TRICHLOROETHYLENE

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

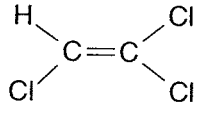
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 79-01-6
Deleted CAS Reg. No.: 52037-46-4
Chem. Abstr. Name: Trichloroethene
IUPAC Systematic Name: Trichloroethylene
Synonyms: Ethinyl trichloride; ethylene trichloride; TCE; 1,1,2-trichlorethylene

1.1.2 Structural and molecular formulae and relative molecular mass



C_2HCl_3 Relative molecular mass: 131.39

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Mobile liquid with chloroform-like odour (Budavari, 1989)
(*b*) *Boiling-point*: 87 °C (Lide, 1993)
(*c*) *Melting-point*: –73 °C (Lide, 1993)
(*d*) *Density*: 1.4642 at 20 °C/4 °C (Lide, 1993)
(*e*) *Spectroscopy data*: Infrared (prism [185]; grating [62]), nuclear magnetic resonance (proton [9266]; C-13 [410]) and mass [583] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).
(*f*) *Solubility*: Slightly soluble in water (1.1 g/L at 25 °C); soluble in ethanol, diethyl ether, acetone and chloroform (Lide, 1993; PPG Industries, Inc., 1994)
(*g*) *Volatility*: Vapour pressure, 100 mm Hg [13.3 kPa] at 31.4 °C (Lide, 1993); relative vapour density (air = 1.0), 4.53 (Budavari, 1989)

(*h*) *Stability*: Photo-oxidized in air by sunlight (half-time, five days) giving phosgene and dichloroacetyl chloride (United States Environmental Protection Agency, 1985)

(*i*) *Reactivity*: Incompatible with strong caustics and alkalis and with chemically active metals such as barium, lithium, sodium, magnesium, titanium and beryllium (United States National Institute for Occupational Safety and Health, 1994a)

(*j*) *Octanol/water partition coefficient (P)*: log P, 2.61 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 5.37 \times ppm$[1]

1.1.4 Technical products and impurities

Commercial grades of trichloroethylene, formulated to meet use requirements, differ in the amount and type of added inhibitor. Typical grades contain > 99% trichloroethylene; they include a neutrally inhibited vapour-degreasing grade and a technical grade for use in formulations. Stabilizers that have been used in formulations of trichloroethylene include neutral inhibitors and free-radical scavengers, amyl alcohol, *n*-propanol, isobutanol, 2-pentanol, diethylamine, triethylamine, dipropylamine, diisopropylamine, diethanolamine, triethanolamine, morpholine (see IARC, 1989a), *N*-methylmorpholine, aniline (see IARC, 1987b), acetone, ethyl acetate, borate esters, ethylene oxide (see IARC, 1994a), propylene oxide (see IARC, 1994b), 1,2-epoxybutane (see IARC, 1989b), cyclohexene oxide, butadiene dioxide, styrene oxide (see IARC, 1994c), pentene oxide, 2,3-epoxy-1-propenol, 3-methoxy-1,2-epoxypropane, stearates, 2,2,4-trimethyl-1-pentene, 2-methyl-1,2-epoxypropanol, epoxycyclopentanol, epichlorohydrin (see IARC, 1987c), tetrahydrofuran, tetrahydropyran, 1,4-dioxane (see IARC, 1987d), dioxalane, trioxane, alkoxyaldehyde hydrazones, methyl ethyl ketone, nitromethanes, nitropropanes, phenol (see IARC, 1989c), *ortho*-cresol, thymol, *para-tert*-butylphenol, *para-tert*-amylphenol, isoeugenol, pyrrole, *N*-methylpyrrole, *N*-ethylpyrrole, (2-pyrryl)trimethylsilane, glycidyl acetate, isocyanates and thiazoles (United States Environmental Protection Agency, 1985; WHO, 1985).

Apart from added stabilizers, commercial grades of trichloroethylene should not contain more than the following amounts of impurities: water, 100 ppm [mg/L]; acidity (as HCl), 5 ppm; insoluble residue, 10 ppm (Mertens, 1993). Free chlorine should not be detectable (PPG Industries, Inc., 1994). Impurities that have been found in commercial trichloroethylene products include: carbon tetrachloride (see IARC, 1987e), chloroform (see IARC, 1987f), 1,2-dichloroethane (see IARC, 1987g), *trans*-1,2-dichloroethylene, *cis*-1,2-dichloroethylene, pentachloroethane (see IARC, 1987h), 1,1,1,2-tetrachloroethane (see IARC, 1987i), 1,1,2,2-tetrachloroethane (see IARC, 1987j), 1,1,1-trichloroethane (see IARC, 1987k), 1,1,2-trichloroethane (see IARC, 1991), 1,1-dichloroethylene, tetrachloroethylene (see monograph, this volume), bromodichloromethane, bromodichloroethylene and benzene (see IARC, 1987l) (WHO, 1985; Mertens, 1993).

