medium average intensity, total	89	1.1 (0.8–1.6)	
					High intensity, total	10	1.8 (0.6–5.9)	
					Low probability	Not reported	1.0 (0.5–1.8)	Age, study area employment in electronics occupations/industries and exposure to other chlorinated aliphatic hydrocarbons
					Medium probability	Not reported	0.5 (0.2–1.3)	
					High probability	Not reported	1.2 (0.4–3.9)	
Paulu *et al.* (1999), 5 upper Cape towns (USA) 1983–86	37 703	Population	Personal interview	Not specified	Drinking-water exposure			Crude Response rates: 86% (cases), 74% (random-digit-dial controls), 76% (Health Care Financing Administration controls), 79% (next-of-kin for deceased controls)
					0 yrs latent period	3	0.6 (0.1–1.7)	
					5 yrs latent period	3	1.0 (0.2–2.9)	
					7 yrs latent period	2	0.9 (0.1–3.0)	
					9 yrs latent period	1	0.7 (0.0–3.4)	

Table 2.8 (continued)

Reference, study location and period	Total cases Total controls	Control source (Hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Neta *et al.* (2012), Arizona, Massachusetts and Pennsylvania (USA), 1994–98	489 glioma, 197 meningioma 799	Hospital	Personal interviews	Glioma or other neuroepitheliomatous neoplasm (ICD-O-2 9380–9473 and 9490–9506), meningioma (ICD-O-2 9530–9538) or acoustic neuroma (ICD-O-2 9560)	Occupational tetrachloroethylene exposure			Age group, race, sex, hospital site and proximity of residence to hospital Response rates: 92% (glioma cases), 94% (meningioma cases), 86% (controls)
					Possible, men	102	0.7 (0.5–1.0)	
					Probable, men	6	1.2 (0.4–3.8)	
					Possible, women	34	0.7 (0.5–1.1)	
					Probable, women	3	0.5 (0.1–1.7)	
					Possible, all	136	0.7 (0.5–0.9)	
					Probable, all	9	0.7 (0.3–1.6)	
Ruder *et al.* (2013) Iowa, Michigan, Minnesota, Wisconsin (USA) 1995–97	798 1175	Population	Personal interviews plus industrial hygienist evaluation	Glioma ICD-O-9380–948	Any tetrachloroethylene	299	0.75 (0.62–0.91)	Age, education, sex
					Men	216	0.81 (0.64–1.04)	
					Women	83	0.66 (0.48–0.91)	

et al. (1999) among 37 cases, in a study setting where exposure occurred through contaminated drinking-water. [Low numbers of brain tumours hampered the estimation of risks.] Only crude associations were reported, showing non-significant protective associations with wide confidence intervals.

2.2.9 Other cancers

Christensen *et al.* (2013) evaluated cancers of the prostate, colon, stomach and rectum, and melanoma associated with occupational tetrachloroethylene exposure. Substantial exposure was associated with a significant increased risk of prostate cancer (9 exposed cases; OR, 6.0; 95% CI, 1.2–30), and non-statistically significant increased risk of colon cancer (3 exposed cases; OR, 1.8; 95% CI, 0.3–11), stomach cancer (2 exposed cases; OR, 2.1; 95% CI, 0.3–17), rectal cancer (1 exposed case; OR, 1.1; 95% CI, 0.1–13) and melanoma (1 exposed case; OR, 2.6; 95% CI, 0.2–33). Pancreatic cancer was evaluated but no cases were exposed to tetrachloroethylene.

Environmental tetrachloroethylene exposure has been investigated by Paulu *et al.* (1999) (see Section 2.2.8) in relation to colorectal cancer (326 cases) and pancreatic cancer (37 cases). The adjusted ORs for colorectal cancer were modestly elevated among ever-exposed subjects, and did vary substantially as more years of latency were assumed. Adjusted ORs for rectal cancer among ever-exposed subjects were more elevated than the corresponding estimates for colon cancer. Low numbers for pancreatic cancer hampered the estimation of risks. Only crude associations were reported, showing non-significant protective associations with wide confidence intervals.

2.3 Ecological studies

Exposure to tetrachloroethylene rarely occurs in an isolated manner. Episodes of water pollution usually occur from industrial sources and have involved different solvents including tetrachloroethylene and trichloroethylene. Most of the ecological studies reviewed in the *Monograph* on trichloroethylene also consider tetrachloroethylene, and results cannot disentangle the effects of the two chemicals. Specific methods, results and limitations concerning these studies are detailed in the *Monograph* on trichloroethylene in this volume. Some of these studies reported increased incidence rates of cancers of the testis and kidney (ATSDR, 2006, 2008), breast (Coyle *et al.*, 2005), bladder (Mallin, 1990) and uterus, and skin melanoma (Morgan & Cassady, 2002), while another study (Isacson *et al.*, 1985) that evaluated cancers of the bladder, breast, colon, lung, prostate, and rectum did not observe associations with exposure.

Haematopoietic cancers have been evaluated in ecological studies, with mixed results. Cohn *et al.* (1994) found increased rates of leukaemia and non-Hodgkin lymphoma among women, and increased rates of childhood acute lymphocytic leukaemia among girls. Vartiainen *et al.* (1993) observed a marginally increased risk of non-Hodgkin lymphoma, while ATSDR (2006) did not find evidence for an association with childhood leukaemia. One study was conducted in Finland (Vartiainen *et al.*, 1993), while the others were conducted in the USA.

Exposure to tetrachloroethylene may also occur through inhalation. Ma *et al.* (2009) conducted an ecological study in New York City, USA, where there were about 900 small dry-cleaning facilities using tetrachloroethylene. The risk of cancer of the kidney was evaluated in association with living near a dry-cleaning facility using tetrachloroethylene. The unit of analysis was the population with a particular postal code. The outcome variable was the number of hospital discharges for each postal code with a diagnosis of cancer of the kidney. The density of dry-cleaning facilities using tetrachloroethylene in each postal code was a surrogate measure of exposure. Higher densities of dry-cleaning facilities using

tetrachloroethylene were associated with higher rate ratios of kidney cancer, with a rate ratio of 1.15 (95% CI, 1.01–1.30) among those living in areas with the highest densities compared with those in the lowest. A non-monotonic increasing dose–response pattern was observed. [*P*-values for trend were not presented.]

2.4 Meta-analyses

In a meta-analysis on cancer of the pancreas and exposure to solvents, Ojajärvi *et al.* (2001) calculated a meta-relative risk for pancreatic cancer among dry-cleaning workers of 1.4 (95% CI, 1.1–2.4; based on eight populations). [Exposures to other solvents also occurred in these populations.]

3. Cancer in Experimental Animals

The carcinogenicity of tetrachloroethylene in experimental animals was last reviewed by an IARC Working Group in 1995 (IARC, 1995), and more recently by the United States Environmental Protection Agency (EPA, 2012).

3.1 Mouse

See Table 3.1

3.1.1 Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age 5–7 weeks) were given tetrachloroethylene (purity, 99%) by gavage in corn oil on 5 days per week for 78 weeks (NCI, 1977; Weisburger, 1977). Groups of 20 male and 20 female mice were given vehicle only and served as controls. Dosage adjustments were made during the exposure period: male mice were given tetrachloroethylene at a dose of 450 or 900 mg/kg body weight (bw) for 11 weeks, and then at 550 or 1100 mg/kg bw for 67 weeks; female mice were given tetrachloroethylene at a dose of 300 or 600 mg/kg bw for 11 weeks, and then at 400 or 800 mg/kg bw for 67 weeks. Time-weighted average doses of tetrachloroethylene were 536 and 1072 mg/kg bw per day, respectively, for males, and 386 and 772 mg/kg bw per day, respectively, for females. The treatment period was followed by a 12-week observation period. Mortality was significantly increased in treated mice compared with controls. Significant dose-related positive trends and increased incidences of hepatocellular carcinoma in all treatment groups were observed in males and females. In male mice, the incidences were 2 out of 20 (vehicle controls), 32 out of 49 (lower dose), and 27 out of 48 (higher dose); the corresponding incidences in females were 0 out of 20, 19 out of 48, and 19 out of 48. Exposure to tetrachloroethylene caused toxic nephropathy (characterized in this study as degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium) in male mice (0/20, 40/49, 45/48) and female mice (0/20, 46/48, 48/48). A rare renal tubular cell carcinoma was observed in a male at the lower dose. [The Working Group noted that the study animals were housed in the same rooms as animals exposed to volatile agents, the group size for vehicle controls was small, and decreased survival and the 78-week exposure period reduced the power of this study to detect the full carcinogenic potential of the test agent.]

3.1.2 Inhalation

Groups of 49–50 male and 49–50 female B6C3F$_1$ mice (age, 8–9 weeks) 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 hours per day on 5 days per week for up to 103 weeks (Mennear *et al.*, 1986; NTP, 1986). Survival was significantly reduced for males at both doses, and for females at the

Table 3.1 Studies of carcinogenicity in experimental animals exposed to tetrachloroethylene

Species, strain (sex) Duration Reference	Route, dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M) 90 wk NCI (1977); Weisburger, (1977)	Gavage in corn oil 0 (vehicle control), 536, 1072 mg/kg bw per day, 5 days/wk for 78 wk, 20, 50, 50/group	Hepatocellular carcinoma: 2/20, 32/49, 27/48	Cochran-Armitage test, Fisher exact test $P < 0.01$ (trend), $P < 0.001$ (lower dose, higher dose)	Purity, 99%, survival (reduction): 50%, 38%, 20%
Mouse, B6C3F$_1$ (F) 90 wk NCI (1977); Weisburger (1977)	Gavage in corn oil 0 (vehicle control), 386, 772 mg/kg bw per day, 5 days/wk for 78 wk, 20, 50, 50/group	Hepatocellular carcinoma: 0/20, 19/48, 19/48	Cochran-Armitage test, Fisher exact test $P < 0.01$ (trend), $P < 0.001$ (lower dose, higher dose)	Purity, 99%, survival (reduction): 90%, 22%, 14%
Mouse, B6C3F$_1$ (M) 24 mo NTP (1986)	Inhalation 0, 100, 200 ppm, 6 h/day, 5 days/wk, 50, 50, 50/group	Hepatocellular adenoma: 12/49, 8/49, 19/50 Hepatocellular carcinoma: 7/49, 25/49, 26/50 Hepatocellular adenoma or carcinoma (combined): 17/49, 31/49, 41/50	Incidental tumour test $P < 0.01$ (trend), $P < 0.05$ (higher dose) $P < 0.01$ (trend), $P < 0.05$ (lower dose, higher dose) $P < 0.001$ (trend), $P < 0.05$ (lower dose, higher dose)	Purity, 99.9%; survival (reduction): 94%, 50%, 64%
Mouse, B6C3F$_1$ (F) 24 mo NTP (1986)	Inhalation 0, 100, 200 ppm, 6 h/day, 5 days/wk, 49, 50, 50/group	Hepatocellular carcinoma: 1/48, 13/50, 36/50 Hepatocellular adenoma or carcinoma (combined): 4/48, 17/50, 38/50	Incidental tumour test $P < 0.001$ (trend), $P < 0.001$ (low dose, high dose) $P < 0.001$ (trend), $P < 0.001$ (low dose, high dose)	Purity, 99.9%; survival (reduction): 73%, 62%, 38%

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crj:BDF1 (M) 24 mo JISA (1993); EPA (2012)	Inhalation 0, 10, 50, 250 ppm, 6 h/day, 5 day/wk, 50/group	Hepatocellular adenoma: 7/50, 13/50, 8/50, 26/50 Hepatocellular carcinoma: 7/50, 8/50, 12/50, 25/50 Hepatocellular adenoma or carcinoma (combined): 13/50, 21/50, 19/50, 40/50 All organs, haemangioma or haemangiosarcoma (combined): 2/50, 1/50, 6/50, 8/50 Spleen, haemangiosarcoma: 1/50, 1/50, 3/50, 5/50 Liver, haemangiosarcoma: 1/50, 1/50, 5/50, 5/50 Harderian gland adenoma: 2/50, 2/50, 2/50, 8/50	Peto test, Fisher exact test $P < 0.001$ (trend), $P < 0.01$ (highest dose) $P < 0.001$ (trend), $P < 0.01$ (highest dose) $P < 0.001$ (trend), $P < 0.01$ (highest dose) $P < 0.05$ (trend) $P < 0.05$ (trend) $P < 0.05$ (trend) $P < 0.01$ (trend)	Purity, 99%, survival (reduction): 62%, 70%, 56%, 44%. The US EPA re-analysed the data on individual animals from this study and reported the overall incidence of haemangioma or haemangiosarcoma (combined) for all organs (primarily liver or spleen) to be 4/50, 2/50, 7/50, 11/50 (EPA, 2012)
Mouse, Crj:BDF1 (F) 24 mo JISA (1993); EPA (2012)	Inhalation 0, 10, 50, 250 ppm, 6 h/day, 5 day/wk, 50/group	Hepatocellular adenoma: 3/50, 3/47, 7/49, 26/49 Hepatocellular carcinoma: 0/50, 0/47, 0/49, 14/49 Hepatocellular adenoma or carcinoma (combined): 3/50, 3/47, 7/49, 33/49 All organs, haemangioma or haemangiosarcoma (combined): 1/50, 0/47, 2/49, 3/49	Peto test, Fisher exact test $P < 0.001$ (trend), $P < 0.001$ (highest dose) $P < 0.001$ (trend), $P < 0.001$ (highest dose) $P < 0.001$ (trend), $P < 0.001$ (highest dose) $P < 0.05$ (trend)	Purity, 99%, survival (reduction): 64%, 57%, 45%, 34%
Rat, Osborne-Mendel (M) 110 wk NCI (1977); Weisburger (1977)	Gavage in corn oil 0 (vehicle control), 471, 941 mg/kg bw per day, 5 days/wk for 78 wk, 20, 50, 50/group	No significant differences in tumour incidence between control and treated animals	NS	Purity, 99%; survival (reduction): 10%, 12%, 4%

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Osborne-Mendel (F) 110 wk NCI (1977); Weisburger (1977)	Gavage in corn oil 0 (vehicle control), 474, 949 mg/kg/d bw, 5 d/wk for 78 wk, 20, 50, 50/group	No significant differences in tumour incidence between control and treated animals	NS	Purity, 99%; survival (reduction): 40%, 34%, 28%
Rat, F344 (M) 24 mo NTP (1986)	Inhalation 0, 200, 400 ppm, 6 h/day, 5 day/wk, 50/group	Mononuclear cell leukaemia (all three stages): 28/50, 37/50, 37/50	Life-table test $P < 0.01$ (trend), $P < 0.05$ (lower dose, higher dose)	Purity, 99.9%; survival (reduction): 46%, 40%, 24%
		Mononuclear cell leukaemia (stage 3 only): 20/50, 24/50, 27/50	$P < 0.05$ (trend), $P < 0.05$ (higher dose)	
		Kidney, tubular cell adenoma or carcinoma (combined): 1/49, 3/49, 4/50	NS	Historical control incidence in NTP studies: 4/1968 (0.2 ± 0.6%, no adenocarcinoma)
		Kidney, tubular cell carcinoma: 0/49, 0/49, 2/50	NS	
		Glioma: 1/50, 0/50, 4/50	Life-table test $P < 0.05$ (trend)	Historical control incidence in NTP studies: 16/1971 (0.8%)
		Testis, interstitial cell tumour: 35/50, 39/49, 41/50	Incidental tumour test $P < 0.05$ (trend), $P < 0.05$ (lower dose, higher dose)	Historical control incidence in NTP studies: 740/1055 (70.1%)
Rat, F344 (F) 24 mo NTP (1986)	Inhalation 0, 200, 400 ppm, 6 h/day, 5 days/wk, 50/group	Mononuclear cell leukaemia (all three stages): 18/50, 30/50, 29/50	Life table test $P = 0.053$ (trend), $P < 0.05$ (lower dose)	Purity, 99.9%
		Mononuclear cell leukaemia (stage 3 only): 10/50, 18/50, 21/50	$P < 0.05$ (trend), $P < 0.05$ (higher dose)	
Rat, F344/DuCrj (M) 24 mo JISA (1993); EPA (2012)	Inhalation 0, 50, 200, 600 ppm, 6 h/day, 5 days/wk, 50/group	Mononuclear cell leukaemia: 11/50, 14/50, 22/50, 27/50	Peto test, Fisher exact test $P < 0.001$ (trend), $P < 0.05$ (highest dose)	Purity, 99%; survival (reduction): 74%, 68%, 60%, 56%
Rat, F344/DuCrj (F) 24 mo JISA (1993); EPA (2012)	Inhalation 0, 50, 200, 600 ppm, 6 h/day, 5 days/wk, 50/group	Mononuclear cell leukaemia: 10/50, 17/50, 16/50, 19/50 Mammary gland fibroadenoma: 3/50, 13/50, 1/50, 0/50	Peto test, Fisher exact test $P < 0.001$ (trend), $P < 0.05$ (lowest dose)	Purity, 99%; survival (reduction): 84%, 68%, 68%, 68%

EPA, Environmental Protection Agency; F, female; h, hour; mo, month; M, male; NS, not significant; NTP, National Toxicology Program; wk, week

higher dose, compared with controls. Significant positive trends were observed in males for the incidence of hepatocellular adenoma and in both sexes for hepatocellular carcinoma. The incidence of hepatocellular carcinoma were also significantly increased at both doses in males (7/49, 25/49, 26/50) and females (1/48, 13/50, 36/50); and the incidence of hepatocellular adenoma or carcinoma (combined) was also significantly increased at both doses in males (17/49, 31/49, 41/50) and females (4/48, 17/50, 38/50). The incidence of hepatic degeneration was increased in male mice at both doses (2/49, 8/49, 14/50) and in female mice at the higher dose (1/49, 2/50, 13/50). The incidence of karyomegaly of renal tubular cells was also increased in exposed mice (males: 4/49, 17/49, 46/50; females: 0/48, 16/49, 38/50). [The Working Group noted that decreased survival reduced the power of this study to detect the full carcinogenic potential of the test agent.]

Groups of 50 male and 50 female Crj:BDF1 mice (age, 5 weeks) were exposed to air containing tetrachloroethylene (purity, 99%) at concentrations of 0, 10, 50, or 250 ppm [0, 68, 340, or 1695 mg/m^3] for 6 hours per day on 5 days per week for up to 103 weeks (JISA, 1993; EPA, 2012). Survival decreased with increasing concentration among males and females; however, no statistical analysis of the survival data was provided. In males and females, significant positive trends in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were observed, and the incidences of these neoplasms were significantly increased in the group at the highest dose, compared with controls. The incidences of hepatocellular carcinoma were 7 out of 50 (control), 8 out of 50 (lowest dose), 12 out of 50 (intermediate dose), 25 out of 50 (highest dose) in male mice, and 0 out of 50, 0 out of 47, 0 out of 49, and 14 out of 49, respectively, in female mice. The incidences of hepatocellular adenoma or carcinoma (combined) were 13 out of 50, 21 out of 50, 19 out of 50, and 40 out of 50, respectively, in male mice, and 3 out of 50, 3 out of 47, 7 out of 49, and 33 out of 49 in female mice. The incidence of hepatic degeneration was also increased at the highest dose in males (1/50, 1/50, 4/50, and 37/50) and in females (0/50, 1/50, 2/50, and 30/50). In addition, there was a positive trend in the incidence of haemangiosarcoma of the liver and of the spleen in males, of haemangioma or haemangiosarcoma (combined) for all organs in males and females (primarily of the liver or spleen in males), and of Harderian gland adenoma in males (2/50, 2/50, 2/50, and 8/50). The incidence of karyomegaly of renal tubular cells was also increased in the highest dose compared with controls (males: 0/50, 0/50, 6/50, 38/50; females: 0/50, 0/50, 1/50, 49/50).

3.1.3 Skin application

Two groups of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) were given tetrachloroethylene [purity not reported] at a dose of 18 or 54 mg per application in 0.2 mL of acetone by repeated topical application (three times per week) for at least 63 weeks. A control group of 30 mice was given an application of 0.1 mL acetone only (Van Duuren *et al.*, 1979). The effects of exposure on survival were not reported. One skin papilloma occurred in a mouse at the lower dose; no skin tumours were observed among controls or in mice at the higher dose. [Interpretation of these findings was limited by the small number of animals tested, the short exposure duration, the incomplete reporting of results, and because the study did not address volatile loss of the test compound.]

3.1.4 Intraperitoneal injection

In a screening assay for induction and increased multiplicity of lung tumours, three groups of 20 male mice of strain A/St (age, 6–8 weeks) were given tetrachloroethylene (purity unspecified, but ≥ 95%) by intraperitoneal

injection in tricaprylin, at doses of 80 mg/kg bw (14 injections), 200 or 400 mg/kg bw (24 injections), three times per week (Theiss *et al.*, 1977). A group of 50 controls was given 24 injections of tricaprylin only. Twenty-four weeks after the first injection, the mice were killed, their lungs were examined under a dissecting microscope, and the number of surface adenomas was counted. Tetrachloroethylene did not increase the number of pulmonary adenomas per mouse in treated animals compared with controls. [The small number of animals studied and the short duration of exposure limited the interpretation of these findings. In addition, the lung was the only organ examined.]

3.2 Rat

3.2.1 Oral administration

Groups of 50 male and 50 female Osborne-Mendel rats (age, 7 weeks) were given tetrachloroethylene (purity, 99%) by gavage in corn oil on 5 days per week for 78 weeks (NCI, 1977; Weisburger, 1977). Groups of 20 male and 20 female rats (age, approximately 11 weeks) were treated with vehicle only and served as controls. Dosage adjustments were made during the exposure period: male rats were given tetrachloroethylene at a dose of 500 or 1000 mg/kg bw for 19 weeks, then 700 or 1400 mg/kg bw for 6 weeks, and 500 or 1000 mg/kg bw for 46 weeks, followed by 26 weeks of cyclic dosing comprising one treatment-free week and 4 weeks at 500 or 1000 mg/kg bw; female rats were given tetrachloroethylene at a dose of 500 or 1000 mg/kg bw for 16 weeks, then 600 or 1200 mg/kg bw for 3 weeks, 700 or 1400 mg/kg bw for 6 weeks, and 500 or 1000 mg/kg bw for 20 weeks, followed by 26 weeks of cyclic dosing with one treatment-free week and 4 weeks at 500 or 1000 mg/kg bw. 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. Mortality was significantly increased in treated rats compared with controls. Toxic nephropathy was observed at the lower and higher doses in 88% and 94% of males, and 50% and 80% of females, respectively, and not in controls. Toxic nephropathy in rats was morphologically similar to that described in Section 3.1.1 for $B6C3F_1$ mice treated with tetrachloroethylene by gavage (NCI, 1977; Weisburger, 1977). There were no significant differences in tumour incidence between the control and treated rats of either sex. [The Working Group noted that high mortality and the 78-week exposure period precluded reliable evaluation of carcinogenicity. In addition, study animals were housed in the same rooms as animals exposed to volatile agents, and the small group size for vehicle controls limited the power of this study.]

3.2.2 Inhalation

In an abstract, Rampy *et al.* (1977) reported no increase in tumour incidence in groups of male or female Sprague-Dawley rats (n = 96 for the treated groups and n = 192 for the control groups) exposed to vapours containing tetrachloroethylene at a concentration of 300 or 600 ppm, for 6 hours per day on 5 days per week for 12 months, and then observed for an additional 18 months. [The Working Group noted that the duration of exposure was too short to adequately evaluate the carcinogenic potential of tetrachloroethylene, and details of experimental methods and results were lacking.]

Groups of 50 male and 50 female Fischer 344/N rats (age, 8–9 weeks) 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 hours per day on 5 days per week for up to 103 weeks (Mennear *et al.*, 1986; NTP, 1986). Survival of male rats in the group at the higher dose was significantly lower than that of controls. Positive trends and increased incidence

of mononuclear cell leukaemia were observed in both sexes. The incidences of mononuclear cell leukaemia in males were: 28 out of 50 (controls), 37 out of 50 (lower dose), and 37 out of 50 (higher dose); and in females, the incidences were: 18 out of 50, 30 out of 50, and 29 out of 50. The historical incidence of mononuclear cell leukaemia in 2-year studies conducted in F344 rats at the study laboratory was 47 ± 15% in males and 29 ± 6% in females. The incidence of advanced (stage 3) mononuclear cell leukaemia (characterized by involvement of multiple organs) was increased in exposed males (20/50, 24/50, 27/50) and females (10/50, 18/50, 21/50). A non-significant increase in uncommonly occurring adenoma or carcinoma (combined) of the kidney tubule was observed in male rats (1/49, 3/49, 4/50); the historical incidence of these neoplasms in control male rats in inhalation studies conducted by the National Toxicology Program (NTP) at that time was 4 out of 1968 (0.2 ± 0.6%). Among the eight male rats that developed tumours of the kidney tubule in the study, carcinomas were observed in two males at the higher dose; malignant tubular cell tumours had not been observed previously in control male F344 rats in NTP inhalation studies. In addition, the incidence of renal tubular cell hyperplasia was increased in exposed male rats (0/49, 3/49, 5/50) and the incidence of karyomegaly (nuclear enlargement) in renal tubular epithelial cells was increased in males (1/49, 37/49, 47/50), and females (0/50, 8/49, 20/50). In male rats, significant positive trends in the incidence of glioma (1/50, 0/50, 4/50) and interstitial cell tumours of the testis (35/50, 39/49, 41/50) were observed. Gliomas are uncommon in male F344 rats; the historical incidence of these neoplasms in all NTP studies conducted at that time was 16 out of 1971 (0.8%). Gliomas were also observed in one female in the control group and in two females at the higher dose. Although the incidence of interstitial cell tumours of the testis was high in male F344 rats in 2-year studies, the mean incidence in historical controls in male rats in inhalation studies conducted by the NTP using NIH-07 diet was 70.1% (740/1055; NTP, 2012), similar to the incidence for controls in this study. Thus, the Working Group considered that in addition to mononuclear cell leukaemia, the increased incidences of renal tubular cell tumours, glioma, and interstitial tumours of the testis in male rats were also associated with exposure to tetrachloroethylene.

Groups of 50 male and 50 female F344/DuCrj rats (age, 5 weeks) were exposed to air containing tetrachloroethylene (purity, 99%) at concentrations of 0, 50, 200, or 600 ppm [0, 340, 1360, or 4080 mg/m^3] for 6 hours per day on 5 days per week for up to 103 weeks (JISA, 1993; EPA, 2012). Survival was lower in exposed rats than in controls, although no statistical analysis of the survival data was provided. Increased incidences of mononuclear cell leukaemia were observed in male rats (control, 11/50; lowest dose, 14/50; intermediate dose, 22/50; highest dose, 27/50) and female rats (10/50, 17/50, 16/50, 19/50); significant positive trends were observed for both sexes, and the incidence in the group at the highest dose was significantly greater than that in controls. The historical incidence of mononuclear cell leukaemia in 2-year studies in F344/DuCrj rats conducted at the study laboratory was 13% (range, 6–22%) in males and 14% (range, 2–26%) in females. Similarly to the NTP (1986) study, exposure to tetrachloroethylene induced an increase in the incidence of karyomegaly in renal tubular epithelial cells in males (0/50, 0/50, 23/50, 48/50), and females (0/50, 0/50, 1/50, 16/50). The incidences of renal tubular cell adenoma in male rats were 1 out of 50, 2 out of 50, 1 out of 50, and 2 out of 50. In female rats, a renal tubular cell adenoma was observed in the control group, and a rare renal tubular cell carcinoma was observed in the group at the highest dose. A significant increase in the incidence of mammary gland fibroadenoma was observed in females at the lowest dose (3/50, 13/50, 1/50, 0/50).

3.3 Studies with mixtures of solvents

Mouse

Groups of 33–43 male and 36–41 female ICR mice were given drinking-water containing a mixture of six chlorinated alkanes and alkenes (including tetrachloroethylene) at three different concentrations for 16 months (males) or 18 months (females) (Wang *et al.*, 2002). The concentrations of tetrachloroethylene in these mixtures were 36.0, 90.3, or 606.5 μg/mL, respectively, accounting for 38–52% of each formulation. Among mice surviving to the end of the study, there was a non-statistically significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) in males at the lowest dose (3/18) and intermediate dose (4/15) compared with controls (1/23), and a significant increase ($P < 0.05$) in the incidence of adenocarcinoma of the mammary gland in females at the highest dose (5/26) compared with controls (0/24). [The Working Group noted that because this study was designed to attain the approximate concentrations of these solvents in groundwater near an electronic appliances factory in Taiwan, China, the doses of tetrachloroethylene were much lower than those used in the study of oral carcinogenicity in mice described in Section 3.1.1 and would not be adequate to evaluate the carcinogenic potential of this chlorinated solvent. Furthermore, the influence of other agents in the mixture has not been studied. The mixture containing tetrachloroethylene at 606 μg/mL appeared to have exceeded the solubility of tetrachloroethylene in water (about 150 μg/mL), but groundwater can contain higher concentrations of this chemical.]

3.4 Initiation–promotion studies

Mouse

Tetrachloroethylene [purity unspecified] in 0.2 mL of acetone was applied as a single dose at 163 mg/mouse to the dorsal skin of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) (Van Duuren *et al.*, 1979). Topical applications (three times per week) of the tumour promoter 12-*O*-tetradecanoylphorbol 13-acetate (5 μg in 0.2 mL of acetone) began 14 days later and were continued for at least 61 weeks. A control group of 90 mice received 12-*O*-tetradecanoylphorbol 13-acetate only. Seven skin papillomas were found in 4 out of 30 treated mice, and seven skin papillomas were found in 6 out of 90 controls. This difference was not statistically significant. [Interpretation of these findings was limited by the incomplete reporting of results (e.g. purity of the compound), and because the study did not address loss of the test compound due to volatility.]

3.5 Carcinogenicity of metabolites

Studies of carcinogenicity with dichloroacetic acid and trichloroacetic acid are summarized in the respective *Monographs* in this volume.

Mouse

Groups of 30 female ICR/Ha Swiss mice (age, 6–8 weeks) received tetrachloroethylene oxide, a metabolite of tetrachloroethylene, by skin application (5 μL [7.5 mg]/mouse followed immediately by 0.1 mL acetone) three times per week for 65 weeks, or by subcutaneous injection (500 μg/mouse in 0.05 mL of trioctanoin) once per week for up to 80 weeks (Van Duuren *et al.*, 1983). Controls received a skin application of 0.1 mL of acetone only. In mice receiving tetrachloroethylene oxide by skin application, a significant increase ($P = 0.014$) in the incidence of skin tumours at the site of application (4/30;

one keratoacanthoma, two squamous cell papillomas, and one squamous cell carcinoma) was observed compared with controls (0/30). The results of the subcutaneous-injection experiment were negative. [The Working Group noted that the half-life of tetrachloroethylene oxide is only 11.5 minutes in aqueous media.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Absorption

(a) Humans

Tetrachloroethylene is a lipophilic solvent of low relative molecular mass that readily crosses biological membranes. Pulmonary uptake is rapid, approaching steady-state within a few hours after the start of exposure.

In a study with six male volunteers, pulmonary uptake decreased during the course of the experiment to 60% of the initial value (Monster, 1979). Measured alveolar retention was 65%, averaged over six or seven volunteers (Monster *et al.*, 1979; Chiu *et al.*, 2007). Increased physical activity increases uptake, but lowers the alveolar partial pressure, thus removing more tetrachloroethylene from the alveoli, resulting in a longer time to reach tissue equilibrium (Pezzagno *et al.*, 1988). The blood–air partition coefficient represents the ratio of the concentrations in the two media at steady-state, and is a factor in determining pulmonary uptake. The partition coefficient has been measured *in vitro* by means of vial-equilibrium methods (Gargas *et al.*, 1989), and mean values ranged from 10 to 17 for humans (Sato & Nakajima, 1979; Koizumi 1989; Gearhart *et al.*, 1993; Fisher *et al.*, 1997; Mahle *et al.*, 2007).

Data on oral absorption are limited. One case report of accidental ingestion suggested that tetrachloroethylene is also readily absorbed by this route of exposure (Köppel *et al.*, 1985). Quantitative estimates of the bioavailability of tetrachloroethylene after oral intake in humans are not available, because the ingested amounts are not precisely known, and because the exposed subjects underwent hyperventilation therapy.

Dermal absorption of tetrachloroethylene vapours by humans has been reported to be relatively insignificant (only 1%) when compared with absorption via inhalation (Riihimäki & Pfäffli, 1978; Nakai *et al.*, 1999). After liquid contact, skin absorption can be more significant: the amount of chemical absorbed during the immersion of one thumb in liquid tetrachloroethylene is equivalent to the uptake during inhalation of two to five times this amount during the same period (Stewart & Dodd, 1964). The permeability of tetrachloroethylene through skin was tested in a penetration model *in vitro* with human skin and skin of hairless guinea-pigs. The results for these two skin types were similar (Frasch & Barbero, 2009). Dermal absorption of tetrachloroethylene from contaminated soil has also been measured (Poet *et al.*, 2002).

(b) Experimental systems

Inhalation studies in experimental animals have been conducted predominantly in adult males. Tetrachloroethylene is readily absorbed via the lungs into the systemic circulation (Pegg *et al.*, 1979; Dallas *et al.*, 1994a, b, 1995). Blood–air partition coefficients for tetrachloroethylene have been measured *in vitro* by means of vial-equilibrium methods (Gargas *et al.*, 1989) and ranged from 13 to 21 for rodents (Koizumi 1989; Gearhart *et al.*, 1993; Reitz *et al.*, 1996; Mahle *et al.*, 2007).

Oral doses of tetrachloroethylene – given by gavage or in drinking-water – are almost completely absorbed from the gut, as reported in several studies in mice, rats, and dogs (Pegg *et al.*, 1979; Schumann *et al.*, 1980; Frantz & Watanabe, 1983; Dallas *et al.*, 1995).

Dermal uptake is minimal compared with pulmonary uptake during exposure to tetrachloroethylene vapour (Tsuruta, 1989), but is greater after direct application to the skin (Jakobson *et al.*, 1982; Bogen *et al.*, 1992). Permeability coefficients have been measured *in vitro* in several studies. Nakai *et al.* (1999) reported lower permeability into human skin for liquid tetrachloroethylene than for trichloroethylene or chloroform. Absorption of tetrachloroethylene from a contaminated soil matrix was higher in rats than in humans (Poet *et al.* 2002).

4.1.2 Distribution and body burden

(a) Humans

Once absorbed, tetrachloroethylene enters the blood circulation and undergoes rapid systemic distribution to tissues. The highest concentrations are expected to occur in adipose and other fatty tissue, due to the lipophilicity of the compound. Data on distribution of tetrachloroethylene in humans *in vivo* come from analyses of tissues taken from autopsies after fatal accidents. The available data show wide systemic distribution in blood and across all tissues tested, including the lung, liver, heart, kidney, and brain (Lukaszewski 1979; Levine *et al.*, 1981; Garnier *et al.*, 1996). Tetrachloroethylene has also been measured in human breast milk (Schreiber 1993, 1997; Schreiber *et al.*, 2002).

Repeated daily exposure of human volunteers to tetrachloroethylene by inhalation resulted in accumulation of the compound in the body, with blood concentrations increasing over several days. Exhalation of the compound continued over several days due to its slow release from adipose tissue (Skender *et al.*, 1991). For a given concentration in blood or air, the half time [the time required to equilibrate the adipose tissue to 50% of its final concentration] is about 25 hours (Monster, 1979). For persons exposed to tetrachloroethylene in a work schedule of 5 days per week, an equilibrium is established over 3–4 weeks.

The of tissue–blood partition coefficient has been measured *in vitro* by use of vial-equilibrium methods in human fat, kidney, muscle, and liver. The highest reported values are for fat (125), as expected due to the lipophilicity of tetrachloroethylene, with values for the remaining tissues ranging from 5 to 6 (Gearhart *et al.*, 1993).

(b) Experimental systems

Studies in experimental animals have been conducted predominantly in adult males. These experiments provide clear evidence that tetrachloroethylene is distributed widely to all tissues of the body. In rats exposed *in vivo*, tetrachloroethylene has been detected and measured in blood, fat, brain, lungs, liver, kidneys, heart, and skeletal muscle. The highest tissue concentrations were found in adipose tissue (≥ 60 times that in blood) and in brain and liver (four and five times higher than in blood, respectively), as was calculated from rat tissue-distribution data (Savolainen *et al.*, 1977; Dallas *et al.*, 1994a, b). The concentration of tetrachloroethylene in fat was 9–18 times higher than the concentrations found in other tissues. Skeletal muscle contained the lowest concentration (Dallas *et al.* (1994b). Tetrachloroethylene readily crosses the blood–brain barrier (Savolainen *et al.*, 1977; Schumann *et al.*, 1980) and the placenta (Ghantous *et al.*, 1986).

Partition coefficients have also been measured *in vitro* for a wide variety of tissues in rats and mice, including fat, liver, muscle, skin, kidney, and brain (Gargas *et al.*, 1989; Koizumi 1989; Gearhart *et al.*, 1993; Mattie *et al.*, 1994; Mahle *et al.*, 2007). The highest reported values were those for fat (90–110), whereas partition coefficients for the remaining tissues were in the range 1–4.

4.1.3 Metabolism

(a) Overview

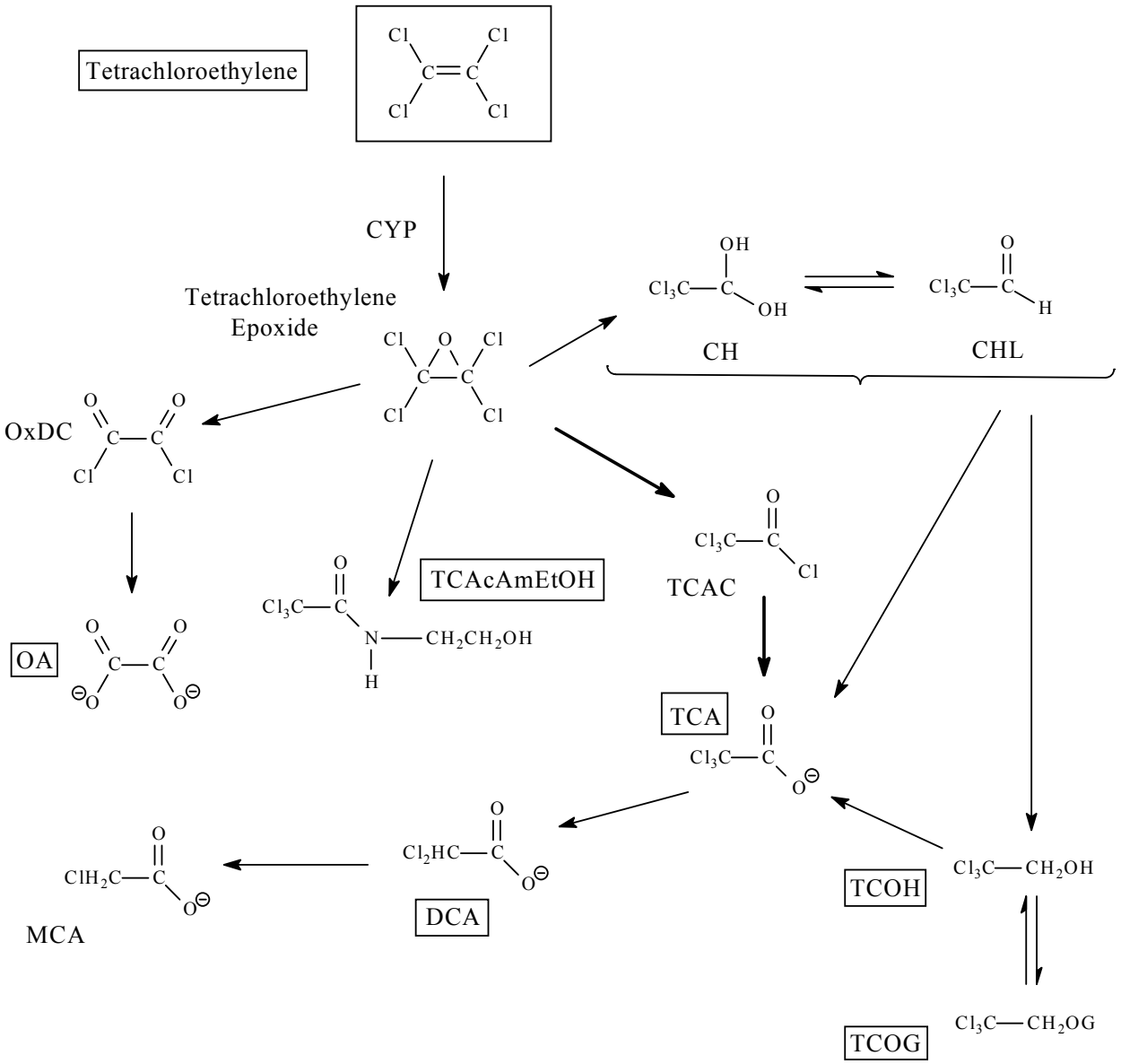
Metabolism is critical to the various adverse effects of tetrachloroethylene in biological systems: with the exception of solvent effects that occur at extremely high exposures to tetrachloroethylene, all the adverse effects of tetrachloroethylene can be attributed to specific metabolites. The basic metabolic pathways for tetrachloroethylene have for the most part been deciphered over many years and have been summarized in various publications as well as a recent review (Green, 1990; IARC, 1995; Lash & Parker, 2001; EPA, 2012). This section will describe the major pathways in the metabolism of tetrachloroethylene, i.e. the cytochrome P450 (CYP)-dependent oxidative pathway and the glutathione (GSH)-conjugation pathway, in humans and experimental animals. Key urinary metabolites that are often used to estimate exposure in environmental or occupational settings have been identified. While the basic outline of the pathways has been known for many years, this section will focus on some of the more recently identified metabolites, particularly those described during the past decade. This section comprises four subsections: (i) an overview of the major pathways of tetrachloroethylene metabolism and the enzymes involved; (ii) a review of each step of the CYP-dependent pathway, providing evidence from humans or human tissues, and from experimental systems; (iii) a review of each step of the GSH-conjugation pathway, likewise providing data from humans or human tissues and from experimental systems; where appropriate, information on membrane transport of metabolites will be discussed; and (iv) a brief discussion of comparisons between the metabolism of tetrachloroethylene and trichloroethylene (see *Monograph* in this volume). Although tetrachloroethylene and trichloroethylene share several metabolic intermediates, have very similar metabolites, or are metabolized by similar enzymes, there are several important differences that need to be carefully considered.

Of the two major pathways, the flux through the oxidative pathway far exceeds that through the GSH-conjugation pathway. Whereas the latter generates several highly reactive metabolites, those generated by the oxidative pathway are in most cases chemically stable, although there are exceptions. [The Working Group noted that some of the chemically stable oxidative metabolites may be linked to adverse effects, but the different chemical reactivities of metabolites generated by the two pathways may render some metabolites in the GSH-conjugation pathway difficult to detect. Interpretations regarding the toxicological importance of such metabolites – based on quantitative differences in estimated flux – must, therefore, be made with caution.]

(i) CYP-dependent oxidation

The overall scheme of the metabolism of tetrachloroethylene via the CYP-dependent oxidative pathway is shown in Fig. 4.1. The initial step is catalysed by CYP and is believed to lead to the formation of tetrachloroethylene epoxide, although a transient intermediate of tetrachloroethylene with CYP may also occur (Yoshioka *et al.*, 2002). Tetrachloroethylene epoxide may follow several reaction pathways (the quantitatively predominant route is indicated by the thicker arrow in Fig. 4.1): the epoxide may be de-chlorinated to oxalate dichloride and oxalate, which is excreted in the urine. Alternatively, the epoxide may be converted to trichloroacetyl aminoethanol (a urinary metabolite), which is a relatively minor pathway. The major metabolic route is conversion to trichloroacetyl chloride, which is subsequently converted to trichloroacetate, the major metabolite recovered in urine of tetrachloroethylene-exposed humans and animals. Finally, some of the trichloroacetate may be converted to dichloroacetate, which has been detected in urine, typically in very low amounts.

Fig. 4.1 Scheme for oxidative metabolism of tetrachloroethylene



Tetrachloroethylene undergoes cytochrome P450 (CYP)-dependent oxidation to primarily form an epoxide intermediate. Further processing yields a variety of metabolites, including chloral (CHL) and chloral hydrate (CH), trichloroacetyl chloride (TCAC), trichloroacetyl aminoethanol (TCAcAmEtOH), or oxalate dichloride (OxDC). Trichloroacetate (TCA) can be generated from either CHL/CH, TCAC, or trichloroethanol (TCOH) and its glucuronide (TCOG). Dichloroacetate (DCA) and monochloroacetate (MCA) are considered minor metabolites. OxDC is dechlorinated to yield oxalate (OA), which is a significant urinary metabolite. Names of metabolites that are recovered in urine are shown in boxes. The thicker arrows indicate the major pathway of metabolite flux.

The major oxidative metabolites formed from tetrachloroethylene, their site of formation or portal of entry, and the source of the information (animals and/or humans), is presented in Table 4.1. Systemic availability is dependent on the chemical stability of the metabolites: those that are relatively stable may be transferred from their site of formation into the blood stream and be delivered to other potential target organs, whereas those that are chemically unstable and reactive (tetrachloroethylene-oxide) tend to remain near their site of formation and react with cellular molecules, including DNA, proteins, and lipids.

(ii) GSH-conjugation

As shown in Fig. 4.2, tetrachloroethylene undergoes an S_N2 nucleophilic displacement reaction with GSH, releasing a chloride ion under formation of *S*-(1,2,2-trichlorovinyl)glutathione (TCVG). Although this initial GSH-conjugation step can take place in many tissues, it occurs primarily in the liver as a result of first-pass metabolism and because of the high content of glutathione-*S*-transferases (GSTs): the various GST isoforms can account for as much as 5% of total cytosolic protein in rat or human liver. This initial step in the metabolism of tetrachloroethylene leads to the formation of reactive metabolites associated with toxic effects in the kidneys, or to a non-toxic mercapturate that is readily excreted in the urine.

After formation of TCVG, which occurs predominantly in the liver but also in the kidneys (Lash *et al.*, 1998), this metabolite is processed by γ-glutamyltransferase (GGT) and dipeptidase on the brush-border plasma membrane of the renal proximal tubular cell, to form the corresponding cysteine conjugate *S*-(1,2,2-trichlorovinyl)-L-cysteine (TCVC). Although GGT and dipeptidase activities are present in other tissues, the inter-organ pathways by which GSH and GSH-conjugates are processed effectively direct the GSH-conjugate to the kidneys.

The formation of TCVC represents a critical branch point in the GSH-dependent metabolism of tetrachloroethylene. This cysteine conjugate serves as a substrate for several enzymes that catalyse reactions towards its bioactivation to chemically reactive metabolites, or to its detoxification. The detoxification route involves *N*-acetylation by the microsomal enzyme *N*-acetyltransferase (NAT) to form *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine (NAcTCVC). Although the latter product has been recovered in the urine of both rats and humans exposed to tetrachloroethylene (Bartels, 1994; Birner *et al.*, 1996; Völkel *et al.*, 1999), it can be metabolized via two alternative routes. First, as a substrate for acylase I, NAcTCVC can be deacetylated to regenerate TCVC (Uttamsingh & Anders, 1999). And second, it can undergo sulfoxidation as catalysed by CYP3A enzymes (CYP3A1/2 in rats and CYP3A4 in humans) (Werner *et al.*, 1996). The resulting TCVC sulfoxide (TCVCS) is highly reactive and cytotoxic.