Trade names for trichloroethylene include: Algylen, Anamenth, Chlorilen, Chlorylen, Densinfluat, Fluate, Germalgene, Narcogen, Narkosoid, Threthylen, Threthylene, Trethylene,

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

Tri, Trichloran, Trichloren, Triclene, Trielene, Trielin, Trieline, Trilen, Trilene, Trimar and Westrosol.

1.1.5 Analysis

Selected methods for the analysis of trichloroethylene in various matrices are identified in Table 1.

Table 1. Methods for the analysis of trichloroethylene

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg/sample	Eller (1994); US Occupational Safety and Health Administration (1990)
	Draw air into sample bag; inject aliquot into gas chromatograph	GC/PID	0.25 ng/sample	Eller (1994)
	Draw air through Tenax sample tube; heat; desorb on cold trap	GC/MS	20 ng	US Environmental Protection Agency (1988a)
	Draw air into cryogenically cooled trap; heat	GC/FID and/or GC/EC	1–5 ng	US Environmental Protection Agency (1988a)
	Draw air into SUMMA® passivated stainless-steel canister; desorb on cold trap	GC/MS or GC/EC-FID-PID	NR	US Environmental Protection Agency (1988a)
Coffee	Isolate sample by closed-system vacuum distillation with toluene	GC/EC or GC/ECD	NR	US Food and Drug Administration (1983)
Grain	Add sample to acetone; store 48 h in the dark; add sodium chloride; add calcium chloride	GC/ECD	NR	Sawyer *et al.* (1990)
Spice oleoresins	Add sample to absolute alcohol/ 1,2-dichloropropane mixture; dilute with absolute alcohol and shake	GC	NR	Fazio (1990)
	Isolate sample by closed-system vacuum distillation with toluene	GC/EC	NR	US Food and Drug Administration (1983)
Water	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD or GC/MCD	0.001 and 0.12 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/MS	0.4 and 1.9 µg/L	US Environmental Protection Agency (1988b, 1994)

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Water (contd)	Purge and trap as above; desorb as vapour onto capillary gas chromatographic column	GC/PID-ECD	0.01–0.06 µg/L	US Environmental Protection Agency (1988b, 1994)
		GC/PID	0.02–0.19 µg/L	
	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto gas chromatographic column	GC/PID	0.01 µg/L	US Environmental Protection Agency (1988b, 1994)
	Add internal standard (isotope-labelled trichloroethylene); purge, trap and desorb as above	GC/MS	10 µg/L	US Environmental Protection Agency (1994)
Liquid and solid wastes	Purge (inert gas); trap on suitable sorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD	0.12 µg/L	US Environmental Protection Agency (1986a)
		GC/MS	PQL	US Environmental Protection Agency (1986b)

GC, gas chromatography; FID, flame ionization detection; PID, photoionization detection; MS, mass spectrometry; NR, not reported; EC, electron capture detection; ECD, electrolytic conductivity detection; MCD, microcoulometric detection; PQL, practical quantification limit: 5 µg/L for groundwater; 5 µg/kg for soil and sediment samples; 250–2500 µg/kg for liquid wastes

Three gas chromatography/mass spectrometry (GC/MS) and three purge-and-trap GC methods for purgeable organic compounds, including trichloroethylene, are usually used for analysing aqueous samples (see also Table 1). The first method (EPA Method 624 and APHA/AWWA/WEF Method 6210B) is a packed-column method useful for the determination of trichloroethylene in municipal and industrial wastes. A similar purge-and-trap method (EPA Method 503.1 and APHA/AWWA/WEF Method 6220C), which includes photoionization detection, is applicable for the determination of trichloroethylene in drinking-water and raw source water. The second GC/MS method (EPA Method 524.1 and APHA/ AWWA/WEF Method 6210C), also involving a packed column, is also applicable for the determination of trichloroethylene in drinking-water and raw source water. Similar purge-and-trap methods (EPA Methods 601 and 502.1 and APHA/AWWA/WEF Methods 6230B and 6230C), including electrolytic conductivity and microcoulometric detection, are applicable for the determination of trichloroethylene in municipal and industrial discharges (6230B) and in drinking-water and raw source water (6230C). The third group of GC/MS and purge-and-trap methods (EPA Method 524.2 and APHA/AWWA/WEF Method 6210D; EPA Method 502.2 and APHA/AWWA/WEF Method 6230D) are identical to the previous ones except that a capillary column is used. The second and third methods are intended primarily for the detection of large numbers of contaminants at very low concentrations, which are not detectable with the first method (Greenberg *et al.*, 1992).

Trichloroethylene can also be determined by colorimetry in the Fujiwara test, in which it is treated with pyridine in an alkaline environment. Solution absorbency is then determined at 535

or 470 nm, with a sensitivity of about 1 mg/kg. Trichloroethylene can also be determined by infrared spectroscopy. Gaseous compound is measured from the optical density of the mixture at a wavelength of 11.8 μm (detection sensitivity, ≥ 0.5 μg/L). High-resolution GC with electron capture detection has been used for determining trichloroethylene in soil. High-resolution GC with MS have been used for confirmation, with a detection threshold of about 10 mg/kg. Similar methods can be used to determine trichloroethylene and its major metabolites, trichloroacetic acid and trichloroethanol, in human tissues and fluids (WHO, 1985).

1.2 Production and use

1.2.1 Production

Trichloroethylene was first prepared in 1864 by Fischer in experiments on the reduction of hexachloroethane with hydrogen (Hardie, 1964). Commercial production of trichloroethylene began in Germany in 1920 and in the United States of America in 1925 (Mertens, 1993).

Until 1968, about 85% of United States production capacity of trichloroethylene was based on acetylene. The acetylene-based process consists of two steps: acetylene is first chlorinated to 1,1,2,2-tetrachloroethane, with a ferric chloride, phosphorus chloride or antimony chloride catalyst, and the product is then dehydrohalogenated to trichloroethylene (Mertens, 1993). The current method of manufacture is from ethylene or 1,2-dichloroethane. In a process used by one plant in the United States, trichloroethylene is produced by noncatalytic chlorination of ethylene dichloride or other C_2 chlorinated hydrocarbons. Another method is to react ethylene dichloride and other C_2 hydrocarbons with a mixture of oxygen and chlorine or hydrogen chloride (Linak *et al.*, 1992).

Trichloroethylene can also be produced by direct chlorination of ethylene in the absence of oxygen, giving a mixture of tetrachloroethane and pentachloroethane. The products are thermally cracked to produce a mixture of trichloroethylene, tetrachloroethylene and hydrochloric acid. This process was developed in Japan and is used there (Linak *et al.*, 1992).

Table 2 shows the production of trichloroethylene in selected countries between 1941 and 1990. Production has declined in recent years. Trichloroethylene is manufactured by one company each in Austria (with an annual capacity of 6000 tonnes), Germany (10 000 tonnes), Italy (15 000 tonnes) and Spain (29 000 tonnes). Two companies manufacture trichloroethylene in France (90 000 tonnes) and the United States (145 000 tonnes). Three companies in Japan produce trichloroethylene, with an estimated annual capacity of 85 000 tonnes (Linak *et al.*, 1992). Two companies in Canada were the only domestic manufacturers of trichloroethylene. In 1976, the total capacity of these plants was 38 000 tonnes, and 22 500 tonnes were produced. One plant closed in 1985, and imports have increased as a result (Moore *et al.*, 1991).

Trichloroethylene is also produced in Argentina, Australia, Belgium, China, India, Macedonia, Poland, Romania, the Russian Federation, Slovakia, South Africa and the United Kingdom (Chemical Information Services Ltd, 1994).

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

Year	Western Europe	Japan	USA[a]
1941			25
1945			84
1955			143[b]
1960			160
1965			197
1970			277
1975		85	133
1980	210	82	121
1981	205	74	177
1982	210	67	86
1983	200	67	91
1984	215	74	91
1985	205	73	79
1986	183	71	77
1987	166	64	88
1988	169	70	82
1989	154	65	79
1990	131	57	79

From Linak *et al.* (1992)

[a] The US International Trade Commission stopped reporting trichloroethylene production and sales in 1982. The data for 1983–90 are estimates from the *Chemical Economics Handbook* (Linak *et al.*, 1992).

[b] From Su & Goldberg (1976)

1.2.2 Use

Trichloroethylene was used earlier as an extraction solvent for natural fats and oils, such as palm, coconut and soya bean oils. It was also an extraction solvent for spices, hops and the decaffeination of coffee (Linak *et al.*, 1992). The United States Food and Drug Administration (1977) banned these uses of trichloroethylene because of its toxicity; its use in cosmetic and drug products was also discontinued (Mertens, 1993).

Demand for trichloroethylene was generated mainly by the development of vapour degreasing after the 1920s and by the growth of the dry cleaning industry in the 1930s, but trichloroethylene was replaced in dry cleaning by tetrachloroethylene in the mid-1950s. By 1989, about 85% of the trichloroethylene produced in the United States was used in metal cleaning; the remaining 15% was equally divided between exports and miscellaneous applications. The pattern in Japan was similar to that in the United States, at 83 and 17%, respectively. In western Europe, 95% was used in vapour degreasing and 5% in other uses (Mertens, 1993). Similar use patterns have been reported for Canada (Moore *et al.*, 1991) and

Finland (Mroueh, 1993). Tables 3–5 present the uses of trichloroethylene in western Europe, Japan and the United States. Because of environmental and occupational health concerns, industry has attempted to restrict solvent emissions and maximize recovery and recycling. Trichloroethylene is, however, replacing 1,1,1-trichoroethane in some applications (Linak *et al.*, 1992).