Apart from the metabolic changes in the mercapturate/mercapturate sulfoxide reaction pathway, TCVC is metabolized to reactive species by either cysteine conjugate β-lyase (CCBL) (Dekant *et al.*, 1986a), which produces 1,2,2-trichlorovinylthiol (TCVT), or by a cysteine conjugate *S*-oxidase activity, identified as a catalytic function of flavin-containing monooxygenase 3 (FMO3) (Ripp *et al.*, 1997), which forms TCVCS. Both TCVC and TCVCS can rearrange spontaneously to form a thioketene, which is the ultimate reactive and toxic acylating agent. These additional metabolic routes leading to the formation of the putative end product of the GSH-conjugation pathway highlight both the complexity of the metabolism of tetrachloroethylene along this pathway, and the potential difficulties in assessing the overall flux through the GSH-conjugation pathway by use of urinary NAcTCVC as a surrogate marker.

The site of formation and systemic availability for the major metabolites from the

Table 4.1 Formation and systemic availablility of tetrachloroethylene metabolites

Compound or metabolite	Portal of entry, or tissue where formed in animals (A) or humans (H)
Tetrachloroethylene	Lung (A, H) Gastrointestinal tract (A, H) Skin (A, H)
Oxidative metabolites	
Tetrachloroethylene epoxide [a]	Liver (A)
Trichloroacetyl chloride	Lung (A)
Trichloroacetate	Liver (A, H) Lung (A)
Dichloroacetate	Kidney (A)
GSH-conjugation metabolites	
TCVG	Liver (A) Kidney (A)
TCVC	Liver (A) Kidney (A)
TCVT [a]	Kidney (A)
TCVCS	Kidney (A)
TCVK	Kidney (A)
NAcTCVC	Liver (A, H) Kidney (A, H)
NAcTCVCS	Liver (A) Kidney (A)

[a] Due to their reactivity, these two metabolites are not systemically available
NAcTCVC, *N*-acetyl-*S*-(1,1,2-trichlorovinyl)-L-cysteine; NAcTCVCS, NAcTCVC sulfoxide; TCVC, *S*-(1,2,2-trichlorovinyl)-L-cysteine; TCVCS, *S*-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide; TCVG, *S*-(1,2,2-trichlorovinyl)glutathione; TCVK, trichlorovinyl thioketene; TCVT, *S*-(1,2,2-trichlorovinyl)thiol

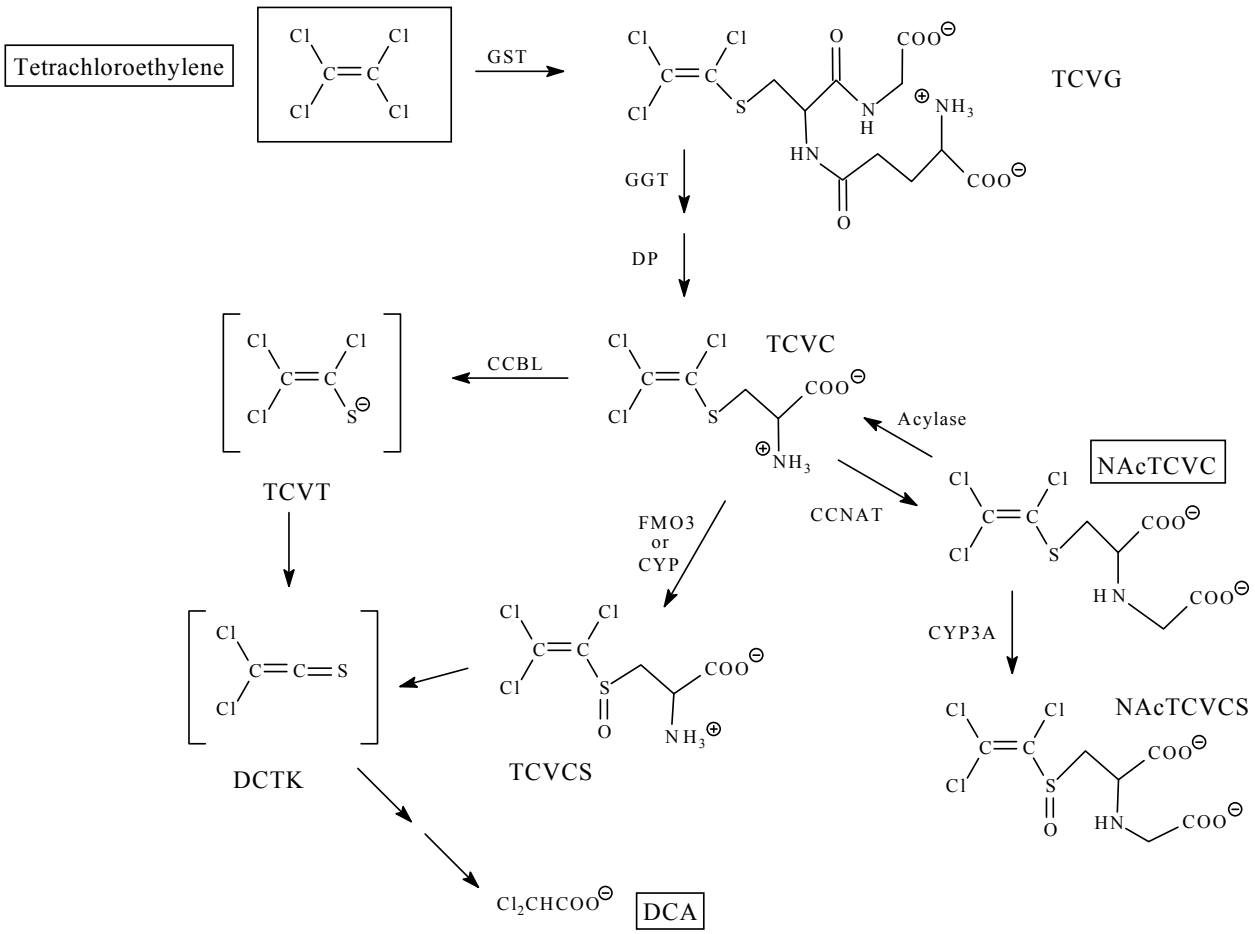
GSH-conjugation pathway is also presented in Table 4.1.

(iii) Enzymes involved in TCVC bioactivation

Of the two major bioactivation pathways for TCVC, i.e. with the enzymes CCBL or FMO3, the former has received most attention, but unlike for DCVC (Lash *et al.*, 2000) it is unclear which of the two pathways predominates. The activity of CCBL is actually a catalytic function of a diverse array of enzymes (Cooper & Pinto, 2006; Lash, 2007) that has been detected not only in the kidneys, but also in liver and other tissues.

Studies in the mid-1960s first identified a thiol metabolite of a sulfonamide that was formed by a C–S lyase activity (Colucci & Buyske, 1965). Others subsequently identified hepatic and renal enzymes from cow and turkey that catalysed this reaction (Anderson & Schultze, 1965; Bhattacharya & Schultze, 1967). More than a decade later the term 'cysteine conjugate β-lyase' was first used to describe this activity in rat liver (Tateishi *et al.*, 1978). All known CCBL enzymes contain pyridoxal-5-phosphate. Although the overall CCBL-catalysed reaction is the cleavage of a C–S-bond to yield a reactive thioacylating species, subsequent studies with the cysteine conjugate of trichloroethylene (i.e. DCVC) showed that the reaction mechanism proceeds via either a direct β-elimination or a transamination reaction with a suitable α-keto acid as co-substrate, to yield either the thiolate or a propionic-acid derivative, respectively; the latter is chemically unstable and rearranges to release the thiolate (Stevens *et al.*, 1986; Elfarra *et al.*, 1987).

Fig. 4.2 Scheme for glutathione-dependent metabolism of tetrachloroethylene



Tetrachloroethylene undergoes conjugation with glutathione (GSH) to yield the GSH S-conjugate TCVG. After processing to yield the cysteine S-conjugate TCVC, three potential fates are detoxication to yield the mercapturate NAcTCVC or bioactivation by either the cysteine conjugate β-lyase to yield trichlorovinylthiol, which rearranges to yield thioacylating species, or the flavin-containing monooxygenase to yield TCVC sulfoxide. The mercapturate can also be deacetylated to regenerate TCVC or it can undergo CYP3A-dependent sulfoxidation. Names of metabolites than are recovered in urine are shown in boxes and those that are chemically unstable or reactive are shown in brackets. Abbreviations: CCNAT, cysteine conjugate *N*-acetyltransferase; CYP3A, cytochrome P-450 3A; DCA, dichloroacetate; DCTK, 1,1-dichlorothioketene; DP, dipeptidase; FMO, flavin-containing monooxygenase; GGT, γ-glutamyltransferase; GSH, glutathione; GST, GSH *S*-transferase; TCVC, *S*-(1,2,2-trichlorovinyl)-L-cysteine; TCVG, *S*-(1,2,2-trichlorovinyl)glutathione; TCVCS, TCVC sulfoxide; NAcTCVC, N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine; NAcTCVCS, NAcTCVC sulfoxide.

Eleven mammalian enzymes are currently known to catalyse the CCBL reaction. Some of these enzymes catalyse both the β-elimination and the transamination reactions, whereas others only catalyse the former. The importance of each of these activities in TCVC bioactivation has been discussed (Cooper & Pinto, 2006; Cooper *et al.*, 2011).

The flavin-containing monooxygenases (FMOs), like the CYP enzymes, represent a multigene family of enzymes. However, although there are more than 50 individual functional CYP enzymes from more than 40 gene families known in humans, only five FMO genes have been identified in mammals. Both systems have several characteristics in common, including localization in the endoplasmic reticulum, requirement for NADPH as a proton donor, and overall catalytic activity in a mixed-function oxidation reaction. Some of the functions of the FMOs are different, however. FMOs catalyse the oxidation of sulfur-, selenium-, and nitrogen-containing chemicals (Ziegler, 1993, 2002; Cashman & Zhang, 2006). Although some FMO and CYP450 enzymes share substrates and catalyse the same overall reactions, FMOs have some distinctive substrates, including cysteine *S*-conjugates of various halo-alkenes and halo-alkanes.

(b) Humans

(i) CYP-dependent oxidation

The predominant route in the metabolism of tetrachloroethylene in all species studied, including humans, is the CYP-dependent oxidation pathway (Reitz *et al.*, 1996). This is particularly true at typical environmental exposures, because the various CYP enzymes that may act on tetrachloroethylene have higher affinities for tetrachloroethylene than do GSTs. Studies of overall metabolism in humans, however, suggest that the capacity of the CYP pathway to metabolize tetrachloroethylene readily saturates and is considered limited (Ohtsuki *et al.*, 1983) and markedly lower than metabolic rates in experimental animals such as mice (Reitz *et al.*, 1996). This conclusion was based on analyses of urine from workers exposed by inhalation to concentrations of tetrachloroethylene of up to 100 ppm for up to 8 hours. During the 8-hour exposure, 38% of the absorbed tetrachloroethylene is excreted unchanged through the lungs and < 2% of the absorbed dose is metabolized, as quantified by measurement of urinary metabolites (primarily trichloroacetate). Consistent with the conclusion that the total capacity for humans to metabolize tetrachloroethylene is limited, the reported half-life of tetrachloroethylene is 144 hours (Ikeda, 1977; Ikeda & Imanura, 1973).

The metabolism of tetrachloroethylene in humans has been modelled on the basis of literature data. The extent of metabolism was found to be quite variable and dependent on dose. Thus, at relatively high exposure levels of up to 144 ppm, as used in the study by Monster *et al.* (1979), < 2% of the absorbed dose was estimated to be metabolized. However, at ambient exposure levels (i.e. around 0.001 ppm, but as high as 1 ppm), the fraction of absorbed tetrachloroethylene estimated to be metabolized was > 36% (Bois *et al.*, 1996).

The toxicokinetics of tetrachloroethylene in humans were also examined at an exposure level of 1 ppm by inhalation (Chiu *et al.*, 2007). During and after a 6-hour exposure period, samples were taken from blood, urine, and alveolar breath at various time-points until up to 6 days after the exposure. The results were generally similar to those of earlier studies, but the variability and the substantial uncertainty in the model were emphasized. Major contributing factors were concentration-dependent differences in toxicokinetics, as previously concluded by Bois *et al.* (1996), and inter-individual differences in metabolism (Chiu *et al.*, 2007).

(ii) GSH-conjugation pathway

Only a few studies are available on the metabolism of tetrachloroethylene via the GSH-conjugation pathway in humans or in human-derived tissues. However, the available data unambiguously confirm the existence of this pathway *in vivo*.

The urinary excretion of tetrachloroethylene metabolites was studied in six workers occupationally exposed in a dry-cleaning store, with ambient air concentrations of tetrachloroethylene of 50 ± 4 ppm. Four subjects were exposed for 8 hours per day, and two subjects for 4 hours per day. The major metabolites detected were trichloroacetate and trichloroethanol; the excretion pattern correlated closely with the duration of exposure of the individuals, with total amounts of 2,2,2-trichloro-compounds ranging from 13.5 to 65.0 nmol/mg creatinine. NAcTCVC was detected at concentrations approximately 5000 times lower (2.2–14.6 pmol/mg creatinine) (Birner *et al.*, 1996).

In another study, three female and three male volunteers were exposed to tetrachloroethylene at 10, 20, and 40 ppm by inhalation for 6 hours. Over the 78 hours after the start of the exposure to the highest dose, a total of 20.4 ± 7.8 µmol of trichloroacetate and 0.21 ± 0.05 µmol of NAcTCVC were excreted. Again, while this study unequivocally demonstrated the presence of an active GSH-conjugation pathway in humans, it suggests that CYP-dependent oxidation greatly predominates. However, the relative flux through the two main pathways should not be estimated solely on the basis of urinary metabolites recovered. If that were done, the conclusion would be that no more than 1% of tetrachloroethylene is metabolized by GSH conjugation. Because NAcTCVC represents only one potential end product of the GSH-conjugation pathway, and since most of the end products are chemically reactive, these metabolites are likely to react with cellular nucleophiles, resulting in covalent adducts. DNA and protein adducts have indeed been found in incubations with tetrachloroethylene (Völkel *et al.*, 1998, 1999).

(c) Experimental systems

(i) CYP-dependent oxidation

The interaction of tetrachloroethylene with hepatic microsomal CYP enzymes and the influence of various CYP inhibitors and inducers were studied in male Long-Evans rats. Trichloroacetate was the major metabolite and neither chloral hydrate nor trichloroethanol were detectable. Induction of CYP3A1 with pregnenolone-16α-carbonitrile, or CYP2B1/2 with phenobarbital both enhanced the metabolism of tetrachloroethylene, suggesting the involvement of these CYP enzymes (Costa & Ivanetich, 1980). In a later study, the absence of trichloroethanol in the urine of chronically dosed mice was confirmed; trichloroacetate was the only metabolite reported (Buben & O'Flaherty, 1985).

Evidence for a role of CYP2B enzymes in the metabolism of tetrachloroethylene was shown in studies with rat liver and enzyme-specific inducers and substrates. Tetrachloroethylene was shown to induce the CYP2B subfamily CYP. Unlike in the studies mentioned above (Costa & Ivanetich, 1980), there was no evidence for an involvement of CYP3A1 (Hanioka *et al.*, 1995a, b). [The Working Group noted that the role of CYP2E1 in the metabolism of tetrachloroethylene has not been demonstrated directly in experimental animals, but is presumably based on the activity of this CYP with the congener trichloroethylene and with the fairly broad range of halogenated organic substrates of CYP2E1].

(ii) GSH-conjugation pathway

The presence of an active GSH-conjugation pathway for tetrachloroethylene has been demonstrated *in vivo* in experimental animals (rats and mice) through detection of NAcTCVC as a urinary metabolite (Bartels 1994; Dekant *et al.*, 1986a). The initial step in the pathway,

conjugation with GSH to form TCVG, has been shown to occur in rat liver (Dekant *et al.*, 1987, 1998), which is presumably the primary site for most of this reaction in the body.

Because GSTs are found in most tissues, it was expected that TCVG formation could also occur in the kidneys. Accordingly, incubations of cytoplasm and microsomes from kidneys of F344 rats (both sexes) and B6C3F1 mice (both sexes) with 2 mM tetrachloroethylene and 5 mM GSH demonstrated readily measurable rates of TCVG formation (Lash *et al.*, 1998). Metabolism in cytoplasm and microsomes from liver of both sexes of both species were also measured for comparison. Rates of GSH conjugation of TCVG were consistently higher in the corresponding fractions and tissues of males than in females in both species. In the kidneys, this difference was 2–3-fold for rats and 1.5–2-fold for mice. As expected, rates of TCVG formation in subcellular fractions of rat liver were 8–30 times higher than those in the corresponding kidney fraction from the same sex. While rates of TCVG formation were significantly higher in mice than in rats, the difference in rates between kidney and liver was much smaller in mice.

[The Working Group noted that although the higher rates of TCVG formation in male rats than in female rats correlates with the higher sensitivity of male rats to renal tumour formation from exposure to tetrachloroethylene, the markedly higher rates in mice of either sex does not correlate with the lack of renal tumours in this species (NTP, 1986).]

In contrast to the results described above, other investigators found no TCVG formation or much lower rates of GSH-conjugation of tetrachloroethylene. One study reported TCVG formation in rodent liver but not in human liver, and another showed TCVG formation in rat kidney at the limit of detection for the assay (i.e. 0.01 nmol/min per mg protein) (Dekant *et al.*, 1987, 1998; Green *et al.*, 1990). The latter value is similar to that reported by Lash *et al.* (1998).

The balance in the metabolism of tetrachloroethylene between CYP-dependent oxidation and GST-conjugation has been directly assessed in two studies.

Incubation of rat hepatocytes with either tetrachloroethylene or the prototypical GST-substrate 1-chloro-2,4-dinitrobenzene and NADPH resulted in a 70–85% reduction in the CYP-dependent oxidation pathway, suggesting that CYP-dependent oxidation can effectively compete with GST-conjugation in metabolizing tetrachloroethylene (Dekant *et al.*, 1987).

The second study addressed the effect of modulating the two metabolic processes in isolated rat hepatocytes and kidney cells. Treatment with non-selective CYP450 inhibitors (e.g. SKF-525A, metyrapone) or with CYP2E1-selective inhibitors (e.g. chlorzoxazone, diethyldithiocarbamate) significantly stimulated TCVG formation in both cell types. Inhibition of the CYP-dependent metabolism also resulted in increased cytotoxicity of tetrachloroethylene, but only in isolated kidney cells (Lash *et al.*, 2007). This finding highlights the importance of the GST-conjugation pathway for tetrachloroethylene-induced nephrotoxicity, but not hepatotoxicity (see Sections 4.5.1a and 4.5.2a for additional discussion of tetrachloroethylene-induced nephrotoxicity). Induction of CYP expression with either clofibrate or pyridine – compounds that enhance renal and hepatic expression of CYP2B1/2 and CYP2E1, respectively (Cummings *et al.*, 1999, 2001) – resulted in increased hepatic CYP-dependent metabolism of tetrachloroethylene in both cases, and increased renal CYP-dependent metabolism of tetrachloroethylene after treatment with clofibrate, but no effect on renal CYP-dependent metabolism of tetrachloroethylene after treatment with pyridine. These results suggest that patterns of CYP-dependent metabolism of tetrachloroethylene differ in rat liver and kidney (Lash *et al.*, 2007).

The differential roles of the CYP-dependent oxidation and GST-conjugation pathways in the bioactivation of tetrachloroethylene in rat liver and kidney were also demonstrated by modulation of the cellular GSH status. Treatment of freshly isolated rat hepatocytes with 5 mM methionine resulted in a ~50% increase in cellular GSH concentration and a significant reduction in tetrachloroethylene-induced cytotoxicity. In contrast, treatment of freshly isolated rat kidney cells with GSH at 5 mM resulted in a doubling of the cellular GSH concentration, but an increase in tetrachloroethylene-induced cytotoxicity. Conversely, depletion of tissue GSH with either L-buthionine-*S*,*R*-sulfoximine (BSO) or diethyl maleate resulted in increased cytotoxicity of tetrachloroethylene in isolated hepatocytes, but had no significant effect on cytotoxicity of tetrachloroethylene in isolated kidney cells. These results also demonstrate the distinct roles of the GSH-dependent metabolism of tetrachloroethylene in liver and kidney. In the liver, therefore, GSH plays its more traditional role with respect to tetrachloroethylene as an antioxidant and cytoprotective agent whereas in the kidneys, GSH functions primarily in the bioactivation and subsequent cytotoxicity of tetrachloroethylene (Lash *et al.*, 2007).

Two studies provide information on the metabolism of TCVC by enzymes with cysteine conjugate β-lyase activity, leading to formation of reactive thioacylating intermediates. In the first study, a bacterial lyase and *N*-dodecylpyridoxal bromide were used as catalysts to convert TCVC into dichloroacetic acid (Dekant *et al.*, 1988). In the second study, incubation of rat-kidney subcellular fractions with either tetrachloroethylene or TCVC produced *N*ε-(dichloroacetyl)-L-lysyl residues in proteins, primarily in mitochondria and cytoplasm. Formation of these adducts was inhibited by pre-incubation with the CCBL inhibitor amino-oxyacetic acid (AOAA), providing further evidence of the function of these enzymes (Birner *et al.*, 1994).

Formation of a TCVC-sulfoxide metabolite was reported to result from incubations of TCVC with rat or rabbit kidney or liver microsomes that exhibited all the properties of an FMO isoenzyme. Of the five FMO isoenzymes, TCVC is a substrate only for FMO3 (Elfarra & Krause, 2007; Ripp *et al.*, 1997; Novick & Elfarra, 2008).

Some of the cytotoxicity of TCVC that was independent of CCBL and FMO3 enzymes was shown to be actually due to formation of a mercapturic acid sulfoxide. By use of various selective inhibitors, including the CYP3A inhibitor troleanodomycin, it was shown that CYP3A enzymes were responsible for the sulfoxidation reaction (Werner *et al.*, 1996). [The Working Group noted that rates of this reaction were within a factor of 2 to 3 of those for CCBL or FMO3, suggesting that this additional pathway may play a role in tetrachloroethylene bioactivation and nephrotoxicity.]

The kinetics of the *N*-acetylation of TCVC in liver and kidney of male and female Wistar rats were determined *in vitro* by incubation of microsomes isolated from these organs with TCVC. Rates of NAcTCVC formation were substantially higher in kidney than in liver, particularly in females. Upon administration of 40 µmol TCVC/kg bw to rats, 40% of the compound was excreted as the mercapturate during 48 hours, and the rest as unmodified cysteine conjugate. This excretion of mercapturate was markedly less than that observed with DCVC (see next section). The authors hypothesized that the more lipophilic conjugates were more readily excreted in an unmodified form (Birner *et al.*, 1997).

(d) Comparison of the metabolisms of tetrachloroethylene and trichloroethylene

An understanding of the differences and similarities between the metabolism and pharmacokinetics of tetrachloroethylene and trichloroethylene is critical because much less direct information is available for tetrachloroethylene and extrapolations are often made from

data with trichloroethylene. Despite the fact that trichloroacetate is a major oxidative metabolite of both chemicals, the rates of formation from tetrachloroethylene and trichloroethylene differ substantially. Trichloroethanol and its glucuronide are oxidative metabolites of trichloroethylene that have not been consistently detected after exposure to tetrachloroethylene, and results may have been confounded in some studies due to co-exposure with trichloroethylene. The available data suggest that tetrachloroethylene is less extensively metabolized than trichloroethylene in both humans and experimental animals because it is a much poorer substrate than trichloroethylene for the CYP-dependent oxidation pathway (Ohtsuki *et al.*, 1983; Völkel *et al.*, 1998; Lash & Parker, 2001). For example, maximal rates of tetrachloroethylene metabolism by CYP-dependent oxidation in rat-liver microsomes have been estimated to be 30 times lower than those for trichloroethylene (Costa & Ivanetich, 1980). Besides its lower affinity for CYPs, tetrachloroethylene is also more lipophilic than trichloroethylene and exhibits greater sequestration in fat than trichloroethylene. This fact alone would slow the distribution of tetrachloroethylene to sites of metabolism in comparison with trichloroethylene.