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

Year	Metal cleaning (vapour degreasing)	Metal cleaning (cold cleaning)	Other
1980	164	25	26
1984	137	10	23
1987	124	10	16
1990	120	10	5

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

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

Year	Metal cleaning	Other
1980	49	16
1983	52	11
1987	49	12
1990	30	8

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

Trichloroethylene has also been used, in limited quantities, to control relative molecular mass (by chain transfer) in the manufacture of polyvinyl chloride. An estimated 5500 tonnes are used annually for this application in the United States. It has also been used as a solvent in the rubber industry, some adhesive formulations and in research laboratories. In the textile industry, it is used as a carrier solvent for spotting fluids and as a solvent in dyeing and finishing (Fishbein, 1976; Linak *et al.*, 1992; Mertens, 1993). It is also used as a solvent in printing inks, paint, lacquers, varnishes, adhesives and paint strippers. It was used as both an anaesthetic and an analgesic in obstetrics (Smith, 1966). Trichloroethylene has been used in the aerospace industry for flushing liquid oxygen (Sax & Lewis, 1987). In a study of potential sources of indoor air pollution in the United States, 25 of 1159 (2.2%) common household products were found to contain trichloroethylene (Sack *et al.*, 1992).

The major use of trichloroethylene is in metal cleaning or degreasing. Degreasing is important in all metalworking and maintenance operations to remove oils, greases, waxes, tars and moisture before final surface treatments, such as galvanizing, electroplating, painting, anodizing and application of conversion coatings. Trichloroethylene is used in degreasing

operations in five main industrial groups: furniture and fixtures, fabricated metal products, electric and electronic equipment, transport equipment and miscellaneous manufacturing industries. It is also used in plastics, appliances, jewellery, automobile, plumbing fixtures, textiles, paper, glass and printing (Papdullo *et al.*, 1985; Linak *et al.*, 1992).

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

Year	Metal cleaning	Other
1971	200	15
1974	153	4
1977	102	20
1980	84	13
1984	72	14
1987	57	9
1990	46	5

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

Metal cleaning operations are of two types: cold cleaning and vapour cleaning. In cold cleaning, trichloroethylene is applied at room temperature; in vapour degreasing, the solvent vapours are condensed on the part to be cleaned. In cold cleaning, the metal parts are either dipped into the solvent solution or the solution is sprayed and wiped onto the object. The cold process is frequently used in maintenance operations and on small parts. Vapour degreasing requires a tank with heating coils on the bottom and a condensing zone near the top. The solvent is heated to boiling, and the hot vapour fills the condensing zone near the top of the tank. Soiled objects are lowered into this zone, where the vapour condenses into a pure liquid solvent on the piece and dissolves and carries off dirt as it drains back into the tank. The part dries immediately (Papdullo *et al.*, 1985; Linak *et al.*, 1992).

1.3 Occurrence

1.3.1 Natural occurrence

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

1.3.2 Occupational exposure

The United States National Institute for Occupational Safety and Health (1994b) indicated that about 401 000 employees in 23 225 plants in the United States are potentially exposed to trichloroethylene. This estimate is based on a survey of companies and did not involve actual measurements. Table 6 summarizes the results of studies of occupational exposure.