A major difference between the GSH-dependent metabolism of trichloroethylene and that of tetrachloroethylene is that amounts of TCVG formed in kidney cells of male rats were approximately 5-fold those of *S*-(1,2,-dichlorovinyl)glutathione (DCVG) (Lash *et al.*, 1998, 2007). The fraction of total GSH-conjugation of trichloroethylene attributable to renal metabolism can be estimated to be 1.8%, and that of tetrachloroethylene 8.6%, i.e. 4.8-higher. In addition, oxidative metabolism of tetrachloroethylene in the liver is significantly slower than that of trichloroethylene. These data suggest that not only does renal GSH-conjugation make a relatively larger contribution towards overall GSH-conjugation for tetrachloroethylene than for trichloroethylene, but that GSH-conjugation contributes more towards the overall metabolism of tetrachloroethylene. The TCVC metabolite generated by CCBL is more chemically reactive than the metabolite generated by the action of CCBL on DCVC (Lash & Parker, 2001).

Besides differences related to the CCBL reaction route, differences also exist between the metabolic conversions of tetrachloroethylene and trichloroethylene in the FMO pathway. Studies with rabbit-liver microsomes showed that TCVC is overall a better substrate than DCVC for FMO3. Although the V_{max} for DCVC as substrate was sevenfold that for TCVC, the affinity of TCVC for the enzyme was nearly 20-fold (i.e. the K_m of FMO3 for TCVC was 20-fold lower than that for DCVC). Therefore, the catalytic efficiency of FMO3 towards TCVC is twice that towards DCVC. However, in a comparison of the kinetics of *S*-oxidation of TCVC and DCVC in bacterial membranes containing rabbit cDNA-expressed FMO3, the K_m for TCVC was about seven times lower than that for DCVC, while the V_{max} for DCVC was 50-fold that for TCVC. In this case, the catalytic efficiency with DCVC is sixfold that for TCVC (Ripp *et al.*, 1997).

The kinetics of *N*-acetylation of DCVC and TCVC in hepatic and renal microsomes from male and female Wistar rats were investigated. The rates of *N*-acetylation for both cysteine conjugates were consistently higher in kidney than in liver. In addition, in both males and females and in both organs the V_{max} values for *N*-acetylation with TCVC as substrate were generally higher than those for DCVC (Birner *et al.*, 1997).

[Considering the data for the metabolism of TCVC and DCVC by CCBL, FMO3, and the cysteine conjugate *N*-acetyltransferase (CCNAT), along with the marked difference in chemical reactivity of the thioketenes and sulfoxides generated from the two conjugates, the Working Group noted that one might expect renal proximal tubular cells to experience greater exposure to more reactive metabolites from

tetrachloroethylene as compared with trichloroethylene. However, no data making this comparison directly are available.]

4.1.4 Excretion

(a) Humans

In humans, the main excretion route of tetrachloroethylene is by exhalation of the unchanged parent compound, with smaller amounts of metabolites excreted in the urine (Ikeda *et al.*, 1972; Köppel *et al.*, 1985; Monster, 1979). Based on measured concentrations in exhaled breath, pulmonary excretion has been estimated to account for 80–100% of the intake (Monster *et al.*, 1979; Chiu *et al.*, 2007). After cessation of exposure, pulmonary excretion occurs in multiple first-order phases due to release from different tissues, with initial half-lives in the range of 5 to 20 minutes, several intermediate phases, and terminal half-lives of around 50–65 hours (Guberan & Fernandez, 1974; Monster *et al.*, 1979; Chien 1997). Urinary excretion of trichloro-metabolites (predominantly trichloroacetic acid) accounts for around 1–3% of intake (Stewart *et al.*, 1970; Essing *et al.*, 1973; Fernandez *et al.*, 1976; Monster *et al.*, 1979; Chiu *et al.*, 2007), with urinary excretion of several GSH-derived metabolic products representing an even smaller fraction (Völkel *et al.*, 1998). However, in these studies the urinary excretion was not followed for more than 3–7 days, and it is possible that a larger percentage of the tetrachloroethylene dose was eventually excreted in the urine. In studies that also measured pulmonary excretion, the entire dose was not always accounted for in the sum of exhaled tetrachloroethylene and urinary excretion of trichloroacetate (Monster *et al.*, 1979; Chiu *et al.*, 2007). Part of the administered dose may become metabolized to biotransformation products that were not measured, including oxidative products such as carbon monoxide, carbon dioxide, or oxalic acid, and additional GSH-conjugation products such as sulfoxides and reactive thiols. Physiologically based pharmacokinetic (PBPK) model-based estimates of the amount excreted via exhalation have ranged widely, with the most recent PBPK model predicting ranges of 90–99% via inhalation and 81–99% via ingestion (Chiu & Ginsberg, 2011).

(b) Experimental systems

In experimental rats and mice, excretion half-lives are in the order of hours, with pulmonary excretion virtually complete (> 99%) within 24 hours (Pegg *et al.*, 1979; Schumann *et al.*, 1980). This indicates that elimination is much more rapid in rodents than in humans. The extent of pulmonary excretion of unchanged tetrachloroethylene is dependent on species and dose. As exposure levels increase, the percentage of the compound excreted unchanged increases, which reflects saturation of metabolism (Pegg *et al.*, 1979; Schumann *et al.*, 1980). Pulmonary excretion appears greater in rats than in mice (Filser & Bolt 1979; Buben & O'Flaherty, 1985). The recently proposed PBPK model predicts the percentage tetrachloroethylene exhaled unchanged at exposures below saturation to be around 90–95% in rats and about 40–80% in mice, depending on the route of administration (Chiu & Ginsberg, 2011).

4.2 Genotoxicity and related effects

4.2.1 Humans

Several small cross-sectional studies have evaluated genotoxic and cytogenetic effects associated with exposure to tetrachloroethylene (Table 4.2). These studies have included assessments of the frequency of chromosomal aberrations and sister-chromatid exchange (SCE), the frequency of acentric fragments, and the presence of markers of oxidative stress.

(a) Chromosomal aberrations and sister-chromatid exchange

A cross-sectional study among 27 dry-cleaning workers and 26 controls in Japan reported no significant increase in the frequency of SCE in association with exposure to tetrachloroethylene. SCE was significantly increased in tetrachloroethylene-exposed male smokers compared with nonsmoking controls (Seiji *et al.*, 1990).

A study of 10 tetrachloroethylene-exposed degreasing workers and 11 non-exposed controls found no significant increase in numerical or structural chromosomal aberrations or in frequency of SCE (Ikeda *et al.*, 1980).

The frequencies of acentric fragments and chromosomal translocations – considered to be suitable indicators of chronic genotoxicity – were assessed in a cross-sectional study in the USA including 18 female tetrachloroethylene-exposed dry-cleaning workers, and 18 laundry workers not exposed to tetrachloroethylene. The average employment duration for the exposed dry-cleaners was 8 years. Air samples in the personal breathing-zone were collected from the dry-cleaning workers and from a subset of the laundry workers. A time-weighted average (TWA) exposure level of 3.8 ppm was measured in the exposed workers, while exposure levels were below the limit of detection in the controls. Chromosome painting was used to evaluate the frequency of cells with chromosomal translocations, insertions, dicentric and acentric fragments, and colour junctions. While the frequencies of each of these end-points, including translocations, were elevated in the exposed dry-cleaning workers compared with the controls, none of the increases were statistically significant (Tucker *et al.*, 2011).

(b) Oxidative stress

An earlier cross-sectional study in 18 dry-cleaning workers and 20 laundry workers (all women) showed a significantly reduced level of 8-OH-dG in leukocytes of the dry-cleaning workers, but this could not be clearly attributed to exposure to tetrachloroethylene. There were no increases in other oxidative stress biomarkers in relation to exposure to tetrachloroethylene (Toraason *et al.*, 2003).

4.2.2 Experimental systems

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; IARC, 1995; ATSDR, 1997b; EPA, 2012). The mechanisms by which tetrachloroethylene causes genotoxicity have been discussed (Henschler, 1987). Table 4.3 presents the studies of genotoxicity published to date. Highlights from these studies are given below.

(a) DNA-and protein-binding

In a study *in vivo*, mice were exposed orally or by inhalation to tetrachloro[^{14}C]ethylene. Labelling was observed in protein and RNA, but not in DNA of the liver (Schumann *et al.*, 1980). In a more sensitive assay and after intraperitoneal injection of the radiolabelled compound, DNA-labelling was detected in mouse liver and kidney, and in rat and mouse stomach. Binding was highest in mouse liver and stomach. Metabolic activation was found to enhance binding of tetrachloroethylene to calf-thymus DNA *in vitro* (Mazzullo *et al.*, 1987).

(b) Mutations

Mutations were not generally observed after exposure of *Escherichia coli* or *Salmonella typhimurium* cells to tetrachloroethylene, with or

Table 4.2 Molecular cross-sectional studies of genotoxicity and exposure to tetrachloroethylene

Reference, study location	Total No. exposed	Total No. controls (unexposed)	Mean exposure levels	End-points evaluated	Notable effects	Comments
Ikeda *et al.* (1980) Japan	10	11	92 ppm (degreasing workshops; $n = 6$) and 10–40 ppm (support department; $n = 4$)	Erythrocytes, leukocytes, haemoglobin, haematocrit, structural and numerical chromosomal aberrations, SCE, mitotic index, proportion of $M_2 + M_3$ metaphases	No significant differences for SCE, chromosomal aberrations, mitotic index between exposed workers and controls	Workers divided into exposure groups based on inferred exposure according to work environment (degreasing shop *vs* support department) and work duration; urine analysis for total trichlorinated compounds and ambient air samples taken, but no personal monitoring; limited information on comparability of exposed and non-exposed groups; no evaluation of smoking
Seiji *et al.* (1990) Japan	27	26	10 ppm	SCE	Significantly elevated SCE frequency in exposed smoking men compared with nonsmoking controls, but not for other groups	Diffuse sampling techniques used to monitor workers in breathing zone as TWA for 8-hour work; concurrent controls matched to exposed workers by age, sex, smoking, location of factory
Toraason *et al.* (2003) USA	18	20	Average 3.1 ppm, for dry-cleaning workers; < 0.02 ppm, for laundry workers (below LOD)	Leukocyte and urine 8-OHdG, urinary 8-epi-PGF	Reduced leukocyte 8-OHdG in dry cleaners compared to launderers (control), but no differences for other markers of oxidative stress	Personal breathing-zone samples collected for all women over 2 days (8-hour TWA); laundry workers matched to dry-cleaning workers by race, age, and smoking status; similar distribution of BMI between groups
Tucker *et al.* (2011) USA	18	18	TWA (8-hour) exposure, 3.8 ppm for exposed group (dry cleaners); below LOD for controls (laundry workers)	Translocations, insertions, acentric fragments, and dicentrics	Significant correlation between exposure levels and percentage of cells with acentric fragments; no differences in translocation frequencies between exposed and controls	Personal breathing zone samples collected from exposed dry-cleaning workers mid-working week; non-exposed laundry workers matched to exposed dry-cleaning workers by age, race, and smoking habits

8-epi-PGF, 8-epi-prostaglandin $F_{2\alpha}$; 8-OHdG, 8-hydroxy-deoxyguanosine; BMI, body-mass index; LOD, limit of detection; SCE, sister-chromatid exchange; TWA, time-weighted average

Table 4.3 Genetic and related effects of tetrachloroethylene and trichloroacetyl chloride

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Tetrachloroethylene				
Binding (covalent) to calf thymus DNA *in vitro*	0	+	9	Mazzullo *et al.* (1987)
SOS chromotest, *Escherichia coli* PQ37	–	–	8150	Mersch-Sundermann *et al.* (1989)
Lambda-prophage induction, *Escherichia coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
Salmonella typhimurium BAL13, forward mutation (*ara* test)	–	–	76	Roldán-Arjona *et al.* (1991)
Salmonella typhimurium TA100, reverse mutation	–	–	660	Bartsch *et al.* (1979)
Salmonella typhimurium TA100, reverse mutation	–	–	167	Haworth *et al.* (1983)
Salmonella typhimurium TA100, reverse mutation	–	–	1000	Connor *et al.* (1985)
Salmonella typhimurium TA100, reverse mutation	–[c]	–	166 (vapour)	Shimada *et al.* (1985)
Salmonella typhimurium TA100, reverse mutation (liver- and kidney-derived microsomes used for metabolic activation)	–	+/(+)[d]	332	Vamvakas *et al.* (1989a)
Salmonella typhimurium TA100, reverse mutation	–	–	1.3 (vapour)	DeMarini *et al.* (1994)
Salmonella typhimurium TA1535, reverse mutation	–	NT	50	Kringstad *et al.* (1981)
Salmonella typhimurium TA1535, reverse mutation	–	–	167	Haworth *et al.* (1983)
Salmonella typhimurium TA1535, reverse mutation	–[c]	(+)	66 (vapour)	Shimada *et al.* (1985)
Salmonella typhimurium TA1537, reverse mutation	–	–	167	Haworth *et al.* (1983)
Salmonella typhimurium TA98, reverse mutation	–	–	167	Haworth *et al.* (1983)
Salmonella typhimurium TA98, reverse mutation	–	–	1000	Connor *et al.* (1985)
Salmonella typhimurium UTH8413, reverse mutation	–	–	1000	Connor *et al.* (1985)
Salmonella typhimurium UTH8414, reverse mutation	–	–	1000	Connor *et al.* (1985)
Escherichia coli K12, forward mutation	–	–	150	Greim *et al.* (1975)
Escherichia coli K12, reverse mutation (*arg*$^+$)	–	–	150	Greim *et al.* (1975)
Escherichia coli K12, reverse mutation (*gal*$^+$)	–	–	150	Greim *et al.* (1975)
Escherichia coli K12, reverse mutation (*nad*$^+$)	–	–	150	Greim *et al.* (1975)
Saccharomyces cerevisiae D7, log-phase cultures, gene conversion	+	NT	1100	Callen *et al.* (1980)
Saccharomyces cerevisiae D7, gene conversion	–	–	9960	Bronzetti *et al.* (1983)
Saccharomyces cerevisiae D7, log-phase and stationary cultures, gene conversion	–	–	2440	Koch *et al.* (1988)

Table 4.3 (continued)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Saccharomyces cerevisiae D7, log-phase cultures, mitotic recombination or other genetic alterations (*ade2*)	+	NT	1100	Callen *et al.* (1980)
Saccharomyces cerevisiae D7, mitotic recombination	–	–	9960	Bronzetti *et al.* (1983)
Saccharomyces cerevisiae D7, log-phase cultures, reverse mutation	(+)	NT	810	Callen *et al.* (1980)
Saccharomyces cerevisiae D7, reverse mutation	–	–	9960	Bronzetti *et al.* (1983)
Saccharomyces cerevisiae D7, log-phase and stationary cultures, reverse mutation	–	–	2440	Koch *et al.* (1988)
Saccharomyces cerevisiae D61.M, growing cells, aneuploidy	(+)	(+)	810	Koch *et al.* (1988)
Tradescantia species, mutation	+	NT	7 (vapour)	Schairer & Sautkulis (1982)
Tradescantia species, micronucleus induction	–	NT	600	Sandhu *et al.* (1989)
Tradescantia species, micronucleus induction	(+)	NT	2 (vapour)	Sandhu *et al.* (1989)
Drosophila melanogaster, sex-linked recessive mutation	–		1000 (injection)	Valencia *et al.* (1985)
Drosophila melanogaster, sex-linked recessive mutation	–		4000 (feeding)	Valencia *et al.* (1985)
Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–[c]	NT	166 (vapour)	Shimada *et al.* (1985)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus	–	–	245	NTP (1986)
Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	–	–	164	Galloway *et al.* (1987)
Micronucleus induction, Chinese hamster ovary (CHO-K1) cells *in vitro*	+	NT	~1.85 ppm (vapour dissolved in medium)	Wang *et al.* (2001)
Micronucleus induction, Chinese hamster lung-cell line (CHL/IU) *in vitro*	–	NT	250 µg/mL	Matsushima *et al.* (1999)
Chromosomal aberrations, Chinese hamster lung (CHL) cells *in vitro*	–	–	500	Sofuni *et al.* (1985)
Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	–	–	136	Galloway *et al.* (1987)
Cell transformation, RLV/Fischer rat embryo F1706 cells *in vitro*	+	NT	16	Price *et al.* (1978)
Cell transformation, BALB/c-3T3 mouse cells *in vitro*	–	NT	250	Tu *et al.* (1985)
Single-cell gel electrophoresis assay (comet), human leukocytes *in vitro*	–	–	5 mM	Hartmann and Speit (1995)
Unscheduled DNA synthesis, human lymphocytes *in vitro*	+	–	10 mM	Perocco *et al.* (1983)

Table 4.3 (continued)

Test system	Result[a]			Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation		With exogenous metabolic activation		
Sister-chromatid exchange, human lymphocytes *in vitro*	–		–	2 mM	Hartmann and Speit (1995)
Micronucleus induction, human lymphoblastoid cell lines with enhanced metabolic activity *in vitro*	AHH-1 (expresses CYP1A1)	+	NT	5 mM	Doherty *et al.* (1996)
	h2E1 (expresses CYP2E1)	+	NT	1 mM	
	MCL-5 (expresses CYP1A2, 2A6, 3A4, 2E1)	+	NT	1 mM	
DNA single-strand breaks (alkaline unwinding), liver/kidney of male NMRI mice *in vivo*	+[e]			660 ip × 1	Walles (1986)
Single-cell gel electrophoresis assay (comet), CD1 mouse hepatocytes *in vivo*	+/–		NT	1000 mg/kg per day[f]	Cederberg *et al.* (2010)
	+/–		NT	2000 mg/kg per day[f]	
Single-cell gel electrophoresis assay (comet), CD1 mouse kidney cells *in vivo*	–		NT	2000 mg/kg per day[f]	
Binding (covalent) to DNA in male B6C3F$_1$ mouse liver *in vivo*	–			1400 in 6 h	Schumann *et al.* (1980)
Binding (covalent) to DNA in male B6C3F$_1$ mouse liver *in vivo*	–			500 po × 1	Schumann *et al.* (1980)
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)
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)
Gene conversion and reverse mutation, *Saccharomyces cerevisiae* D7 recovered from liver, lungs and kidneys of CD-1 mice *in vivo*	–		NT	11 000 po × 1	Bronzetti *et al.* (1983)
Gene conversion and reverse mutation, *Saccharomyces cerevisiae* D7 recovered from liver, lungs and kidneys of CD-1 mice *in vivo*	0		–	2000 po × 12	Bronzetti *et al.* (1983)
Micronucleus induction, mouse reticulocytes, *in vivo*	–		NT	1 × 2000	Murakami and Horikawa (1995)
Micronucleus induction, mouse hepatocytes, *in vivo*	+		NT	1 × 1000 mg/kg bw[g]	

Table 4.3 (continued)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Micronucleus induction, mouse hepatocytes, *in vivo (cont.)*	–	NT	1 × 2000 mg/kg bw[h]	
Oxidative DNA damage (8-OHdG), Fischer rats *in vivo* (urine, lymphocytes, liver)	–[i]	NT	1 × 100–1000	Toraason *et al.* (1999)
DNA single-strand breaks, male F344 rats *in vivo*	–	NT	1 × 1000 (p.o.)	Potter *et al.* (1996)
Enzyme-altered foci in male Osborne Mendel rat liver *in vivo* (promotion protocol, with or without NDEA as an initiator)	+		1000 (p.o.), 5 days/wk, 7 wks	Milman *et al.* (1988)
Enzyme-altered foci in male Osborne Mendel rat liver *in vivo* (initiation protocol with phenobarbital as a promoter)	–		1000 (p.o.)	Milman *et al.* (1988)
Sister chromatid exchange, human lymphocytes *in vivo*	–		88 inh	Ikeda *et al.* (1980)
Sister-chromatid exchange, human lymphocytes *in vivo*	–	NT	10 ppm (geometric mean)	Seiji *et al.* (1990)
Chromosomal aberrations, human lymphocytes *in vivo*	–		88 inh	Ikeda *et al.* (1980)
Chromosomal aberrations, human lymphocytes *in vivo*	+	NT	144 mg/m^3 (contaminated with trichloroethylene)	Fender (1993)
Trichloroacetyl chloride				
Lambda-prophage induction, *Escherichia coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
Salmonella typhimurium TA100, reverse mutation	+	+	2.6	DeMarini *et al.* (1994)

[a] +, positive; (+), weakly positive, inadequate study; –, negative; ?, inconclusive (variable responses in several experiments, inadequate study)
[b] In-vitro tests, µg/ml; in-vivo tests, mg/kg bw
[c] Tetrachloroethylene with stabilizers was positive with and without metabolic activation
[d] Equivocal increase in activity with S9 from rat liver, unequivocal increase with kidney microsomes and glutathione (GSH); strong (fourfold) increase with rat-kidney microsomes, GSH and GSH *S*-transferase; the effect was diminished upon addition of serine borate or AOAA.
[e] Negative in lung
[f] Number of days not given
g After partial hepatectomy
[h] Without hepatectomy
[I] Substantial morbidity at the high dose limits interpretation of this result
LED, lowest effective dose; HID, highest ineffective dose; inh, inhalation ; i.p., intraperitoneal NDEA, *N*-nitrosodiethylamine; NT, not tested; p.o., oral

without the standard metabolic activation by S9. In the diploid D7 strain of the yeast *Saccharomyces cerevisiae*, tetrachloroethylene caused mitotic gene conversion and recombination in one study (Callen *et al.*, 1980), but failed to do so in two other studies (Bronzetti *et al.*, 1983; Koch *et al.*, 1988).

Tetrachloroethylene was not active in the SOS chromotest with *E. coli* and was not mutagenic to bacteria in the absence of metabolic activation. Purified tetrachloroethylene was not mutagenic to *S. typhimurium* or *E. coli* when tested in the presence of a metabolic-activation 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. In another study, purified tetrachloroethylene clearly increased the number of revertants in *S. typhimurium* TA100 in the presence of rat-liver GST, glutathione and kidney microsomes. This study was intended to simulate the multistep bio-activation pathway by GSH-conjugation (Vamvakas *et al.*, 1989a). The mutagenicity was accompanied by time-dependent formation of *S*-(1,2,2-trichlorovinyl) glutathione, a pro-mutagen activated by kidney microsomes, and did not occur in the absence of GSH, GST, or kidney microsomes. Bile collected from an isolated rat-liver system perfused with tetrachloroethylene was clearly mutagenic in the presence of rat-kidney particulate fractions. In both assay systems, the mutagenicity was reduced, but not abolished, by the presence of the γ-glutamyl transpeptidase inhibitor, serine borate, and the β-lyase inhibitor AOAA, suggesting that the important steps in the metabolic activation of tetrachloroethylene in renal fractions are GST-mediated GSH-conjugation, followed by γ-glutamyl-transpeptidase-mediated formation of an *S*-cysteine conjugate, and bio-activation 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 compound of 99% purity induced a slight increase in the frequency of micronucleus formation.

Studies in *Drosophila melanogaster* were negative for sex-linked recessive lethal mutations (Beliles et al., 1980; Valencia et al., 1985; NTP, 1986).

(c) Micronucleus formation, SCE, and chromosomal aberrations

Tetrachloroethylene increased the frequency of micronucleus formation in hepatocytes, but not in peripheral blood reticulocytes of ddY mice given single intraperitoneal injections after, but not before, partial hepatectomy (Murakami & Horikawa, 1995). Micronucleus induction was not observed in a Chinese hamster lung cell line (CHL/IU) exposed to tetrachloroethylene (Matsushima *et al.*, 1999). When Chinese hamster ovary (CHO K1) cells were exposed to tetrachloroethylene in a closed vapour-exposure system, a significant, dose-dependent increase in the frequency of micronuclei was found (Wang *et al.*, 2001) Micronucleus induction was studied in AHH-1 human lymphoblastoid cells and in two daughter cell lines (h2E1 and MCL5) stably expressing various human metabolic enzymes. The parental AHH-1 cells possess native CYP1A1 activity and considerable GST activity; the h2E1 cells express human CYP2E1; and MCL-5 cells express human CYP1A2, 2A6, 3A4, 2E1, and microsomal epoxide hydrolase. Tetrachloroethylene induced an increase in micronuclei formation by threefold in AHH-1

cells and ninefold in h2E1 and MCL-5 cells (Doherty *et al.*, 1996). Similar results were reported with the MCL-5 cell line (White *et al.*, 2001).