Table 6. Occupational exposures to trichloroethylene

Country	No. of plants	Job, task or industry	No. of samples[a]	Air concentration (mg/m^3)		Reference
				Mean	Range	
Finland 1982–85	11	Vapour degreasing	24 (A) 13 (P) TWA	[43.0] [37.6]	< [5.4–20.9] < [5.4–161]	Rantala *et al.* (1992)
	1	Rubber bonding	1 (A) TWA		[32.2]	
	1	Museum textile restoration	2 (P) 1-h		[3303]	
Netherlands	9	Rubber degreasing, cementing	137	4		Kromhout *et al.* (1994)
Sweden	14	Degreasing	336 (A)	[328]	[0–2230]	Ahlmark *et al.* (1963)
	570	Degreasing	35 000–40 000 (A)	[86]	3% [> 161]	
	19	Degreasing	29 (P)	27	3–144	Ulander *et al.* (1992)
Switzerland	10	Degreasing	96 (P)	[304]	[5.4–1799]	Grandjean *et al.* (1955)
United Kingdom	32	Degreasing	212 (P)	91% < [161] 97% < [269] 99% < [537]		Shipman & Whim (1980)
USA	60	Degreasing	433 (P)			Morse & Goldberg (1943)
		Condenser, nonvented	187	[725]	[16–4833]	
		Condenser, vented	149	[515]	[27–2110]	
	NR	Degreasing	146 (A)[b]	86% < [537] 96% < [1074]		Hargarten *et al.* (1961)
	1	Degreasing	11 (P)	[302]	[199–419]	Vandervort & Polakoff (1973)
	1	Degreasing ignition coils	(P)		0–[537]	Bloom *et al.* (1974)
	1	Electronic cleaning	3 (P)	[446]	[408–483]	Gilles & Philbin (1976)
	1	Semi-conductor degreasing	10 (P)	16.1	2–57	Gunter (1977)
	1	Degreasing operator	20 (P)	[736]	[140–2024]	Kominsky (1978)
		Degreasing operator	7 (P)	[88.1]	[37.6–456]	
		Degreasing operator	6 (P)	[67.7]	[37.6–199]	
		Lathe operator next to degreaser	7 (P)	[52.1]	[37.6–129]	
	1	Aircraft degreasing	4 (P)	[21.5]	[5.4–37.6]	Okawa *et al.* (1978)
	1	Tank relining	8 (P)	[1.3]	ND–[5.4]	Burroughs (1980)

Table 6 (contd)

Country	No. of plants	Job, task or industry	No. of samples[a]	Air concentration (mg/m^3)		Reference
				Mean	Range	
USA (contd)	1	Degreasing sheet metal	2 (P) 2 (A)	11 11	10–12 4–18	Johnson (1980)
	1	Degreasing, custom finishing	23 (P) 2 (A)	8.3 6	1–38 4–8	Ruhe & Donohue (1980)
	1	Vapour degreasing	14 (P)	[333]	[26.9–1670]	Burgess (1981)
	1	Degreasing, bus maintenance	3 (A)	3.0	ND–8.9	Love & Kern (1981)
	1	Degreasing	24 (STEL) 9 (TWA)	742 145	56–2000 37–357	Ruhe *et al.* (1981)
	1	Degreasing, plastics	2 (P)	[4.8]	[2.7–7.0]	Burroughs & Moody (1982)
	1	Degreasing, electronics	79 (P)	10.2	ND–209	Lee & Parkinson (1982)
	1	Degreasing, medical	5 (P) 2 (A)	5.4 6.5	1–16 4–9	Ruhe (1982)
	1	Degreasing, energy conservation products	2 (P) 10 (A)	[36.5] [1.1]	[22–51] [0.54–3.2]	Almaguer *et al.* (1984)
	1	Degreasing Silk screening	9 (P) 2 (A) 5 (P)	[716] [184] [23.6]	[39–2288] [0.54–367] [1.6–81.1]	Belanger & Coye (1984)
	1	Degreasing aircraft	29 (TWA, P) 11 (TWA, A) 22 (STEL)	[30.7] [28.5] [320]	[ND–208] [2–121] [ND–1256]	Gorman *et al.* (1984)
	1	Taxidermy	2 (A) 2 (P)	[8.9] [8.9]	[1.1–16.6] [1.7–16]	Kronoveter & Boiano (1984)
	1	Degreasing	(TWA) (STEL)	205 1084	117–357 413–2000	Landrigan *et al.* (1987)

ND, not detected; NR, not reported. Most measurements were taken after observation of operating deficiencies of degreasers between 1952 and 1957.

[a] P, personal air samples (breathing zone); A, area samples; STEL, short-term exposure limit; TWA, time-weighted average

1.3.3 Environmental occurrence

Trichloroethylene has been reported in the air, rainwater, surface waters, drinking-water, seawater, marine sediments, marine invertebrates, marine mammals, foods and human tissues (McConnell *et al.*, 1975).

(a) Air

The levels of trichloroethylene in air have been measured throughout the world (Table 7). In a compilation of the results of surveys of ambient air in the United States before 1981 (Brodzinsky & Singh, 1983; United States Agency for Toxic Substances and Disease Registry, 1989), representing 2353 monitoring points, the mean concentrations were 30 ppt [0.2 μg/m^3] in rural areas, 460 ppt [2.5 μg/m^3] in urban and suburban areas and 1200 ppt [64 μg/m^3] in industrialized areas near sources of trichloroethylene emissions. Industrial releases of trichloroethylene to the environment in the United States were 24 430 tonnes in 1988, 22 400 tonnes in 1989, 17 680 tonnes in 1990 and 15 950 tonnes in 1991 (United States Environmental Protection Agency, 1993).

Air emissions in western Europe in 1980 are reported in Table 8. In the Netherlands, emissions of trichloroethylene to the air were 6.5 tonnes in 1970, 5.4 tonnes in 1975, 4.2 tonnes in 1979, 3.7 tonnes in 1980, 2.6 tonnes in 1981 and 2.2 tonnes in 1982 (Besemer *et al.*, 1984).