Tetrachloroethylene-induced DNA damage was not observed in the SCE assay in cultured human blood cells at a dose that reduced viability by 40% due to cytotoxicity (Hartmann & Speit, 1995). Neither chromosomal aberrations nor SCE were induced in cultured Chinese hamster ovary cells after exposure to tetrachloroethylene (Sofuni *et al.* 1985; Galloway *et al.*, 1987). Chinese hamster ovary cells exposed to tetrachloroethylene in the presence or absence of S9 fraction (derived from livers of Sprague Dawley rats) showed no increase in SCE frequency (NTP, 1986). Beliles *et al.* (1980) assessed chromosomal aberrations and aneuploidy in bone marrow of male and female Sprague-Dawley rats after single and short-term exposures to tetrachloroethylene by inhalation. The only effect reported with a single exposure was a slight increase in the percentage of cells with aberrations and aneuploidy in male, but not female rats. No significant effects were observed in any of the groups exposed for short periods. No chromosomal aberrations were found in Chinese hamster ovary cells exposed to tetrachloroethylene with or without metabolic activation (NTP, 1986).

Studies in *Drosophila melanogaster* were negative for chromosomal aberations (Beliles *et al.*, 1980; Valencia *et al.*, 1985; NTP, 1986).

(d) Unscheduled DNA synthesis and DNA strand breaks

Human fibroblasts (WI 38 cells) were tested for the induction of unscheduled DNA synthesis after exposure to tetrachloroethylene; the results were equivocal (Beliles *et al.*, 1980). However, the positive controls were only weakly positive in this study. In other studies, no evidence of unscheduled DNA synthesis was observed in human lymphocytes, human fibroblasts, or rat and mouse hepatocytes (Perocco *et al.*, 1983; Costa & Ivanetich, 1984; Shimada *et al.*, 1985; Milman *et al.*, 1988).

The results of the few assays for DNA strand break after exposure to tetrachloroethylene *in vivo* were equivocal. DNA single-strand breaks were measured in the liver and kidney of male mice exposed by intraperitoneal injection, but this effect was reversible within 24 hours (Walles, 1986). A second study examined DNA strand breaks after oral exposure of male F-344 rats to tetrachloroethylene for 1 week, and demonstrated no DNA breakage (Potter *et al.*, 1996). A recently published report on DNA strand breaks in hepatocytes showed a marginal increase in tail intensity in the comet assay after oral exposure of mice to tetrachloroethylene (Cederberg *et al.*, 2010); the statistical and biological significance of this result has been disputed (Lillford *et al.*, 2010; Struwe *et al.*, 2011).

(e) Cell transformation

Treatment with tetrachloroethylene for 3 days without metabolic activation did not induce cell transformation in BALB/c 3T3 cells after a 30-day post-treatment incubation period (Tu *et al.*, 1985). However, cells from Fischer rat embryos were transformed upon treatment with tetrachloroethylene in the absence of metabolic activation (Price *et al.*, 1978).

(f) Genotoxicity of metabolites of tetrachloroethylene

A limited number of experimental studies on the genotoxicity of tetrachloroethylene metabolites have been performed (see Table 4.4).

Trichloroacetyl chloride results from oxidative metabolism of tetrachloroethylene, and has been tested for mutagenicity in *S. typhimurium*, with inconsistent results. An early study found no mutagenicity after incubation in liquid suspension with *S. typhimurium* TA98 and TA100 strains, with or without S9 activation (Reichert *et al.*, 1983). In a second study, trichloroacetyl chloride as a vapour was tested for mutagenicity

in *S. typhimurium* TA100 and found to give positive results in the presence or absence of metabolic activation; the chemical induced mostly GC > TA transversions (the predominant background mutation). Trichloroacetyl chloride gave negative results for prophage induction in *E. coli* in the same study (DeMarini *et al.*, 1994).

Tetrachloroethylene epoxide, an intermediate in the CYP450-mediated oxidative metabolism of tetrachloroethylene (Henschler, 1977; Henschler & Bonse, 1977), has been tested for mutagenicity in a single study. It was mutagenic in *S. typhimurium* TA1535, but not in *E. coli* WP2*uvr*A (Kline *et al.*, 1982). Mutagenicity was observed at the lower doses in *S. typhimurium*, but not at higher doses, most likely due to cytotoxicity.

Only a small number of studies were available that assessed the genotoxicity of metabolites in the GSH-conjugation pathway of the metabolism of tetrachloroethylene.

TCVG formed from tetrachloroethylene in isolated perfused rat liver and excreted into bile was mutagenic in *S. typhimurium* in the presence of a rat-kidney homogenate, which contained high concentrations of GGT (Vamvakas *et al.*, 1989a). In this study, the mutagenicity assay was conducted with *Salmonella* strains TA100, TA98, and TA2638, and with tetrachloroethylene, TCVG, and bile from liver perfusates of tetrachloroethylene-exposed rats. The results show that the GST metabolites, or tetrachloroethylene in the presence of bile containing GST, led to gene mutations in *S. typhimurium* TA100. In a more recent study, TCVG showed an unequivocal dose-dependent mutagenic response in *Salmonella* TA100 in the presence of S9 protein fraction from rat kidney; TCVC was mutagenic without metabolic activation in this strain (Dreessen *et al.*, 2003). TCVC (1–10 nmol/plate) was also mutagenic in *Salmonella* strains TA98 and TA100, but not in TA2638, and β-lyase activity was blocked by the addition of AOAA (Dekant *et al.*, 1986b). A further study from the same group indicated that *Salmonella* bacteria were capable of deacetylating the urinary metabolite NAcTCVC (50–100 nmol/plate) when TA100 showed a clearly positive response without exogenous activation (Vamvakas *et al.*, 1987). Addition of cytosolic protein increased the mutagenic response, while addition of the β-lyase inhibitor AOAA reduced it.

A concentration-related increase in unscheduled DNA synthesis was found in LLC PK1 cells (derived from porcine kidney) exposed to TCVC; this effect was abolished by a β-lyase inhibitor. To determine cytotoxicity, release of lactate dehydrogenase was measured, but no increase was found (Vamvakas *et al.*, 1989c).

4.3 Non-genotoxic effects and organ toxicity

4.3.1 Kidney

The available studies in humans and experimental animals have addressed multiple non-genotoxic mechanisms for kidney carcinogenicity associated with exposure to tetrachloroethylene. These include accumulation of α2u-globulin, cytotoxicity unrelated to α2u-globulin, and peroxisome proliferator-activated receptor-α (PPARα) activation.

(a) Accumulation of α2u-globulin

Accumulation of α2u-globulin is a histopathological phenomenon elicited in the kidney of the male rat by long-term exposure to chemicals. The hypothesized sequence of key events comprises:

- Excessive accumulation of hyaline droplets containing α2u-globulin in renal proximal tubules;
- Subsequent cytotoxicity and single-cell necrosis of the tubule epithelium;
- Sustained regenerative tubule cell proliferation;

Table 4.4 Studies of genotoxicity with metabolites of tetrachloroethylene

Metabolite	Test system/end-point	Results[b]		Dose[a] (LED or HID)	Reference
		Without exogenous metabolic activation	With exogenous metabolic activation		
Tetrachloroethylene epoxide	*S. typhimurium* TA1535, reverse mutation	+	NT	2.5 mM	Kline *et al.* (1982)
	E. coli WP2 *uvr*A, reverse mutation	–	NT	25 mM	Kline *et al.* (1982)
Trichloroacetyl chloride (TCAC)	Lambda-prophage induction, *E. coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
	S. typhimurium TA100, reverse mutation	+	+	300/200 ppm[c]	DeMarini *et al.* (1994)
	S. typhimurium TA100, reverse mutation	–	–	5 µL/2 mL	Reichert *et al.* (1983)
Trichlorovinyl-glutathione (TCVG)	*S. typhimurium* TA100, reverse mutation	–	+	50 nmol/plate	Dreessen *et al.* (2003)
	S. typhimurium TA100, reverse mutation	–	+	25 nmol/plate	Vamvakas *et al.* (1989a)
	Unscheduled DNA synthesis, cultured porcine LLC-PK1 (kidney) cells, *in vitro*	+	NT	7.5×10^{-6} M	Vamvakas *et al.* (1989b)
Trichlorovinyl-cysteine (TCVC)	*S. typhimurium* TA100, reverse mutation	+	NT	50 nmol/plate	Dreessen *et al.* (2003)
	Unscheduled DNA synthesis, cultured porcine LLC-PK1 (kidney) cells, *in vitro*	+	NT	5×10^{-6} M	Vamvakas *et al.* (1989c)
NAcTCVC	*S. typhimurium* TA100, increased mutation frequency	+	+	< 50 nmol [d]	Vamvakas *et al.* (1987)

[a] LED, lowest effective dose; HID, highest ineffective dose; NA, not available
[b] Results: +, positive; (+), weakly positive; –, negative; NT, not tested
[c] Tested with the vaporization technique; doses in ppm given without/with activation
[d] Lower concentrations that indicate mutagenicity not specified in the article

- Development of intraluminal granular casts from sloughed cellular debris associated with tubule dilatation and papillary mineralization;
- Foci of tubule hyperplasia in the convoluted proximal tubules;
- Tumours of renal tubules.

Seven criteria are specified for demonstrating the α2u-globulin mechanism for carcinogenesis in male rat kidney (IARC, 1999), namely:

- Characteristic histopathology
- Specificity to male rats
- Accumulation of α2u-globulin
- Reversible binding to α2u-globulin
- Increased cell proliferation
- Similarities in dose–response relationships for histopathology and tumour outcome
- Lack of genotoxicity

This mechanism is posited to occur only in rodents; accordingly, only studies in experimental animals were identified, and are discussed below.

Three studies provide evidence satisfying four of the seven above-mentioned criteria (characteristic histopathology, specificity for the male rat, accumulation of α2u-globulin, and increased cell proliferation) for supporting the α2u-globulin mechanism, at doses of tetrachloroethylene in excess of those observed to induce tumorigenesis. These studies demonstrate that tetrachloroethylene induces accumulation of α2u-globulin and hyaline-droplet nephropathy in male rats (see Table 4.5).

Increased α2u-hyaline droplet formation was seen in male, but not female, F344 rats treated by gavage for 10 days with tetrachloroethylene at 1000 mg/kg bw per day. This finding was correlated with both protein-droplet nephropathy (crystalloid accumulation) and enhanced cellular proliferation. Cell replication was increased in the male rats specifically in damaged P_2 segments, suggesting a link between the α2u-globulin accumulation and the ensuing proliferative response (Goldsworthy *et al.*, 1988).

In short-term, high-dose, studies, oral administration of tetrachloroethylene at 1500 mg/kg bw per day for up to 42 days caused accumulation of α2u-globulin in the proximal renal tubules of male rats (Green *et al.*, 1990). [The Working Group noted the lack of a parallel experiment in female rats in this study].

Accumulation of α2u-globulin was also demonstrated to occur in P_2 segments of proximal tubule cells after oral exposure of male, but not female, rats to tetrachloroethylene at 500 mg/kg bw per day in corn oil 4 weeks (Bergamaschi *et al.*, 1992).

The primary limitation to the mechanistic support for the α2u-globulin mechanism concerns the criterion of similarities in dose–response relationships for histopathology and tumour outcome. The NTP cancer-bioassay (NTP, 1986) did not provide evidence of hyaline droplets in rats exposed to carcinogenic doses of tetrachloroethylene for up to 2 years. However, the NTP protocol at that time was not designed specifically to detect hyaline droplets or accumulation of α2u-globulin in the kidney (NTP, 1990). In addition, the nephropathy observed at the end of a 2-year bioassay would be difficult to distinguish from the nephropathy associated with advanced age in these rats. Other relevant findings concerning the correspondence in dose–response relationships for histopathology and tumour outcome are those reported by Green *et al.* (1990), who found no evidence of hyaline-droplet formation in tests with lower doses of inhaled tetrachloroethylene of up to 400 ppm for 6 hours per day, for 28 days. Because animals were killed up to 18 hours after termination of the final exposure, recovery may have been possible. The authors raised the possibility that a longer exposure to tetrachloroethylene at 400 ppm would be required for the hyaline-droplet accumulation in the rat kidney. However, accumulation has been demonstrated after

Table 4.5 Formation of renal α2u-globulin in rodents exposed to tetrachloroethylene

Test system (species, strain, sex, number)	Dose	Effects	Reference
Mouse, B6C3F$_1$, (M and F, groups of 49 or 50 mice of each sex, total of ~300 mice)	100, 200 ppm, 6 h/day, 5 days/wk for 103 wk, inhalation	Karyomegaly and cytomegaly of the proximal tubules in all exposed mice; nephrosis in exposed females, casts increased in all exposed males and in females at higher dose	NTP (1986)
Rat, F344, (M and F, groups of 50 mice of each sex, total of ~300 mice)	200, 400 ppm, 6 h/day, 5 days/wk for 103 wk, inhalation	Karyomegaly and cytomegaly of the proximal tubules in all exposed rats	NTP (1986)
Rat, F344 (M and F, 3 per group)	1000 mg/kg bw per day for 10 days, corn oil, gavage	Increases in α2u-hyaline droplets in exposed male but not female rats, correlated with increased cell proliferation and protein-droplet nephropathy	Goldsworthy *et al.* (1988)
Rat, F344 (M and F, 12 per group)	500 mg/kg bw per day for 4 wk, corn oil, gavage	Increases in α2u-hyaline accumulation in proximal tubule cells, correlated with albuminuria	Bergamaschi *et al.* (1992)
Rat, F344 (M and F) and mouse, B6C3F$_1$ (M and F) (10 per group for oral studies, 5 per group for inhalation studies)	1000 or 1500 mg/kg bw per day for 42 days, corn oil, gavage; 1000 ppm, 6 h/day for 10 days, by inhalation	After oral gavage, accumulation of α2u-globulin in proximal tubules of male rats; nephrotoxicity also observed in male rats (formation of granular tubular casts and evidence of tubular cell regeneration). Inhalation exposure induced formation of hyaline droplets in kidneys of male rats	Green *et al.* (1990)

F, female; h, hour; M, male; wk, week

short-term exposure (even after a single dose) to several agents, such as d-limonene, decalin, unleaded gasoline, and trimethylpentane (Charbonneau *et al.*, 1987; NTP, 1990). The renal pathology reported in the NTP bioassay is also not entirely consistent with the general findings for other chemicals that induce accumulation of α2u-globulin (NTP, 1986). For example, mineralization in the inner medulla and papilla of the kidney was not seen with tetrachloroethylene, but is a frequent finding in bioassays with chemicals that induce accumulation of α2u-globulin (e.g. for pentachloroethane, the incidence of renal papillar mineralization was 8% in controls, 59% in the group at the lowest dose, and 58% in the group at the highest dose) (NTP, 1983).

Concerning the remaining two criteria, no direct evidence demonstrating binding to α2u-globulin was identified. The evidence presented in Section 4.2 does not clearly rule out the potential role of genotoxicity, particularly in the kidney. Indeed, metabolites of tetrachloroethylene known to be produced in the kidney (e.g. TCVG and NAcTCVC) have been demonstrated to be genotoxic *in vitro*. In one study in mammalian cells, unscheduled DNA synthesis in porcine kidney cells was observed to increase in a dose-dependent manner after exposure to TCVC (Vamvakas *et al.*, 1989c). Bacterial assays found TCVG (Vamvakas *et al.*, 1989a; Dreessen *et al.*, 2003) and NAcTCVC (Vamvakas *et al.*, 1987) to be mutagenic in the presence of metabolic activation, while TCVC was mutagenic in the absence of activation (Dreessen *et al.*, 2003).

(b) *Cytotoxicity and sustained chronic nephrotoxicity, not associated with α2u-globulin*

This hypothesized mechanism for development of renal neoplasms involves renal cytotoxicity and subsequent cellular proliferation without regard to accumulation of α2u-globulin. Experimental evidence in humans and animals supporting this mechanism is summarized below.

(i) *Humans*

The renal toxicity of tetrachloroethylene has been demonstrated in studies with patients receiving high intentional exposures, and in occupational settings. High concentrations of inhaled tetrachloroethylene given as an anaesthetic are associated with symptoms of renal dysfunction, including proteinuria and haematuria (Hake & Stewart, 1977; ATSDR, 1997a). The study by Calvert *et al.* (2011) supports an association between inhalation exposure to tetrachloroethylene and end-stage renal disease, particularly hypertensive end-stage renal disease. There was an increase of more than 2.5-fold in incidence (SIR, 2.66; 95% CI, 1.15–5.23; 15 cases) among subjects who worked in a shop where tetrachloroethylene was the primary cleaning solvent compared with the expected incidence based on rates in the USA population. An exposure–response pattern was further suggested because the risk for hypertensive end-stage renal disease was highest among those employed for 5 years (SIR, 3.39; 95% CI, 1.10–7.92; five cases).

Other studies of the chronic effects of inhaled tetrachloroethylene on the kidney used measurements of urinary renal proteins as an indicator of kidney function. No effect on several urine parameters or blood urea nitrogen (a measure of kidney function) was reported with controlled inhalation exposure to tetrachloroethylene (25 or 100 ppm for 11 weeks, 12 healthy individuals) [Stewart *et al.* (1977), as reported in ATSDR (1997a)]. However, Mutti *et al.* (1992) observed an elevated prevalence of abnormal values for brush-border antigens, a higher geometric mean concentration of brush-border antigens in urine, and a higher concentration of tissue non-specific alkaline phosphatase in urine among 50 exposed dry-cleaning workers compared with 50 blood donors matched by sex and age with the exposed group. The markers of renal damage were highly

predictive of exposure status in discriminant analyses. The amount of β_2-microglobulin was not elevated among exposed subjects as compared with controls in this and two other studies that examined this protein (Lauwerys *et al.*, 1983; Vyskocil *et al.*, 1990). In two studies that measured β-glucuronidase or lysozyme, respectively, a statistically significant increase was reported in mean urinary concentration of these proteins among dry-cleaning workers compared with controls (Franchini *et al.*, 1983; Vyskocil *et al.*, 1990).

Several studies examined urinary indicators of renal tubule function – retinol-binding protein, *N*-acetyl-β-D-glucosaminidase, or alanine aminopeptidase – in workers in dry-cleaning exposed to tetrachloroethylene. One study reported a statistically significantly increased prevalence of abnormal values of retinol-binding protein, but no difference in geometric mean concentration between exposed and controls (Mutti *et al.*, 1992). Another study did find a higher geometric mean concentration of retinol-binding protein for exposed workers compared with controls (Verplanke *et al.*, 1999). However, no effect of tetrachloroethylene was seen in four studies that measured urinary excretion of *N*-acetyl-β-D-glucosaminidase (Mutti *et al.*, 1992; Verplanke *et al.*, 1999; Trevisan *et al.*, 2000) or in one that measured alanine aminopeptidase (Verplanke *et al.*, 1999).

Primary cultures of proximal tubular cells from both rat and human kidney were used to study the role of CCBL in the acute cytotoxicity caused by DCVC, TCVC, and two fluorinated cysteine conjugates of halogenated solvents. Incubation in the presence of the CCBL inhibitor AOAA resulted in partial protection only. Nonetheless, the study demonstrated a requirement for CCBL-dependent metabolism for DCVC to exert a toxic effect on human kidney cells. TCVC was less cytotoxic than DCVC. CCBL activity in proximal tubular cells from the rat kidney was threefold that in the human cells (McGoldrick *et al.*, 2003).

(ii) Experimental animals

Adverse effects on the kidney have been observed in studies of rodents exposed by inhalation (JISA, 1993; NTP, 1986) and oral gavage (NCI, 1977; Goldsworthy & Popp, 1987; Goldsworthy *et al.*, 1988; Green *et al.*, 1990; Ebrahim *et al.*, 1996, 2001; Jonker *et al.*, 1996; Philip *et al.*, 2007).

While neoplasia in the renal tubules is observed to occur only in male rats, tetrachloroethylene has been reported to produce nephrotoxicity across species, and in both sexes. Signs of tetrachloroethylene-induced kidney damage appeared in both rats and mice during the early phases of the NTP cancer bioassay (inhalation study), for example, indicating that animals of both species surviving to the scheduled termination of the study had long-standing nephrotoxicity. Although the female rats did not develop any tumours in the renal tubules, the incidence of karyomegaly was significantly elevated in females as well as in males, and one of the 50 female rats exposed at the highest dose developed tubul cell hyperplasia (NTP, 1986).

In the NTP inhalation study with mice, 'nephrosis' – generally defined as non-inflammatory degenerative kidney disease – was noted to occur at increased incidences in dosed females, casts (cylindrical structures formed from cells and proteins released from the kidney) were observed at increased frequency in exposed males and in females at the highest dose, and karyomegaly of the tubule cells was seen at increased incidences in both sexes of exposed mice (NTP, 1986). The severity of the renal lesions was dose-related, and one male at the lowest dose had a renal tubule cell adenocarcinoma. In the NCI cancer bioassay (gavage study) in B6C3F_1 mice and Osborne-Mendel rats treated with tetrachloroethylene, toxic nephropathy was not detected in control animals, but did occur in both male and female rats as well as in mice (NCI, 1977).

Nephrotoxicity after exposure to tetrachloroethylene administered by inhalation was observed in a 2-year cancer bioassay in groups of 50 male and female Fischer rats (0, 50, 200, or 600 ppm) and Crj:BDF1 mice (0, 10, 50, or 250 ppm) exposed for 6 hours per day, 5 days per week, for 104 weeks. Compared with controls, survival was decreased in all groups at the highest dose; this decrease was considered to be treatment-related. Relative kidney weight was increased in male and female rats (exposed at 200 or 600 ppm) and in male and female mice (exposed at 250 ppm). Karyomegaly in the proximal tubules of the kidneys was observed among male and female rats and mice. An increase in atypical tubular dilation of the proximal tubules was noted in male and female rats at the highest dose, and exacerbation of chronic renal disease was observed in male rats at the highest dose only (JISA, 1993).

Hayes *et al.* (1986) reported renal effects in rats exposed to tetrachloroethylene in drinking-water. The rats were given nominal amounts of 14, 400, and 1400 mg/kg bw per day for 90 consecutive days. There were no treatment-related deaths. Increased kidney-to-body weight ratios were observed.

Nephrotoxicity and increased relative kidney weights were observed in female Wistar rats treated with tetrachloroethylene at 600 or 2400 mg/kg bw per day in corn oil by gavage for 32 days. One rat at the higher dose died as a result of the treatment. Nephrotoxic effects were noted at the higher dose, with significant changes in all clinical chemistry markers related to kidney function (urea, total protein, albumin, *N*-acetyl-β-D-glucosaminidase) measured in the urine at the end of week 1 or week 4, except for urinary density, glucose, and creatinine. Karyomegaly was also observed at the higher dose in four out of five animals exposed (Jonker *et al.*, 1996).

Oral administration of tetrachloroethylene in sesame oil (3000 mg/kg bw per day for 15 days) to male and female albino Swiss mice caused a significant increase in kidney weight, an increase in glomerular nephrosis, and a decrease in blood glucose concentrations compared with controls (Ebrahim *et al.*, 1996). Concurrent administration of 2-deoxy-D-glucose (500 mg/kg bw per day, intraperitoneal injection) or vitamin E (400 mg/kg bw per day, gavage) prevented tetrachloroethylene-induced biochemical and pathological alterations. Exposure to tetrachloroethylene alone led to a decrease in blood glucose concentrations, which returned to near-normal levels with concomitant exposure to 2-deoxy-D-glucose and vitamin E. Elevated levels of glycolytic and gluconeogenic enzymes after exposure to tetrachloroethylene were also observed to decrease to near-normal levels after exposure to these two agents. Histopathology of the kidney showed hypercellular glomeruli after exposure to tetrachloroethylene, but this was not observed in mice treated with tetrachloroethylene and 2-deoxy-D-glucose, or tetrachloroethylene and vitamin E (Ebrahim *et al.*, 1996).