Indoor air concentrations of trichloroethylene can increase when trichloroethylene-contaminated water is used domestically. A community water supply that contained 40 mg/L of trichloroethylene was estimated to contribute about 40 mg/m^3 to the air of a bathroom during showering, and the weekly dose through inhalation was estimated to be 48 mg trichloroethylene (assuming 1-h showering), due to off-gassing of trichloroethylene from the water. About 42 mg of trichloroethylene were ingested from the water per week (Andelman, 1985). Similar conclusions were reached by Bogen *et al.* (1988).

(b) Water

Trichloroethylene occurs at low levels in all water supplies and frequently in groundwater, owing to its widespread use and physical characteristics. Table 9 summarizes the concentrations of trichloroethylene found in surface waters, groundwater and drinking-water worldwide.

Trichloroethylene was detected in an estimated 3% of surface water samples and 19% of groundwater samples analysed, at geometric mean concentrations of 27.3 ppb [μg/L] in groundwater and 40.2 ppb in surface water (United States Environmental Protection Agency, 1989). In a computerized database on water quality, the reported median concentrations of trichloroethylene in 1983–84 were 5.0 μg/L in industrial effluents (19.6% detectable, 1480 samples), 0.1 μg/L (28% detectable, 9295 samples) in ambient water, < 50 μg/kg dry weight (6% detectable, 338 samples) in sediment and < 50 μg/kg (none detectable, 93 samples) in biota (Staples *et al.*, 1985).

The concentrations of trichloroethylene in sediment and animal tissue collected near the discharge zone of the Los Angeles County, CA, waste-treatment plant in 1980–81, were 17 μg/L in the effluent, < 0.5 μg/kg dry weight in sediment and 0.3–7 μg/kg wet weight in various marine animal tissues (Gossett *et al.*, 1983).

Table 7. Concentrations of trichloroethylene in ambient air

Area	Year	Concentration [μg/m³]		Reference
		Mean	Range	
Remote				
Pacific Ocean (latitude 37° N)	1977	[0.07]		US Environmental Protection Agency (1985)
Panama Canal Zone (latitude 9° N)	1977	[0.08]		US Environmental Protection Agency (1985)
Northern hemisphere	1985		[0.06–0.09]	US Environmental Protection Agency (1985)
Southern hemisphere	1981		[< 0.02]	Singh *et al.* (1983)
Rural				
Badger Pass, CA, USA	1977	[0.06]	[0.005–0.09]	US Environmental Protection Agency (1985)
Whiteface Mountains, NY, USA	1974	[0.5]	[< 0.3–1.9]	Lillian *et al.* (1975)
Reese River, NV, USA	1977	[0.06]	[0.005–0.09]	US Environmental Protection Agency (1985)
Jetmar, KS, USA	1978	[0.07]	[0.04–0.11]	US Environmental Protection Agency (1985)
Western Ireland	1974	[0.08]		Lovelock (1974)
Urban and suburban				
Phoenix, AZ, USA	1979	[2.6]	[0.06–16.7]	Singh *et al.* (1981)
Los Angeles, CA, USA	1976	[1.7]	[0.14–9.5]	US Environmental Protection Agency (1985)
Lake Charles, LA, USA	1976–78	[8.6]	[0.4–11.3]	US Environmental Protection Agency (1985)
New Jersey, USA	1973–79	[9.1]	[ND–97]	Lillian *et al.* (1975); US Environmental Protection Agency (1985)
New York City, NY, USA	1974	[3.8]	[0.6–5.9]	Lillian *et al.* (1975)
Denver, CO, USA	1980	[1.07]	[0.15–2.2]	US Environmental Protection Agency (1985)
St Louis, MO, US	1980	[0.6]	[0.1–1.3]	US Environmental Protection Agency (1985)
Portland, OR, USA	1984	[1.5]	[0.6–3.9]	Ligocki *et al.* (1985)
Philadelphia, PA, USA	1983–84	[1.9]	[1.6–2.1]	Sullivan *et al.* (1985)
Brussels, Belgium	1974–75	[21.5]	[5.9–31.2]	Su & Goldberg (1976)
Geneva, Switzerland	1974	[31.2]		Su & Goldberg (1976)
Moscow, Russian Federation	1974	[19.3]	[14.0–28.5]	Su & Goldberg (1976)
Paris, France	1975	[4.0]		Su & Goldberg (1976)
Grenoble, France	1975	[19.3]	[6.4–28.5]	Su & Goldberg (1976)
Kyoto, Japan	1975	[5.1]		Su & Goldberg (1976)
Tokyo, Japan	1975	[1.8]		Su & Goldberg (1976)
Yokohama, Nagoya and Kawasaki, Japan	1985–86	[5.4]	[3.4–7.5]	Urano *et al.* (1988)

Table 8. Estimated emissions of trichloroethylene to the air in western Europe, 1981

Country or region	Air emission (tonnes/year)
Netherlands	2.7
Belgium/Grand Duchy of Luxembourg	2.9
Western Germany	46.0
France	45.0
Italy	27.0
Spain	15.0
Austria	5.5
United Kingdom	50.0
Norway	0.9
Sweden	12.0
Finland	2
Portugal	1
Switzerland	7
Denmark	2

From Besemer *et al.* (1984); figures include secondary emissions from water and solid waste

Table 9. Concentrations of trichloroethylene in water

Area	Concentration (µg/L)		Reference
	Mean	Range	
Surface waters			
Seawater			
Eastern Pacific Ocean	0.0003	0.0001–0.0007	Singh *et al.* (1983)
Coastal waters			
Sea coast, industrial area, United Kingdom		0.1–1	Herbert *et al.* (1986)
West coast, Sweden	0.015		Herbert *et al.* (1986)
Northern coast, Greece		0.06–2.8	Fytianos *et al.* (1985)
Rivers			
Tributaries of the Rhine		0.06–7.0	Herbert *et al.* (1986); Bauer (1981a); Hellman (1984)
Elbe, Germany		0.7–52.3	Hellman (1984)
Weser, Germany		0.5–1.5	Herbert *et al.* (1986)
Rhine		0.1–2.4	Herbert *et al.* (1986)
United Kingdom		0.01–1.0	Herbert *et al.* (1986)
Danube, Vienna, Austria	0.6		Herbert *et al.* (1986)
Netherlands		0.1–1.5	Herbert *et al.* (1986)

Table 9 (contd)

Area	Concentration (μg/L)		Reference
	Mean	Range	
Jackfish Bay, Canada		4.1–120	Comba *et al.* (1994)
Canada		< 0.001–42	Moore *et al.* (1991)
Rainwater			
Portland, OR, USA	0.006	0.002–0.02	Ligocki *et al.* (1985)
Groundwater			
Gloucester, Ontario, Canada		< 1–583	Lesage *et al.* (1990)
Zurich, Switzerland		1.1–1.9	Herbert *et al.* (1986)
Dubendorg, Germany	85		Herbert *et al.* (1986)
Northern Switzerland	0.92		Herbert *et al.* (1986)
Frankfurt, Germany		0.4–159	Herbert *et al.* (1986)
Mannheim, Germany		< 0.16–120	Herbert *et al.* (1986)
Italy		0.1–158	Ziglio *et al.* (1984a,b)
United Kingdom		< 0.1–70	Fielding (1981)
Netherlands		< 0.1–1100	Zoeteman *et al.* (1980); Trouwborst (1981)
Minnesota, USA, near landfill		0.7–125	Sabel & Clark (1984)
New Jersey, USA, near landfill		≤ 1530	Burmaster (1982)
Pennsylvania, near landfill		≤ 27 300	Burmaster (1982)
Japan, near electronics factory		≤ 10 000	Hirata *et al.* (1992)
Phoenix, Arizona, USA		8.9–29	Flood *et al.* (1990)
Drinking-water			
Southern Philippines		0.03	Trussell *et al.* (1980)
Northern Philippins		0.01	Trussell *et al.* (1980)
Egypt		1.2	Trussell *et al.* (1980)
United Kingdom		0.4	Trussell *et al.* (1980)
Nicaragua		0.05	Trussell *et al.* (1980)
USA 1976–77		0.2–49	Thomas (1989)
1977–81		Trace–53	
1978		0.5–210	
		Trace–35 000 (with local contamination)	
New Jersey	23.4	Max. 67	Cohn *et al.* (1994)
Woburn, Massachusetts		Max. 267	Lagakos *et al.* (1986)

1.3.4 Food

The concentrations of trichloroethylene in food in the United Kingdom were: 0.3–10 ppb [μg/kg] in dairy products, 12–22 ppb in meat, none detected (ND)–19 ppb in oils and fats, ND–60 ppb in beverages, ND–7 ppb in fruits and vegetables and 7 ppb in cereals. In marine organisms, the concentrations varied from ≤ 1 ppb in invertebrates to 10 ppb in the flesh of fish

to a maximum of 50 ppb in the eggs of sea birds and the blubber of seals (McConnell *et al.*, 1975). Molluscs from Liverpool Bay, United Kingdom, contained a mean of 85 μg/kg on a dry-weight basis (range, 2–250 μg/kg). Various fish had a mean concentration of 106.5 μg/kg (range, 7–479 μg/kg) (Dickson & Riley, 1976).