Mechanistic information on the nephrotoxicity of tetrachloroethylene was relatively sparse. Most studies have concentrated on the metabolites in the GSH pathway rather than on the parent compound, because much of the available information for both tetrachloroethylene and trichloroethylene suggests that this pathway generates the reactive chemical species responsible for nephrotoxicity.

The role of the GSH metabolites of tetrachloroethylene, particularly TCVC and TCVCS, in kidney toxicity was examined in a study in two groups of four male Sprague-Dawley rats exposed to TCVC or TCVCS (115 or 230 µmol/kg bw in saline) given by single intraperitoneal injections. The rats were killed 24 hours after dosing. Serum was analysed for blood urea nitrogen, and urine samples were analysed for γ-glutamyl transpeptidase activity as markers of nephrotoxicity. Rats exposed to the higher dose of TCVCS showed visible signs of kidney necrosis, while none of the other treated groups did. Histologically,

kidneys from rats exposed to TCVC or TCVCS at the lower dose showed slight-to-mild acute tubular necrosis. Analysis of kidneys at 24 hours after exposure showed mild-to-moderate acute tubular necrosis in rats exposed to TCVC at the higher dose, and severe tubular necrosis in those exposed to TCVCS at the higher dose. A significant fourfold increase in blood urea nitrogen was observed in rats exposed to TCVCS at the higher dose compared with controls, but no significant increases were noted after exposure to TCVC. Variable increases in urinary glucose concentrations and γ-glutamyl transpeptidase activity were seen after exposure to TCVC or TCVCS. A second part of this experiment demonstrated enhanced toxicity by pre-treatment with the β-lyase inhibitor AOAA (500 μmol/kg bw), given by intraperitoneal injection 30 minutes before administration of TCVC at the higher dose. In a third experiment, groups of four rats were exposed to TCVC or TCVCS (higher dose) and killed after 2 hours to investigate non-protein thiol status in the kidney. TCVCS significantly decreased non-protein thiols, but did not affect non-protein disulfides, whereas TCVC was without effect. Histological examination of the kidneys showed scattered foci of mild acute tubular necrosis (after TCVC) or widespread acute tubular necrosis, intratubular casts, and interstitial congestion and haemorrhage (after TCVCS). These results show that TCVCS has greater nephrotoxicity than TCVC (Elfarra & Krause, 2007)

The tetrachloroethylene-*S*-conjugate metabolites TCVG and TCVC caused dose-related cytotoxicity in renal cell preparations, which was prevented by a β-lyase enzyme inhibitor. Renal β-lyases are known to cleave TCVC to yield an unstable thiol, 1,2,2-trichlorovinylthiol, which may give rise to formation of a highly reactive thioketene, a chemical species that can form covalent adducts with cellular nucleophiles (Vamvakas *et al.*, 1989d). In addition, sulfoxidation of both TCVC and its *N*-acetylated product resulted in formation of toxic metabolites (Werner *et al.*, 1996; Ripp *et al.*, 1997). A study by Lash *et al.* (2002) characterized the cytotoxicity of tetrachloroethylene and TCVG in suspensions of isolated kidney cells from male and female F344 rats and the mitochondrial toxicity of tetrachloroethylene and TCVG in suspensions of renal cortical mitochondria from the kidneys of male and female F344 rats and $B6C3F_1$ mice. In both cases, responses to tetrachloroethylene and TCVG were compared with those to trichloroethylene and DCVG, respectively, from a parallel study (Lash *et al.*, 2001). Although the parent compounds are not particularly potent as acute cytotoxic agents, both tetrachloroethylene and trichloroethylene at concentrations of 1 mM each produced a modest degree of cytotoxicity in 3-hour incubations of isolated kidney cells from male F344 rats, as assessed by release of lactate dehydrogenase; tetrachloroethylene and trichloroethylene caused 38% and 24% release, respectively. In contrast, neither parent compound produced significant release of lactate dehydrogenase in isolated kidney cells from female rats. A larger difference was observed when the cytotoxicity of the GSH conjugates was compared. In 3-hour incubations with either TCVG or DCVG at 1 mM, isolated kidney cells from male rats exhibited 40% and 26% release of lactate dehydrogenase, respectively, while isolated kidney cells from female rats exhibited 18% release with both conjugates. Thus, tetrachloroethylene and its GSH-conjugate TCVG were clearly more acutely cytotoxic to isolated renal cells than trichloroethylene and DCVG, and kidney cells from male rats are significantly more sensitive than kidney cells from female rats to these compounds. Tetrachloroethylene and TCVG also induced toxic effects in mitochondria (i.e. mitochondrial dysfunction, such as a reduced respiratory control ratio and inhibition of state-3 respiration by specific inhibition of several sulfhydryl-containing enzymes) in male rats, and in

male and female mice (Lash & Parker, 2001; Lash *et al.*, 2002).

(c) PPARα activation

(i) Humans

No studies were identified on PPARα activation or peroxisome proliferation in human kidney after exposure to tetrachloroethylene. However, in transactivation studies *in vitro*, human PPARα was activated by the metabolites dichloroacetate and trichloroacetate, while tetrachloroethylene itself was relatively inactive (Maloney & Waxman, 1999). A few studies have examined PPARα activation by dichloroacetate and trichloroacetate in cultured human liver cells (e.g. Walgren *et al.*, 2000), but the evidence of these effects from studies of human kidney *in vivo* or *in vitro* is weak.

(ii) Experimental animals

Two studies addressed peroxisome proliferation in rodent kidney after short-term exposure to tetrachloroethylene (see Table 4.6), but there were no data available concerning activation of the receptor in kidney tissue.

Five male F344 rats and five male B6C3F$_1$ mice were given tetrachloroethylene at a dose of 1000 mg/kg bw per day by gavage in corn oil for 10 days. In exposed rats, cyanide-insensitive palmitoyl-coenzyme A (palmitoyl-coA) oxidation activity was modestly—although not significantly—elevated in the kidney (1.7-fold increase). In mice, the treatment enhanced palmitoyl-coA oxidation activity by 2.3-fold in the kidney. Relative kidney weight was unaffected. A comparison of corn oil with methylcellulose revealed no effect of the gavage vehicle on tetrachloroethylene-induced palmitoyl-coA oxidation. A less-than-additive effect on palmitoyl-coA oxidation was seen when trichloroethylene (1000 mg/kg bw) was administered together with tetrachloroethylene (Goldsworthy & Popp, 1987).

In the second study, male and female F344 rats and B6C3F$_1$ mice were exposed to tetrachloroethylene by inhalation (400 ppm, 6 hours per day for 14, 21, or 28 days; 200 ppm, 6 hours per day for 28 days), and palmitoyl-coA oxidation activity was measured in liver and kidney. Due to insufficient material, the analysis of the mouse kidney tissues was done on pooled samples. Slight increases in palmitoyl-coA oxidation were observed in the kidney of male mice (maximum increase of 1.6-fold at 21 days, 400 ppm), but no change in female mice. Modest increases were noted in the kidney of male rats at 200 ppm at 28 days (1.3-fold) but not at 400 ppm at 14, 21, or 28 days. In female rat kidney, palmitoyl-coA oxidation activity was elevated (approximately 1.6-fold) at all doses and times. However, peroxisome proliferation was not observed in rat or mouse kidney when analysed by microscopy (Odum *et al.*, 1988).

4.3.2 Liver

(a) Epigenetic effects

(i) Humans

No data were available from studies in humans regarding a role for epigenetic effects in tetrachloroethylene-induced tumorigenesis.

(ii) Experimental animals

No data were available from studies in experimental animals regarding a role for alteration in DNA methylation in tetrachloroethylene-induced tumorigenesis. However, experimental support for hypomethylation of DNA is available from studies in mice exposed to the metabolites trichloroacetate and dichloroacetate.

When female B6C3F$_1$ mice received an intraperitoneal injection of *N*-methyl-*N*-nitrosourea (MNU) as an initiator followed by exposure to trichloroacetate or dichloroacetate in drinking-water, DNA methylation in the resulting hepatocellular adenomas and carcinomas was about half that observed in non-tumour tissue

Table 4.6 Renal peroxisome proliferation in rodents exposed to tetrachloroethylene

Test system (species, strain, sex, number)	Dose	Effect	Reference
Rat, F344 (male only, 5/group) and mouse, B6C3F$_1$ (male only, 7/group)	1000 mg/kg bw per day for 10 days, corn oil, gavage	Rats: no increase in PCO activity, but increased kidney weight Mice: increased PCO activity in all exposed mice	Goldsworthy & Popp (1987)
Rat, F344; and mouse, B6C3F$_1$ (males and females, 5/group)	200 ppm, 6 h/day, 28 days; and 400 ppm, 6 h/day, 14, 21, 28 days, by inhalation	Rats of both sexes: modest increases in PCO observed in male rat kidneys only at 200 ppm for 28 d, and in female rat kidneys at all doses and times Mice: analysis limited to pooled tissue showed slight increases in β-oxidation in male mouse kidney	Odum *et al.* (1988)

d, day; h, hour; PCO, cyanide-insensitive palmitoyl coenzyme A oxidase activity

from the same animal or from animals given MNU alone (Tao *et al.*, 1998). Exposure of female B6C3F$_1$ mice to drinking-water containing trichloroacetate or dichloroacetate for 11 days reduced total liver-DNA methylation by 60% (Tao *et al.*, 1998). In a further study, changes in methylation of the c-*jun* and c-*myc* genes, and alterations in gene expression were measured in liver tumours initiated by MNU and promoted by dichloroacetate and trichloroacetate in female B6C3F$_1$ mice. Hypomethylation and overexpression of these genes were found in liver tumours promoted by dichloroacetate and trichloroacetate (Tao *et al.*, 2000). Subsequently, these investigators reported hypomethylation of a region of the *IGF-II* gene in liver and tumours from mice initiated with MNU and then exposed to trichloroacetate or dichloroacetate (Tao *et al.*, 2004).

(b) Cytotoxicity and secondary oxidative stress

(i) Humans

A group of 49 workers in the metal-processing industry was exposed to trichloroethylene and tetrachloroethylene at different concentrations. The workers were divided in three groups based on job descriptions, but no exposure assessment was performed. Several markers to assess liver functions were investigated: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, copper, and zinc. The bromphthaleine test was also performed. Statistically, there were no differences between the values found for exposed and controls, the outcome of the tests all being in the normal range (Szadkowski & Körber, 1969).

A health-surveillance study was conducted among 22 workers exposed to tetrachloroethylene (time-weighted average, 21 ppm; range, 9–38 ppm) in six dry-cleaning shops. Results of behavioural, renal, hepatic, and pulmonary tests on these workers were compared with those obtained for 33 subjects not exposed to organic solvents. No differences were observed in mean serum hepatic enzyme concentrations (Lauwerys *et al.*, 1983) [The Working Group noted the lack of proper statistical analysis].

The hepatic health status of 133 dry-cleaning plant workers (women and men) exposed to tetrachloroethylene and 107 controls was assessed by measuring ALT, AST, fatty acids, prothrombin index, bilirubin and iron in serum, by recording a proteinogram, and by conducting the thymol turbidity test. Among women, no statistically significant differences were found between exposed and controls. Among men, statistically significant differences in values (mean and standard deviation) for aminotransferases were observed. Increased activities of serum enzymes were seen in workers exposed to high concentrations of tetrachloroethylene (Gluszczowa, 1988).

Results were presented of a five-year follow-up of 130 workers exposed to tetrachloroethylene in dry-cleaning shops. The study involved measurement of exposure conditions (personal dosimetry, exposure tests) and clinical investigations (ALT, AST, alkaline phosphatase, GGT, alanine aminopeptidase, cholinesterase) and plasma concentrations of bilirubin, cholesterol and triglycerides. No signs of hepatotoxicity due to exposure to tetrachloroethylene were observed (Müller *et al.*, 1989).

Subjective symptoms and clinical indicators of liver injury were evaluated among 56 dry-cleaning workers (29 men, 27 women) who had been exposed to tetrachloroethylene vapour (20 ppm, 8-hour TWA) for several years. A control group (32 men, 37 women) of similar age recruited from the same factories was not exposed to solvents. There was an exposure-related increase in the prevalence of symptoms such as dizziness, floating sensation, and headache among the exposed workers. In haematological assays and serum biochemistry tests, no significant changes were seen in AST or ALT, alkaline phosphatase or leukocyte alkaline phosphatase, GGT or total bilirubin (Cai *et al.* (1991).

The isoenzyme pattern of serum GGT was studied in 141 male and female workers in dry-cleaning shops exposed to tetrachloroethylene (8-hour TWA, 11.3 ppm) and in 130 control subjects. None of the workers showed clinical symptoms of liver disease and their enzymatic profiles, including AST, ALT, 5′nucleotidase, alkaline phosphatase, and GGT, were within the normal range. A statistically significant increase in total GGT in serum was found in the exposed subjects, which was due to an increase in one of the two fractions normally present in healthy individuals (GGT-2), and to the appearance and progressive increase in the level of a fraction (GGT-4) considered to be indicative of hepato-biliary impairment. [It should be noted that individuals who had liver enzyme activity above the normal range, and those who had past or current liver disease were not included in this study (Gennari *et al.*, 1992).]

A study was conducted to determine whether subclinical hepatotoxicity is associated with exposure to tetrachloroethylene at concentrations commonly experienced in the workplace, and whether surveillance with serum hepatic transaminase activity underestimates such effects. Included in the study were 29 dry-cleaning operators (8-hour TWA, 16 ppm) and a control group of 29 non-exposed laundry workers. Hepatic parenchymal tissue was scanned by means of ultrasonography; hepatic transaminase activity in serum was also measured. ALT activities of up to 1.5 times the normal limits were found in five out of 27 (19%) dry-cleaning workers compared with one out of 26 (4%) laundry workers. In contrast, ultrasonography revealed a twofold increase in hepatic parenchymal changes in 18 out of 27 dry-cleaning workers (67%), compared with 10 of 26 (39%) laundry workers (Brodkin *et al.*, 1995).

(ii) Experimental animals

Numerous studies in experimental animals, including long-term bioassays, have demonstrated that tetrachloroethylene is hepatotoxic, with the mice being more sensitive than rats (NCI, 1977; Schumann *et al.*, 1980; NTP, 1986; JISA, 1993). Male and female NMRI mice were exposed by whole-body inhalation to various concentrations of tetrachloroethylene (9–3600 ppm) in different experimental designs (continuous or intermittent exposure, from 4 to 120 days). In mice continuously exposed to tetrachloroethylene for 30 days, the increase in plasma butyrylcholinesterase activity became significant at exposure levels > 37 ppm. Compared with controls, the increase was 1.7-fold in female mice and 2.5-fold in male mice after exposure for 120 days to 150 ppm. Under these conditions, the increase in liver weight was 2.3-fold in female mice and 1.9-fold in male mice. The activity of butyrylcholinesterase returned to normal within

30 days after cessation of exposure, but a 10% increase in liver weight remained. No signs of cholestasis were found upon histopathological examination of the liver (Kjellstrand *et al.*, 1984).

Hepatic toxicity was observed in rodents during short- and long-term (lifetime) bioassays with tetrachloroethylene administered by inhalation (NTP, 1986). In a 13-week study, male and female rats and mice were exposed to tetrachloroethylene (0, 100, 200, 400, 800, or 1600 ppm) by inhalation (6 hours per day, 5 days per week). In the group at the highest dose, some rats (males, 4 out of 10; females, 7 out of 10) and some mice (males, 2 out of 10; females, 4 out 10) died before the end of the study. Exposure to tetrachloroethylene (200 ppm and above) increased the incidence of hepatic congestion in male and female rats. In mice of both sexes, liver inflammatory lesions (leukocytic infiltration, centrilobular necrosis, and bile stasis) were observed at 400, 800, or 1600 ppm. Tetrachloroethylene was also administered by inhalation to F344 rats (0, 200, or 400 ppm) or $B6C3F_1$ mice (0, 100, or 200 ppm) for 103 weeks (6 hours per day, 5 days per week). In male and female mice, in addition to liver tumours (see Section 3), liver degeneration was reported in 2 out of 49, 8 out of 49, and 14 out of 50 males, and in 1 out of 49, 2 out of 50, and 13 out of 50 females in the three groups. Degeneration was characterized by cytoplasmic vacuolization, hepatocellular necrosis, inflammatory cell infiltrates, pigmented cells, oval cell hyperplasia, and regenerative foci. Liver necrosis was observed at increased incidence in males (1 out of 49, 6 out of 49, and 15 out of 50) and in females at 400 ppm (3 out of 48, 5 out of 50, and 9 out of 50). Nuclear inclusions increased in male mice (2 out of 49, 5 out of 49, and 9 out of 50). No dose-related effects on the liver were reported in the rats.

Male Swiss-Cox mice were exposed to tetrachloroethylene by oral gavage (0, 20, 100, 200, 500, 1000, 1500, or 2000 mg/kg bw per day) on 5 days per week for 6 weeks. Liver necrosis, polyploidy in the centrilobular region, and lipid accumulation were evident upon histopathological examination of mice at 200 or 1000 mg/kg bw. Liver:body weight ratios and liver triglycerides were significantly increased at doses ≥ 100 mg/kg bw per day. Enlarged hepatocytes, polyploidy in the centrilobular region, and lipid accumulation were evident upon histopathological examination of mice exposed to 200 or 1000 mg/kg bw. The percentage increase in the liver:body weight ratio was highly correlated with the amount of tetrachloroethylene metabolized (urinary levels of metabolites). Other indices of tetrachloroethylene hepatotoxicity (e.g. increased serum ALT activity) were significantly increased at doses ≥ 500 mg/kg bw (Buben & O'Flaherty, 1985).

An inhalation study by the Japanese Industrial Safety Association (JISA) used male and female Crj/BDF1 mice (exposed at 0, 10, 50, and 250 ppm tetrachloroethylene) and F344/DuCrj rats (exposed at 0, 50, 200, and 600 ppm). Exposure was for 104 weeks and the mice were killed at 110 weeks. In mice, in addition to hepatocellular carcinomas and adenomas (see Section 3), focal liver necrosis was observed in males at doses of 50 ppm and higher. Liver degeneration was noted at 250 ppm in males and females. In male but not female rats, an excess incidence of spongiosis hepatitis was reported at 200 ppm and 600 ppm (JISA, 1993).

Female F344 rats were dosed by oral gavage either once (0, 150, 500, 1500, and 5000 mg/kg bw), or daily for 14 consecutive days (0, 50, 150, 500, 1500 mg/kg bw per day). An increase in the concentration of serum ALT was seen in rats at the highest dose in the 14-day exposure experiment (Berman *et al.*, 1995).

Tetrachloroethylene-associated hepatotoxicity was evaluated after exposure of female Wistar rats at 600 or 2400 mg/kg bw per day via oral gavage in corn oil for 32 days. At the higher dose, the activities of ALT and AST in serum were significantly increased. There was also a significant increase in relative liver weight (Jonker *et al.*, 1996).

The hepatotoxic effect of repeated exposure was investigated in male Swiss Webster mice that were given tetrachloroethylene as three doses (150, 500, or 1000 mg/kg bw) via aqueous gavage, daily for up to 30 days. Tissue injury was monitored regularly during the dosing regimen on days 1, 7, 14, and 30, and over a time course of 24–96 hours after the last dose. Significant increases in serum ALT were observed after a single exposure at all three doses. Higher levels of ALT were also found in the group receiving the highest dose after 7 days, and in all three groups after 14 days of continuous exposure, but no longer after 30 days of exposure, nor in the follow-up samples. Mild to moderate centrilobular degeneration was observed in the liver of mice in the groups receiving the intermediate and highest dose after 1 day of exposure. By 30 days, both groups showed a reduction of tissue damage compared with day 1, as well as evidence of tissue repair, primarily visible as an increase in hepatocellular mitotic figures (Philip *et al.*, 2007).

A limited number of studies focused on tetrachloroethylene-induced hepatic oxidative stress. When tetrachloroethylene was given orally in sesame oil to male and female Swiss mice at 3000 mg/kg bw per day for 15 days, a significant increase in liver weight was seen, as well as degeneration and necrosis of hepatocytes. These changes occurred simultaneously with a decrease in blood glucose, enhanced activity of the enzymes hexokinase, aldolase, and phosphoglucoisomerase, and reduced activities of enzymes involved in gluconeogenesis. Most of these effects were mitigated by concomitant exposure to 2-deoxy-D-glucose or vitamin E (Ebrahim *et al.*, 1996).

In a further study, the potential protective properties of 2-deoxy-D-glucose, vitamin E, and taurine against membrane damage were investigated with a similar treatment protocol. Male albino Swiss mice were exposed to the same doses of tetrachloroethylene as used in the previous study, with the addition of a taurine-exposed group. Membrane-bound Na^+K^+-ATPase and Mg^{2+}-ATPase activity were significantly decreased ($P < 0.001$), while Ca^{2+}-ATPase activity was increased ($P < 0.001$) after exposure to tetrachloroethylene alone. These levels remained close to normal in mice exposed to tetrachloroethylene together with 2-deoxy-D-glucose, vitamin E, or taurine. This return to normal levels after exposure to vitamin E and taurine may be due to their activity as an antioxidant, and the ensuing reduction in oxidative stress in exposed cells (Ebrahim *et al.*, 2001).

(c) Cell proliferation

Increased cell proliferation in mice has been reported after exposure to tetrachloroethylene. To study the extent to which tetrachloroethylene alters cell proliferation and apoptosis, several studies have measured hepatocyte proliferation in mice in response to treatment with the metabolite trichloroacetate (Sanchez & Bull, 1990; Dees & Travis, 1994; Pereira, 1996; Stauber & Bull, 1997; DeAngelo *et al.*, 2008). For instance, Dees & Travis (1994) observed relatively small (two- to threefold) but statistically significant increases in [^{3}H]thymidine incorporation in hepatic DNA in mice exposed by gavage for 11 days to trichloroacetate at doses (100–1000 mg/kg bw) that increased the relative liver weight. Increased hepatic DNA labelling was seen at doses lower than those associated with evidence of necrosis, suggesting that trichloroacetate-induced cell proliferation is not due to regenerative hyperplasia.

In the study by Philip *et al.* (2007) above, a dose-dependent increase in [^{3}H]thymidine incorporation was observed in all dose groups on day 7 of treatment, which was sustained until 14 days in the groups at the intermediated dose and highest dose. A lower level of cell proliferation was evident after 30 days than after 14 days exposure to all three doses. PCNA immunohistochemistry was performed to confirm the findings of S-phase stimulation determined by the

[^{3}H]thymidine pulse-labelling study. The immunochemistry results and the pulse-labelling data were consistent (Philip *et al.*, 2007).

(d) PPARα activation

Tetrachloroethylene or its metabolites have been shown to induce activation of PPARα or markers of peroxisome proliferation in the liver.

(i) Humans

No studies were available on peroxisome proliferation or the key events in PPARα activation in human liver. However, transactivation studies *in vitro* have shown that in humans PPARα is activated by trichloroacetate and dichloroacetate, while tetrachloroethylene itself is relatively inactive (Zhou & Waxman, 1998). A limited number of studies focused on PPARα activation by the tetrachloroethylene metabolites dichloroacetate and trichloroacetate in cultured human liver cells. In one of these studies, trichloroacetate and dichloroacetate did not increase palmitoyl-CoA oxidation and caused a decrease in DNA synthesis in human hepatocyte cultures, in contrast to the response seen in rodents (Walgren *et al.*, 2000).

(ii) Experimental animals

Several studies in experimental animals *in vivo* examined the effect of tetrachloroethylene on peroxisome proliferation or its markers in the liver (Table 4.7).

Groups of five male and five female F344 rats and B6C3F$_1$ mice were exposed by inhalation for 6 hours per day to tetrachloroethylene at 200 ppm for 28 days, or at 400 ppm for 14, 21, or 28 days. In both sexes and in both species, hepatic palmitoyl-coA oxidation activity was increased (mice, up to 3.6-fold; rats, up to 1.3-fold). Hepatic peroxisome proliferation was noted by electron microscopy in all exposed mice, and the proportion of the cytoplasm occupied by peroxisomes was increased. In rats, variable increases in peroxisome volume were noted at 200 ppm, but results lacked statistical significance. Catalase, another peroxisomal enzyme, was unaffected by tetrachloroethylene: male mice exposed at 400 ppm showed only a moderate increase (1.4-fold). Mitochondrial proliferation was observed at 28 days in male mice in the group at 400 ppm. In addition, a time-dependent proliferation of smooth endoplasmic reticulum in the liver of males and females correlated well with centrilobular hypertrophy. Tetrachloroethylene caused centrilobular lipid accumulation in male and female mice. Relative liver weight was increased in male and female mice (Odum *et al.*, 1988).

Five male F344 rats and five male B6C3F$_1$ mice were given tetrachloroethylene (1000 mg/kg bw) in corn oil by gavage, daily for 10 days. In the rats, palmitoyl-coA oxidation was modestly, although not statistically significantly, elevated in the liver (1.4-fold). In exposed mice, palmitoyl-coA oxidation was increased 4.3-fold in. Relative liver weight was increased in rats and mice. A comparison between corn oil and methylcellulose showed no effect of the gavage vehicle on tetrachloroethylene-induced palmitoyl-coA oxidation. Administration of trichloroethylene (1000 mg/kg bw) together with tetrachloroethylene had a less-than-additive effect on induction of palmitoyl-coA oxidation (Goldsworthy & Popp, 1987).

Kyrklund *et al.* (1990) exposed male Sprague-Dawley rats to tetrachloroethylene at 320 ppm continuously for 90 days, followed by a 30-day recovery period. Relative liver weight was significantly increased in rats examined at the end of the exposure period. A slight increase in relative liver weight was also observed in the recovered, solvent-treated group.

SV129 PPARα-deficient mice exposed to trichloroacetate at doses up to 2 g/L in drinking-water for 7 days did not show the characteristic induction of acyl-coenzyme A oxidase, palmitoyl-coA oxidase, and CYP4A associated with PPARα activation and peroxisome proliferation in wild-type animals. In addition, the livers

Table 4.7 Studies of induction of hepatic peroxisome proliferation or its markers in rodents exposed to tetrachloroethylene

Test system (species, strain, sex, number)	Dose	Effect	Reference
Rat, F344 (male only, 5/group) and mouse, $B6C3F_1$ (male only, 7/group)	1000 mg/kg bw per day for 10 days, corn oil, gavage	Mice: increased relative liver weight; 4.3-fold PCO increase Rats: increased relative liver weight; modest (1.4-fold) PCO increase, not significant	Goldsworthy & Popp (1987)
Rat, F344; and mouse, $B6C3F_1$; males and females (5/group)	200 ppm, 6 h/day, 28 days; and 400 ppm, 6 h/day, 14, 21, 28 days, by inhalation	Male and female mice: increased relative liver weight, centrilobular lipid accumulation and peroxisome proliferation; increased PCO (up to 3.7-fold)	Odum *et al.* (1988)
	400 ppm, inhalation; 28 days	Male mice: mitochondrial proliferation	
	200, and 400 ppm, inhalation; 14, 21, 28 days	Male and female rats: increased PCO (up to 1.3-fold)	
Mouse, Swiss-Webster, male (4/group)	150, 500, and 1000 mg/kg bw per day, aqueous gavage; 24 h to 14 days after initial exposure	Increased plasma ALT	Philip *et al.* (2007)
	500 and 1000 mg/kg bw per day, aqueous gavage; 24 h to 30 days after initial exposure	Mild to moderate fatty degeneration and necrosis, with focal inflammatory cell infiltration	
	150, 500, and 1000 mg/kg bw per day, aqueous gavage; peaked on day 7, sustained at 14–30 days	Increased mitotic figures and DNA synthesis	
	1000 mg/kg bw per day, aqueous gavage; 7 days, but not 14 days	Increased expression of CYP4A	

d, day; h, hour; ALT, alanine aminotransferase; PCO, cyanide-insensitive palmitoyl coenzyme A oxidase activity

from wild-type, but not PPARα-deficient, mice exposed to trichloroacetate at 2 g/L developed centrilobular hepatocyte hypertrophy, although no significant increase in relative liver weight was seen (Laughter *et al.*, 2004).

CYP4A, a marker for PPARα-activation, was transiently increased (only on day 7 of a 30-day treatment) in Swiss Webster mice, and only at the highest of three oral doses (150, 500, 1000 mg/kg bw per day) (Philip *et al.*, 2007). [The Working Group noted that in the NCI cancer bioassay, liver tumours had appeared at doses around 500 mg/kg bw per day (NCI, 1977), at which no increased CYP4A activity was reported. The sensitivity of the Swiss Webster mouse strain relative to that of the $B6C3F_1$ mice used in the cancer bioassay is unknown.]

(e) Disruption of gap-junctional intercellular communication

The lucifer-yellow scrape-load dye-transfer technique was used to examine the effect of tetrachloroethylene, dichloroacetate, and trichloroacetate on cultures of clone-9 normal rat-liver cells after exposure during 1, 4, 6, 24, 48, and 168 hours. Tetrachloroethylene caused a significant effect at 0.01 mM after 48 hours. Over a 24-hour treatment period the relative efficiencies, expressed as the concentration needed to produce a 50% reduction in intercellular communication, were 0.3 mM for tetrachloroethylene, 3.8 mM for trichloroacetate, and 41 mM for dichloroacetate. The time course of the effect was similar for the three compounds (Benane *et al.*, 1996).

4.3.3 Immune system

(a) Humans

Several recent studies have evaluated the immunotoxicity of exposure to tetrachloroethylene. A small cross-sectional study conducted in the Czech Republic included 21 exposed workers in the dry-cleaning industry and 16 controls from the same plant. Several immunological markers were measured, including α-macroglobulin, phagocyte activity, T lymphocytes, concentrations of the complement proteins C3 and C4, and immunoglobulins. These parameters were compared with laboratory reference values from blood donors and healthy individuals in the same region. Biological monitoring of the workers over an 8-hour working shift showed tetrachloroethylene in exhaled air in the range of 9 to 344 mg/m^3 at the end of the shift. Compared with controls, the exposed workers had significantly elevated serum concentrations of the proteins C3 and C4 and higher salivary concentrations of IgA. Compared with reference values from 41 healthy blood donors, the serum concentration of C3 of the exposed workers was higher, while the number of T lymphocytes was reduced (Andrýs *et al.*, 1997).

In terms of sample size and the use of an appropriately matched control group, the strongest study examining immunological and haematological effects of exposure to tetrachloroethylene was that among 40 male dry-cleaning workers who had mean exposure levels up to 140 ppm, and a mean exposure duration of 7 years. Statistically significant decreases in erythrocyte count and haemoglobin levels, and increases in total leukocyte counts and lymphocyte counts were observed in the exposed workers compared with age- and smoking-matched controls. In addition, increases in several other immunological parameters, including T-lymphocyte and natural killer-cell subpopulations, IgE, and interleukin-4 levels were reported. These immunological effects suggest an augmentation of Th2 responsiveness (Emara *et al.*, 2010).

Case–control studies that evaluated the risk of autoimmune disease in relation to exposure to tetrachloroethylene have not suggested that there is a significant association.

The association with exposure to tetrachloroethylene was evaluated in 60 patients who were positive for ANCA (anti-neutrophil cytoplasmic antibody) and 120 age- and sex-matched controls in France (Beaudreuil *et al.*, 2005). Cases included hospital in-patients (admitted in 1990–2000) who were ANCA-positive, and in-patient controls (admitted in 2000–2001) matched to cases by age (± 5 years) and sex. An interviewer-administered questionnaire was used to evaluate occupational exposure to several solvents and other chemicals. The exposure assessment included both qualitative and semiquantitative methods and was assessed by a panel of experts blinded to the disease status of the patients. A total of five ANCA-positive patients were reported to be exposed to tetrachloroethylene; leading to a twofold non-significantly increased risk of ANCA-positivity associated with exposure to tetrachloroethylene.

A case–control study of 205 female patients with undifferentiated connective tissue disease (UCTD) and 2095 population-based controls in the USA evaluated the association between UCTD and exposure to petroleum distillate solvents, including tetrachloroethylene. Exposures to solvents were self-reported in a personal interview, which included an assessment of the number of years each woman had worked with the solvent, whether protective equipment was used, and job activities. The only available risk estimate was for nine exposed cases in dry-cleaning workers; the risk of UCTD in these workers was marginally elevated, but not statistically significant (Lacey *et al.*, 1999).

Two studies of children in Germany have evaluated formation of IgE antibodies to food and allergens and measured the number of

cytokine-producing peripheral T-cells in relation to exposure to tetrachloroethylene and other volatile organic compounds. In the first study, serum IgE concentrations were measured in 121 children, while cytokine measurements were available for 28 children. Exposures to tetrachloroethylene and other volatiles were passively monitored in the bedroom of each child for 4 weeks; the median exposure level was reported for tetrachloroethylene to be 2.54 μg/m^3. This indoor exposure was not significantly associated with allergic sensitization to egg white or milk, or with cytokine-producing T-cells (Lehmann *et al.*, 2001).

In a study of 22 Hispanic children with asthma living in Los Angeles, USA, symptom diaries were completed for 3 months, while outdoor 24-hour air samples were collected from a central site to assess airborne concentrations of tetrachloroethylene, other volatile organic compounds, and reference air-pollutants. The mean level of exposure to tetrachloroethylene was reported to be 0.51 ppb. More severe asthma symptoms were significantly associated with exposure to tetrachloroethylene, but this association was attenuated and no longer statistically significant after further adjustment for levels of sulfur dioxide and nitrogen dioxide (Delfino *et al.*, 2003a).

(b) Experimental animals

No studies were available on the toxicity of tetrachloroethylene in putative target tissues in the immune system in F344 rats, i.e. bone marrow, spleen, or target cells of mononuclear cell leukeamia. However, in mice the haematopoietic toxicity of tetrachloroethylene has been demonstrated in several studies.

In albino Swiss mice, administration of tetrachloroethylene in sesame oil (3000 mg/kg bw per day, for 15 days) by oral intubation resulted in a significant decrease in haemoglobin, haematocrit (erythrocyte volume fraction), and erythrocyte and platelet counts, and a significant increase in leukocyte counts (Ebrahim *et al.*, 2001). These findings are similar to those observed in studies in humans exposed to tetrachloroethylene (Emara *et al.*, 2010).

Female NMRI mice were given tetrachloroethylene in drinking-water at nominal doses of 0.05 or 0.1 mg/kg bw per day for 7 weeks. The treatment resulted in reversible haemolytic anaemia, and there was evidence from microscopical analyses of splenic involvement. Tetrachloroethylene accumulated in the spleen to a significantly greater extent than in liver, brain, or kidney; levels of tetrachloroethylene in the spleen were 20-fold those in the liver after 7 weeks (Marth, 1987). Tetrachloroethylene was also found in the spleen and fatty tissue of treated mice up to 2 months after the end of the 7 weeks of exposure (Marth *et al.*, 1989).

Female hybrid mice (C57/BL/6 × DBA/2) were exposed to tetrachloroethylene at a concentration of 270 ppm for 6 hours per day, 5 days per week for 11.5 weeks, and at 135 ppm for 6 hours per day for 7.5 weeks, followed by a 3-week exposure-free period. There was a reduction in erythrocyte count, supported by decreases in colony-forming units (CFU) and burst-forming units (BFU) of erythroid cells, and evidence of reticulocytosis. Reversible reductions in the numbers of lymphocytes/monocytes and neutrophils were also observed. The slight depression in number of granulocyte progenitor cells (CFU-C), which persisted after the exposure, could indicate the beginning of disturbance at all levels of progenitor cell (Seidel *et al.*, 1992).

Several leukaemogens (e.g. benzene) inhibit the production of both erythrocytes and various types of leukocyte in blood. A decrease in CFU-Ss has commonly been reported, but this effect is not observed after exposure to tetrachloroethylene. Leukaemogens also cause a decrease in number of several myeloid progenitors in the bone marrow; CFU-E/BFU-E was also reduced by tetrachloroethylene (Seidel *et al.*, 1989a, b). Thus, there is indirect evidence that

tetrachloroethylene induces effects associated with leukaemogenesis (NRC, 2010).

Some studies focused on the immunotoxicity of tetrachloroethylene, but their number was too small to establish whether tetrachloroethylene affects immune parameters in a way that would confirm its leukaemia-inducing potential.

Immunosuppression was observed in female $B6C3F_1$ mice given tetrachloroethylene in drinking-water (maximum concentration, 6.8 ppm) in a mixture of 24 contaminants of groundwater occurring frequently near Superfund sites in the USA (i.e. an uncontrolled or abandoned place where hazardous waste is located; Germolec *et al.*, 1989). Mice exposed to the highest dose of this mixture for 14 or 90 days showed suppression of haematopoietic stem cells and of antigen-induced antibody-forming cells. There were no effects on T-cell function or in numbers of T and B-cells in any exposed group. No changes were evident upon challenge with *Listeria monocytogenes* or PYB6 tumour cells.

Aranyi *et al.* (1986) exposed female CD-1 mice to tetrachloroethylene at a concentration of 25 or 50 ppm by inhalation as a single (3 hours) or repeated dose (5 days per week, 3 hours per day). Susceptibility to *Streptococcus zooepidemicus* aerosol infection and pulmonary bactericidal activity to inhaled *Klebsiella pneumoniae* were evaluated. A single 3-hour exposure to tetrachloroethylene at 50 ppm significantly increased susceptibility to respiratory infection and mortality after exposure to *S. zooepidemicus*. In addition, the 3-hour exposure to tetrachloroethylene at 50 ppm was associated with a statistically significant decrease in pulmonary bactericidal activity. No significant differences were observed in mice exposed to tetrachloroethylene at 25 ppm.

4.3.4 Central nervous system

No data were available directly concerning either the metabolites or the mechanisms that may contribute to the induction of rare tumours of the brain (glioma) occurring in rats exposed to tetrachloroethylene (see Section 3). Studies in humans and experimental animals indicate an association of neurobehavioural defects with exposure to tetrachloroethylene (see Bale *et al.* 2011 for a recent review). The primary neurobehavioural changes observed after exposure to tetrachloroethylene are changes in vision, cognitive deficits, and increased reaction time. The acute effects of tetrachloroethylene appear to have much in common with those of other chlorinated solvents such as trichloroethylene and dichloromethane, as well as toluene, volatile anaesthetics, and alcohols. It is not known how the different neurological effects are induced, but there is information available to help elucidate which areas in the brain and which specific molecular targets may be involved in the ensuing neurotoxicological outcome.

(a) Humans

Data on neurotoxicity in humans were available from controlled experimental chamber studies (Altmann *et al.*, 1990) and epidemiological investigations that used standardized neurobehavioural batteries (Altmann *et al.*, 1995; Echeverria *et al.*, 1995; Spinatonda *et al.*, 1997) or assessment of visual function (Schreiber *et al.*, 2002; Storm *et al.*, 2011), a neurological outcome known to be sensitive to volatile organic compounds. Seven epidemiological studies examined occupational exposure to tetrachloroethylene (Seeber, 1989; Ferroni *et al.*, 1992; Cavalleri *et al.*, 1994; Echeverria *et al.*, 1995; Spinatonda *et al.*, 1997; Gobba *et al.*, 1998; Schreiber *et al.*, 2002), three epidemiological studies examined residential exposure to tetrachloroethylene (Altmann *et al.*, 1995; Schreiber *et al.*, 2002; Storm *et al.*, 2011), and two were

experimental chamber studies of acute effects (Hake & Stewart, 1977; Altmann *et al.*, 1990).

Results from the studies of both occupational and residential exposure support an inference of visual deficits after long-term exposure to tetrachloroethylene. Notably, decrements in colour confusion were reported among all workers exposed to a mean TWA of 6 ppm for an average of 8.8 years (Cavalleri *et al.*, 1994).

Studies of acute effects in humans reported increased latencies of up to 3.0 ms in visual evoked potentials (Altmann *et al.*, 1990) and changes in electroencephalograms [magnitude of effect not specified] (Stewart *et al.*, 1970; Hake & Stewart, 1977) at higher exposures ranging from 340 to 680 mg/m^3.

Effects on visiospatial memory (increased response times or cognition errors) in humans were also reported in each of the studies that examined this parameter (Seeber, 1989; Echeverria *et al.*, 1994, 1995; Altmann *et al.*, 1995), in occupational and residential settings.

An occupational exposure study (n = 60) (Ferroni *et al.*, 1992) and a residential exposure study (n = 14) (Altmann *et al.*, 1995), with mean exposure levels of 15 and 0.7 ppm, respectively, reported significant increases in simple reaction time of 24 ms (11% increase) and 40 and 51.1 ms (15 and 20% increases, respectively, for two separate measurements) for the exposed subjects. A third study reported better performance on simple reaction time in 21 exposed workers (mean TWA, 21 ppm) compared with controls when measured before a work shift, but not when measured after work (Lauwerys *et al.*, 1983).

(b) Experimental animals

Mechanistic neuropathological studies have been conducted in animal models (rats, mice, gerbils) to determine how tetrachloroethylene may give rise to the neurological effects observed. Changes in fatty-acid composition of the brain after exposure to tetrachloroethylene at 320 ppm for 30 or 90 days have been reported, and some of these changes persisted for up to 30 days after cessation of exposure (Kyrklund *et al.*, 1988, 1990). Studies that examined the entire brain of animals reported reductions in astroglial proteins (GFAP and S-100), decreased brain RNA content, and decreased levels of glutamine, threonine, and serine (Savolainen *et al.*, 1977; Honma *et al.*, 1980a, b; Kyrklund *et al.*, 1984, 1987, 1988, 1990; Rosengren *et al.*, 1986; Wang *et al.*, 1993). Brain regions examined after exposure to tetrachloroethylene included the frontal cortex, the hippocampus, the striatum, and the cerebellum. Notable changes included decreased DNA content in the frontal cortex after continuous exposure at 600 ppm for 4 weeks in rats (Wang *et al.*, 1993), or exposure at 60 ppm for 3 months in Mongolian gerbils (Karlsson *et al.*, 1987). Decreased levels of taurine were noted in the cerebellum and hippocampus after exposure to tetrachloroethylene at 120 ppm for 12 months in Mongolian gerbils, but there were no changes in levels or uptake of γ-aminobutyric acid (GABA) (Briving *et al.*, 1986).

Reduced concentrations of acetylcholine were noted in the striatum of male rats exposed to tetrachloroethylene at 800 ppm for 1 month (Honma *et al.*, 1980a, b).

Voltage- and ligand-gated ion channels have been implicated in many neurological functions and have been studied as potential neurological targets for tetrachloroethylene and structurally related chlorinated solvents (e.g. trichloroethylene, 1,1,1-trichloroethane, dichloromethane). Tetrachloroethylene has been shown to perturb voltage-sensitive calcium-channel function in nerve growth factor-differentiated pheochromocytoma cells (Shafer *et al.*, 2005) and to block various acetylcholine-induced currents in human neuronal nicotinic acetylcholine receptors by 40–60% (Bale *et al.*, 2005). On the basis of the structural similarity of tetrachloroethylene and other chlorinated solvents, as well as similar neurobehavioural and mechanistic findings, it is likely that tetrachloroethylene also interacts with

the other molecular targets. This solvent class, in particular trichloroethylene, has been shown to interact with ion channels such as the $GABA_A$ and glycine receptors (Beckstead *et al.*, 2000; Krasowski & Harrison, 2000; Lopreato *et al.*, 2003). In addition, this class of solvents block the sodium-channel (Shrivastav *et al.*, 1976) and the voltage-sensitive calcium-channel function (Shafer *et al.*, 2005) when the membrane is held at or near the resting membrane potential. Overall, these solvents appear to potentiate the function of inhibitory receptors and inhibit the function of excitatory receptors (see Bowen *et al.* (2006) and Bushnell *et al.* (2007) for reviews).

Evidence from the available studies in humans and experimental animals indicated that long-term exposure to tetrachloroethylene can result in decrements in colour vision, visuospatial memory, and possibly other aspects of cognition and neuropsychological function, including reaction time.

4.4 Susceptibility

4.4.1 Genetic polymorphisms

Genetic variation is likely to play a role in the response to exposure to tetrachloroethylene in humans. Individual uptake of tetrachloroethylene was estimated from the concentrations of the parent compound and its metabolites in blood, urine, and exhaled air after a single exposure at 70 or 140 ppm for 4 hours (Monster & Houtkooper, 1979). The concentrations of tetrachloroethylene in blood at 2 hours or 20 hours after exposure, and in exhaled air at 2 hours after exposure provided a coefficient of inter-individual variation of 20–25%.

The metabolism of tetrachloroethylene differed by about fivefold among seven samples of liver from adults (Reitz *et al.*, 1996), and a twofold difference in the concentration of tetrachloroethylene in blood was reported among nine adults (Opdam, 1989); the latter difference may be attributable to differing amounts of body fat of the subjects.

The oxidative metabolism of tetrachloroethylene is mediated by several cytochrome P450 enzymes, but it is not clear which role is played by specific isoforms. CYP2E1 facilitates the metabolism of tetrachloroethylene to genotoxic intermediates (Doherty *et al.*, 1996). However, induction of CYP2E1 with pyridine had little effect on tetrachloroethylene-induced cytotoxicity (Lash *et al.*, 2007). Human lymphoblastoid cell lines expressing individual human CYP450 isoforms were used to identify the enzymes responsible for the formation of immunoreactive protein by microsomal fractions upon incubation with tetrachloroethylene. CYP1A2, CYP2B6 and CYP2C8 appeared to be responsible for the immunoreactivity, but no activation of tetrachloroethylene by CYP2E1 could be detected (White *et al.*, 2001). While CYP2E1 is a key enzyme in the metabolic activation of a variety of toxicants including nitrosamines, benzene, vinyl chloride, and halogenated solvents such as trichloroethylene (reviewed in Neafsey *et al.*, 2009), there is little evidence for a potential role of CYP2E1 polymorphisms in differences in the metabolism and toxicity of tetrachloroethylene.

Formation of reactive thiols after metabolism of tetrachloroethylene is considered a critical pathway leading to toxicity and cancer in the kidney. GSTs, β-lyase, FMOs and CYP3A enzymes have been implicated in this mechanism. Genetic variants in CYP3A enzymes are well established in humans as one of the major pharmacogenomic factors for a variety of drugs and environmental chemicals (McGraw & Waller, 2012). While it has not been firmly established which GSTs are important in the metabolism of tetrachloroethylene, allelic polymorphisms of these enzymes in humans have been reported (Rodilla *et al.*, 1998; Cummings *et al.*, 2000; Tzeng *et al.*, 2000). It is not clear, however, how the possible inter-individual differences in these isoenzymes are related to differences in the toxic

effects of tetrachloroethylene, because the specificities and reaction rates of these enzymes are not well understood.

Several transporter molecules that mediate the entry of organic ions into the renal proximal tubular cells (e.g. the organic-anion transporters OAT1 and OAT3) are known to be polymorphic in humans (Erdman *et al.*, 2006; Lash *et al.*, 2006; Urban *et al.*, 2006). These transporters are likely to be responsible for the uptake and cellular accumulation of TCVG and TCVC, two nephrotoxic metabolites of tetrachloroethylene. Thus, dependent on this transporter polymorphism, human populations may have markedly different capacities to accumulate TCVG or TCVC, which may affect their susceptibility to nephrotoxicity.

4.4.2 Life-stage susceptibility and vulnerability

Differences in the effects of exposure to tetrachloroethylene at different stages of life have been reported. Tetrachloroethylene and its metabolite trichloroacetic acid were found in the fetus and in amniotic fluid after exposure of pregnant rats by inhalation (Ghantous *et al.*, 1986). Maternal and fetal/neonatal blood and tissue dose-metrics during pregnancy and lactation were evaluated by use of a physiologically-based pharmacokinetic model for tetrachloroethylene (Gentry *et al.*, 2003). Blood concentrations of tetrachloroethylene in the fetus during gestation were found to be about 600-fold those in the neonate during the lactation period.

During perinatal development, several additional factors may contribute to a higher exposure of children to tetrachloroethylene compared with adults. Because children spend more time indoors and have a greater ventilation rate, i.e. they breathe more rapidly, they may be more vulnerable. Indoor environments in households where dry-cleaning workers live have been found to contain concentrations of tetrachloroethylene that are up to 100-fold those in control homes (Aggazzotti *et al.*, 1994; Storm *et al.*, 2011). Breast milk is an additional and unique exposure source in early life stages (Bagnell & Ellenberger, 1977; Schreiber *et al.*, 2002). Differences in diet between children and adults may lead to higher ingestion of tetrachloroethylene by children (per body weight compared with adults). Collectively, these factors may play a role in greater absorption of tetrachloroethylene in children, but this has not been evaluated quantitatively.

With regards to distribution, one study based on physiologically based pharmacokinetic modelling estimated that blood concentrations of tetrachloroethylene will be lower in children than in adults (Clewell *et al.*, 2004). Another model showed that for a given set of exposures, the younger a person is, the greater the estimated concentration of tetrachloroethylene in the brain (Rao & Brown, 1993).

It is well established that expression of most CYP450 enzymes and GSTs in fetal liver is very different from that in the adult liver. Expression of several CYP450 enzymes and GSTs has been detected in some samples of the developing fetus and is dependent on stage of pregnancy (Carpenter *et al.*, 1996; Tateishi *et al.*, 1997; McCarver and Hines, 2002; Johnsrud *et al.*, 2003). CYP3A7 accounts for up to 50% of total fetal hepatic CYP450 content, but expression of this enzyme decreases rapidly after birth. CYP1A1 and CYP2D6 have also been detected in human fetal liver, but expression of CYP2E1 remains controversial (Ring *et al.*, 1999). Within months after birth, the metabolic capacity of the human liver changes and becomes more similar to that in the adult tissue. Thus, the differences in tetrachloroethylene metabolism between early stages of life and adulthood may represent a potential determinant of susceptibility, even though there is no direct evidence to demonstrate this apart from the information collected from physiologically based pharmacokinetic modelling (Gentry *et al.*, 2003; Clewell *et al.*, 2004).

Some studies have suggested greater susceptibility to tetrachloroethylene-associated impairments in visual contrast sensitivity in children than in adults (Laslo-Baker *et al.*, 2004; Storm *et al.*, 2011). Studies that focused on possible life stage-specific susceptibility to immune system-related adverse health outcomes and hepatotoxicity after exposure to tetrachloroethylene gave inconsistent results, or were not conducted in a way that allows proper comparison between age groups.

Overall, from the available epidemiological studies and studies in experimental animals, there was little evidence of increased susceptibility to cancer from exposure to tetrachloroethylene during early life-stages.

Only few studies examined the exposure to tetrachloroethylene in the elderly (age > 65 years), and in none of these studies was a direct comparison made with another age group.

4.4.3 Sex differences

One study examined sex differences in toxicokinetic parameters of tetrachloroethylene by means of physiologically based pharmacokinetic modelling. Sex-specific differences in the metabolism of tetrachloroethylene were small but significant (Clewell *et al.*, 2004).

Expression and function of organic anion transporters have been shown to exhibit sex-dependent differences in humans and experimental animals (Gotoh *et al.*, 2001; Kobayashi *et al.*, 2002; Buist & Klaassen, 2004; Ljubojevic *et al.*, 2004; Sekine *et al.*, 2006; Sabolić *et al.*, 2007), suggesting that differences in transport into the renal tubular cells may be another factor involved in sex differences in susceptibility to the effects of tetrachloroethylene and its metabolites.

Suspensions of rat kidney cells and renal mitochondria from rats or mice were used to assess the sex- and species-dependence of acute toxicity attributable to tetrachloroethylene and its glutathione conjugate TCVG. A marked sex difference in the acute cytotoxicity – release of lactate dehydrogenase – was observed for both compounds, with a greater effect in males. In suspensions of isolated mitochondria from kidneys of male and female rats, a generally similar pattern of sensitivity was observed. Respiratory function in mitochondria from male and female mice was also significantly inhibited by tetrachloroethylene and TCVG, but there was little sex dependence in the degree of inhibition. Renal toxicity was higher in male than in female rats in a long-term bioassay with exposure to tetrachloroethylene by inhalation (NTP, 1986; see Section 3).

4.5 Mechanistic considerations

Two important metabolic pathways of tetrachloroethylene have been characterized in humans and in experimental animals. The major pathway is CYP450-mediated oxidation, resulting in formation of a variety of short- and long-lived metabolites. In all species, the oxidative metabolite trichloroacetic acid is formed in much larger amounts than other oxidative metabolites, such as dichloroacetic acid. A list of the major oxidative metabolites of tetrachloroethylene, the site of their formation, and the species in which they were detected is given in Table 4.1. There are quantitative differences in the extent of oxidative metabolism of tetrachloroethylene among species, with greater oxidative metabolism in rodents than in humans.

GSH conjugation is another important metabolic pathway for tetrachloroethylene, resulting in the formation of short-lived, reactive metabolites. The initial conjugation reaction to TCVG occurs primarily in the liver, with subsequent processing in the kidney by GGT, dipeptidase, β-lyase, *N*-acetyltransferase, FMO, and via CYP-mediated sulfoxidation. A list of the major metabolites of tetrachloroethylene formed after GSH-conjugation, the site of their formation, and

the species in which they were detected is given in Table 4.1.

Data were lacking to characterize the extent of GSH-conjugation in all species. It should be noted that dichloroacetic acid, a minor product of oxidative metabolism, is also formed through GSH conjugation.

The parent compound tetrachloroethylene and several of its metabolites have been evaluated for genotoxic potential. Tetrachloroethylene itself has been tested in a large number of assays for genotoxicity *in vitro*. The results did not clearly indicate that it is directly mutagenic in the absence or presence of metabolic activation from the standard S9 microsomal preparations from rat liver. However, when tetrachloroethylene was pre-incubated with rat liver GST, GSH, and a microsomal fraction from rat kidney, a clear dose–response relationship was obtained. These findings support a role of metabolic activation via the GSH-conjugation pathway for tetrachloroethylene in genotoxicity *in vitro*. Among the GSH-conjugation metabolites that have been tested in mutagenicity assays, TCVG and NAcTCVC were reported to be mutagenic in the presence of activation, while TCVC was mutagenic without activation. The Working Group concluded that these metabolites of tetrachloroethylene are genotoxic, particularly in the kidney, where metabolism in situ occurs. The genotoxicity of dichloroacetic and trichloroacetic acid is discussed in the respective *Monographs* in this Volume. There are few data available on the genotoxicity of other oxidative metabolites of tetrachloroethylene, i.e. trichloroacetyl chloride and tetrachloroethylene-epoxide.

Tetrachloroethylene has been associated with cancer of the kidney and liver, and of the immune and central nervous systems. For each of these, some mechanistic considerations are given below.

4.5.1 Kidney

In mammalian species, the kidney is a target organ for toxicity of tetrachloroethylene and other related chlorinated ethanes and ethylenes. There is some evidence that tetrachloroethylene is carcinogenic in the kidney in male rats (see Section 3). Besides genotoxicity, the following mechanisms of carcinogenesis have been considered: α2u-globulin-associated nephropathy, cytotoxicity not associated with accumulation of α2u-globulin, and peroxisome proliferation mediated by the receptor PPARα. Regarding the first mechanism, several experimental studies have shown an increase in hyaline droplets in the proximal tubule cells of treated male rats. However, the overall data indicated that α2u-globulin nephropathy is not the sole mechanism for nephrotoxicity or carcinogenesis. Long-term exposure to tetrachloroethylene is indeed associated with kidney damage in humans and in male and female rats and mice. Two studies *in vivo* have shown that short-term exposure to tetrachloroethylene induces peroxisome proliferation in the rodent kidney, but the effects were weak. There is no direct evidence of activation of the PPARα receptor in the kidney, and whether peroxisome proliferation is causally linked to kidney cancer has not been experimentally demonstrated for tetrachloroethylene or other compounds. With regard to cytotoxicity and peroxisome proliferation, these effects occurred in male and female rats and mice, suggesting a lack of sex- and species-specificity in these mechanisms. Overall, available data supports the notion that the likely mechanism of carcinogenisis in the kidney involves the genotoxicity of kidney-derived metabolites of this compound.

4.5.2 Liver

Tetrachloroethylene and its oxidative metabolites induce several effects that may contribute to development of hepatocellular tumours. They

include DNA hypomethylation, cytotoxicity and oxidative stress, alterations in cell proliferation and apoptosis, clonal expansion, PPARα activation, and disruption of gap-junctional intercellular communication. The epigenetic effects of trichloroacetic and dichloroacetic acid, together with the fact that changes in methylation represent common early molecular events in most tumours, support the plausibility that dysregulation of gene methylation may play a role in tetrachloroethylene-induced tumorigenesis. However, there was no specific information available to test this hypothesis. Numerous studies in humans and experimental animals, including long-term bioassays in rodents, have demonstrated that tetrachloroethylene is hepatotoxic, even though the metabolites trichloroacetic and dichloroacetic acid are not. In experimental animals treated with tetrachloroethylene, the characteristics of the hepatic injury include increased liver weight, changes in fatty acids, necrosis, inflammatory cell infiltration, increased levels of triglycerides, and regenerative cell proliferation. Reactive oxygen species can also play a role in mediating hepatotoxicity of tetrachloroethylene. Few studies were available on tetrachloroethylene-induced hepatic oxidative stress. Increased transient liver-cell proliferation in mice has been reported after exposure to tetrachloroethylene. In addition, several studies in mice have shown transient hepatocyte proliferation in response to exposure to trichloroacatic acid. Based on data from tetrachloroethylene alone, there was only limited evidence for the mechanism via PPARα activation, and a concordance with the tumour response in the liver was lacking. It is worth noting that the metabolites trichloroacetic and dichloroacetic acid do activate both human and mouse PPARα, but at concentrations that are an order of magnitude higher than for other peroxisome proliferators. Overall, there was strong evidence that the liver is a target for tetrachloroethylene, and multiple mechanisms of liver carcinogenesis are likely operational.

4.5.3 Immune system

In humans, tumours of the immune system associated with exposure to tetrachloroethylene include non-Hodgkin lymphoma and multiple myeloma. In experimental animals, cancer findings of primary concern are the increased incidence of mononuclear cell leukeamia in both sexes in the NTP (1986) and JISA (1993) inhalation bioassays (see Section 3).

Studies in humans and experimental animals in support of a mechanism for cancers of the immune system were limited to studies that focused on immunological and haematological toxicity. The mechanism by which tetrachloroethylene induces immunotoxicity, or by which the toxicity may ultimately lead to carcinogenesis, could not be identified. A limited number of studies have evaluated exposure of workers to tetrachloroethylene in association with alterations in immune-system parameters. There was some evidence that exposure to tetrachloroethylene is associated with altered blood-cell counts and immune markers indicative of immune activation and dysregulation. However, the findings were inconsistent and the sample sizes were small for nearly all studies. Although there is a well established connection between immune status and carcinogenesis in general, overall the evidence was not sufficiently strong to support a conclusion about a mechanism for tetrachloroethylene-induced carcinogenesis in cells of the immune system.

The limited available data from studies in children (Lehmann *et al.*, 2002; Delfino *et al.*, 2003a, b) do not provide substantial evidence of an effect of exposure of tetrachloroethylene during childhood on allergic sensitization or exacerbation of asthma symptomology. The observed association between exposure to tetrachloroethylene measured in the home, and reduced numbers of interferon-gamma-producing type-1 T-cells in blood samples from the umbilical cord may reflect a sensitive stage of development, and points to the

limited understanding of the potential immunotoxic effects of prenatal exposures. The available data (e.g. Emara *et al.*, 2010) pertaining to risk of autoimmune disease associated with exposure to tetrachloroethylene are limited by problems regarding ascertainment of disease incidence and by difficulties with exposure-assessment in population-based studies.

4.5.4 Other target organs

The central nervous system is clearly a target tissue for tetrachloroethylene induced toxicity. Studies in humans and experimental animals provide evidence of the association of neurobehavioural deficits, including visual changes, cognitive deficits, increased reaction time, and exposure to tetrachloroethylene. No data were available to identify the mechanism(s) that may contribute to the induction of the rare brain gliomas occurring in exposed rats.

On the basis of the number of molecular targets reported in the studies, it is likely that several mechanisms are responsible for the neurotoxicological effects of tetrachloroethylene.

4.5.5 Susceptible populations

The bladder and oesophagus may be target tissues for tetrachloroethylene-induced carcinogenesis in humans; however, there were no studies to suggest mechanisms underlying these effects.

The carcinogenicity of tetrachloroethylene is associated with its metabolism and, therefore, the susceptibility to this agent may be influenced by genetic factors, sex, life-stage and other conditions. Polymorphisms in genes involved in the oxidative metabolic pathways (e.g. CYP2E1, CYP3A) and in GSH conjugation (e.g. GSTs) are commonly found in human populations, but it is not clear what role, if any, they play in the carcinogenicity of tetrachloroethylene. With respect to life-stage susceptibility, data were available to suggest that individuals at early stages of life, especially at the prenatal and neonatal phase, may be more vulnerable to exposure to tetrachloroethylene. Most of such evidence is based on either differences in exposure routes (e.g. transplacental transfer and ingestion via breast milk in early life), or in life stage-specific differences in toxicokinetics. Sex differences have been noted in adverse health outcomes associated with exposure to tetrachloroethylene, namely a greater susceptibility of males to kidney toxicity, which could result from differences in physiological factors (e.g. hormonal status), and toxicokinetics.

5. Summary of Data Reported

5.1 Exposure data

Tetrachloroethylene is one of the most important chlorinated solvents worldwide; it has been produced commercially since the early 1900s. Between the 1950s and 1980s, the most important use of tetrachloroethylene was in dry-cleaning. Smaller amounts were used for degreasing metals and in the production of chlorofluorocarbons. Since the 1990s, the largest use has been as a feedstock for the synthesis of fluorocarbons.

Tetrachloroethylene is detected in indoor and outdoor air, water, food and in animal and human tissues.

Exposure to tetrachloroethylene occurs primarily by inhalation. Occupational exposure has been and continues to be widespread. Technological advances in dry-cleaning and degreasing have resulted in a considerable reduction in exposure, and concentrations to which workers are exposed have decreased by two orders of magnitude since the 1940s in the USA and Europe, although high-exposure situations continue to exist in some countries. Individuals living or working in the vicinity of

dry-cleaning shops are also exposed, although at lower concentrations.

5.2 Human carcinogenicity data

The Working Group focused its evaluation of the epidemiological data on studies that assessed exposure to tetrachloroethylene specifically, or that focused on employment in dry-cleaning. Excluded were studies that characterized exposure by employment in occupational or industrial categories combining 'laundry and dry-cleaning' and studies of mixed solvent exposure without further distinction. The largest cohort studies were those of dry-cleaning workers in the USA and in four Nordic countries. The studies in the USA compared cancer mortality among exposed workers and in the general population, while the Nordic study compared cancer incidence in dry-cleaning workers with that in unexposed laundry workers. None of the cohort studies specifically controlled for tobacco smoking or alcohol consumption. However, the internal comparison in the Nordic study controlled indirectly for social class, which is an effective proxy for tobacco smoking in those countries.

5.2.1 Cancer of the bladder

Information about bladder cancer was available from the cohort studies of dry-cleaning workers in the USA and Europe and from 11 case–control studies that reported data on exposure to tetrachloroethylene, or work in dry-cleaning shops in several countries. All three dry-cleaning cohorts showed an increased risk of bladder cancer, which was statistically significant in the Nordic study. This study was based on cancer incidence, which is a better outcome measure than mortality, given the low case-fatality of bladder cancer. Two of the cohort studies found no evidence of an exposure–response relationship, but one study reported a statistically significant increase in risk among workers employed for more than 5 years, with 20 years of latency. All case–control studies included adjustments for tobacco smoking and other potential confounders. Three case–control studies specifically assessed occupational or environmental exposure to tetrachloroethylene. One found a positive association for men, but did not report data for women, while another study, based on small numbers, showed an excess risk in the group with the highest exposure. The third study found a negative association, also based on small numbers. All eight studies that evaluated employment in dry-cleaning showed positive associations with bladder cancer. Three of these were from the United States National Bladder Cancer Study, and they all showed positive associations, although statistically significant only in one; furthermore two of the studies included dry-cleaners, ironers and pressers. Three other case–control studies were small, with inconsistent results. The last case–control study was based on a surveillance system and showed a statistically non-significant excess risk. While positive associations with bladder cancer were observed in several cohort and case–control studies, and smoking was adequately controlled for in the majority, employment in dry-cleaning was in most cases the only indicator of exposure to tetrachloroethylene, the number of exposed cases was small, and support for an exposure–response relationship was lacking.

5.2.2 Other cancer sites

Several studies evaluated exposure to tetrachloroethylene and the risk of cancers at other sites, including oesophagus, kidney, cervix, and non-Hodgkin lymphoma. No consistent patterns were seen across studies. Statistically significant increases in mortality from cancer of the oesophagus were observed in two studies of dry-cleaning workers in the USA, with a larger increase among the longest-employed workers; increased mortality from lung cancer in these studies points

to potential confounding by tobacco smoking among exposed workers. No increase in incidence of cancer of the oesophagus was found in the Nordic dry-cleaners study, which controlled for social class as a proxy indicator of tobacco and alcohol consumption. Two studies of aerospace workers in the USA who were also exposed to trichloroethylene reported a non-significant increase in mortality from oesophageal cancer. Two small case–control studies provided information on the association of oesophageal cancer with potential exposure to tetrachloroethylene: one evaluated employment in dry-cleaning and reported a non-significant positive association, while the other assessed exposure to tetrachloroethylene, but had no exposed cases.

For cancer of the kidney, some case–control studies were suggestive of a positive association for occupations involving exposure to tetrachloroethylene. However, the cohort studies generally did not find an association between tetrachloroethylene exposure and cancer of the kidney, and most studies did not evaluate or failed to show positive exposure– or duration–response relationships. The studies also did not account for coexposure to trichloroethylene, which has been associated with cancer of the kidney in many other studies. Increased risk of cervical cancer was seen in the two dry-cleaner cohorts in the USA and in a study of Swedish dry-cleaners, but not in the Nordic dry-cleaner study. For non-Hodgkin lymphoma, three cohort studies showed an increased risk based on small numbers, and the largest study with the best control of potential confounders did not. Case–control studies on non-Hodgkin lymphoma did not find significant associations.

5.3 Animal carcinogenicity data

Tetrachloroethylene was evaluated for carcinogenicity in male and female mice and rats exposed by gavage or by inhalation.

In mice given tetrachloroethylene in corn oil by gavage, there were increases in the trend and in the incidence of hepatocellular carcinoma in males and females. In two separate studies in mice of two different strains exposed by inhalation, significant increases in the incidence of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) were observed in males and females. In one of the studies in mice exposed by inhalation, there was a positive trend in the incidence of haemangioma or haemangiosarcoma (combined) in males and females, a positive trend in the incidence of haemangiosarcoma of the liver and of the spleen in males, and a positive trend in the incidence of adenoma of the Harderian gland in males.

In two studies in rats, exposure to tetrachloroethylene by inhalation for 2 years caused an increase in the incidence of mononuclear cell leukaemia in males and females. In one of these studies, an increased incidence of interstitial cell tumours of the testis and a positive trend in the incidence of brain glioma were observed in males. The incidences of brain glioma, and kidney adenoma or carcinoma (combined) were not statistically significantly increased compared with concurrent controls, but were markedly higher than incidences for historical controls. In the other study in rats exposed by inhalation there was an increase in the incidence of fibroadenoma of the mammary gland in the group at the lowest dose. The study in rats exposed by gavage gave negative results.

In a study in mice, skin application of tetrachloroethylene oxide, a metabolite of tetrachloroethylene, induced a statistically significant increase in the incidence of benign or malignant skin tumours (combined) at the site of application.

5.4 Mechanistic and other relevant data

A comprehensive body of literature exists to characterize the absorption, distribution, metabolism and excretion of tetrachloroethylene in humans and in experimental animals. Tetrachloroethylene is readily absorbed via all exposure routes (oral, dermal, by inhalation) in all species studied, including humans. Rapid systemic distribution has been observed in humans and experimental animals. Because of its high lipophilicity, tetrachloroethylene is distributed widely to all tissues, especially those with a high lipid content. As it is poorly metabolized in humans, a large fraction of tetrachloroethylene is expired unchanged. In rats and mice, due to more extensive metabolism, the proportion of tetrachloroethylene that is excreted unchanged is smaller, although it rises with increasing exposure. The major urinary excretion product is trichloroacetic acid.

There are qualitative similarities between humans and rodents with respect to the two important metabolic pathways of tetrachloroethylene. The major pathway is cytochrome P450-mediated oxidation, resulting in formation of a variety of short- and long-lived metabolites. In all species, the oxidative metabolite trichloroacetic acid is formed in much larger amounts than other oxidative metabolites (e.g. dichloroacetic acid). There are quantitative differences among species in the extent of oxidative metabolism of tetrachloroethylene, with rodents showing more extensive oxidative metabolism than humans. Glutathione conjugation is another important metabolic pathway for tetrachloroethylene, resulting in formation of short-lived, reactive metabolites. The initial conjugation reactions occur in the liver (formation of trichlorovinyl-glutathione), while subsequent processing primarily takes place in the kidney. Dichloroacetic acid is also formed through conjugation with glutathione. Only few data exist to further characterize the glutathione-conjugation pathway.

Tetrachloroethylene and several of its metabolites have been evaluated for genotoxic potential. Metabolic activation via the glutathione-conjugation pathway leads to the formation of genotoxic metabolites. Among the glutathione-conjugation metabolites that have been tested, trichlorovinyl-glutathione and *N*-acetyl-*S*-(1,1,2-trichlorovinyl)-L-cysteine are genotoxic. There is some evidence that dichloroacetic acid may cause genotoxicity and that trichloroacetic acid is not genotoxic (see the *Monographs* on dichloroacetic acid and trichloroacetic acid in this Volume). For other oxidative metabolites of tetrachloroethylene, i.e. trichloroacetyl chloride and tetrachloroethylene epoxide, there is weak evidence for their genotoxicity. Thus tetrachloroethylene can be converted to genotoxic metabolites, particularly in the kidney, where metabolism in situ occurs.

Tetrachloroethylene has been associated with adverse health outcomes in the kidney, liver, and the immune and central nervous systems. There is evidence from toxicological studies in experimental animals that the kidney is a target organ for tetrachloroethylene and that genotoxic metabolites are formed in that organ. The data in support of a non-genotoxic mechanism of kidney carcinogenesis are less convincing. There is also strong evidence from toxicological studies in experimental animals that the liver is a target organ for tetrachloroethylene; with respect to liver carcinogenesis, it is likely that multiple mechanisms are operational in view of the evidence supporting genotoxic and non-genotoxic mechanisms. The information that pertains to a mechanism of carcinogenesis related to the immune system is limited to studies of immunological and haematological toxicity. Multiple observations of neurobehavioural effects in exposed humans and experimental animals provide evidence that the central nervous system is a target for tetrachloroethylene. However, the relevance of

these findings to the potential cancer hazard of this compound to the central nervous system is not known. The bladder has been identified as a target organ for tetrachloroethylene-induced carcinogenesis in humans; however, there are no mechanistic studies available to support this.

Adverse health effects of tetrachloroethylene, particularly in the liver and kidney, are associated with its metabolism. Therefore, the susceptibility to tetrachloroethylene may be influenced by genetic factors, sex, life-stage and other conditions that may have an impact on the extent and nature of the metabolism. Polymorphisms in genes involved both in oxidative metabolism (e.g. CYP2E1, CYP3A) and in glutathione-conjugation pathways (e.g. glutathione-*S*-transferases) are common in the human population. However, it is not clear what role, if any, these polymorphisms play in affecting the toxicity of tetrachloroethylene. With respect to life-stage susceptibility, differences in exposure route (e.g. transplacental transfer and ingestion via breast milk in early stages of life), or on life stage-specific differences in toxicokinetics have been observed.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of tetrachloroethylene. Positive associations have been observed for cancer of the bladder.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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