The average concentrations of trichloroethylene in food in the United States were 0.9 (0–2.7) μg/kg in grain-based foods, 1.8 (0–12) μg/kg in 'table-ready' foods, 73.6 (1.6–980) μg/kg in butter and margarine, 3.8 (0–9.5) μg/kg in cheese products, 0.5 (0–1.7) μg/kg in peanut butter, 3.0 (0–9.2) μg/kg in ready-to-eat cereal products and 1.3 (0–4) μg/kg in highly processed foods (Heikes & Hopper, 1986; Heikes, 1987). In an evaluation of process waters and food commodities collected at 15 food processing plants, trichloroethylene was found at 3–7.8 ppb [μg/L] in three process waters but in none of the food products (Uhler & Diachenko, 1987). It was detected in five of 372 fatty and non-fatty food samples at concentrations of 2–94 μg/kg, with a mean of 49 μg/kg (Daft, 1989).

Trichloroethylene was found at a concentration of 100–500 ppb [μg/kg] in one of 70 samples of margarine taken from shops in the United States in 1980–82 and 1984 but at < 50 ppb in 20 samples. In 1984, the levels were all < 50 ppb (Entz & Diachenko, 1988). The mean daily intake of trichloroethylene from food, water and air in Germany was estimated to be 32–51 μg/day (Bauer, 1981b; von Düszeln *et al.*, 1982).

1.3.5 Biological monitoring

Individual exposure to trichloroethylene in Germany was determined in non-occupational and a number of occupational environments by biological monitoring. Trichloroethylene was detected in 31% of all blood samples from persons not occupationally exposed to volatile halogenated hydrocarbons (median, < 0.1 μg/L; range, < 0.1–1.3 μg/L). The median levels of trichloroacetic acid, a metabolite of trichloroethylene, were 21.4 μg/L (range, 4.8–221 μg/L) in 43 blood samples and 6.0 μg (range, 0.6–261 μg) in 94 samples of 24-h urine from these unexposed persons. The blood levels of trichloroethylene were < 0.1–0.2 μg/L in nine motor vehicle mechanics, < 0.1 μg/L in three painters, 0.1–15.5 μg/L in three precision instrument makers and 0.2–7.1 μg/L in six dry cleaners (Hajimiragha *et al.*, 1986).

In a plant in the United States where trichloroethylene was used in five degreasing operations in the manufacture of steel tubing, the concentrations of trichloroethylene in air were 117–357 mg/m^3, with short-term exposures as high as 2000 mg/m^3. Urine samples collected from exposed workers before the shift contained, on average, 298 mg/L (range, 4–690 mg/L) of total trichloroethylene metabolites, while the mean concentration after the shift was 480 mg/L (range, 63–1050 mg/L) (Ruhe *et al.*, 1981).

The average blood plasma levels of trichloroethylene of 157 employees at two metal-working plants in the United States were 2.5 ppb [μg/L] (range, 0–22 ppb) and undetectable; in the second plant, the major exposure was to a solvent that contained chloroform. A control population living several miles from the first plant also had undetectable levels of trichloroethylene (Pfaffenberger *et al.*, 1984).

The concentration of total trichloro compounds in the urine of workers in a degreasing operation at a United States aircraft factory were 0.5–83.4 mg/g creatinine. These concentrations

correlated well with the air concentrations, which averaged 5.7 ppm [30.6 mg/m^3] (Gorman *et al.*, 1984).

The levels of trichloroacetic acid in the urine of 73 workers in 24 workshops in Switzerland where degreasing was performed were 8–444 mg/L, with a mean of 86.7 mg/L. The levels in the 96 air samples were 1–335 ppm [5.37–1800 mg/m^3] with a mean of 56.7 ppm [304 mg/m^3] (Grandjean *et al.*, 1955).

The relationship between concentrations of trichloroethylene in the air near degreasing operations and urinary excretion of total trichloro compounds was reported in Japan. Eight workers had an average urinary concentration of 243.9 mg/L (range, 95–787 mg/L) total trichloro compounds after exposure to 40.7 ppm [217 mg/m^3] trichloroethylene in air. The calculated estimated air levels corresponding to the urine levels found were 41.7 (range, 22.3–67.4) ppm [224 (120–362) mg/m^3] (Nomiyama, 1971).

A total of 31 employees in 19 vapour degreasing plants in central Sweden were exposed to trichloroethylene at a mean level in ambient air of 27 mg/m^3; 86% of the air samples contained < 50 mg/m^3. A weak correlation was found between the concentrations of *N*-acetyl-β-D-glucosaminidase and trichloroacetic acid in urine ($r = 0.48$; $p < 0.01$), but no correlation was seen with ambient air levels ($r = 0.08$; $p = 0.66$) (Seldén *et al.*, 1993).

In China, the relationship between the time-weighted average exposure to trichloroethylene at the end of a work week and the concentrations of metabolites in urine was investigated in 140 exposed and 114 control workers. In a plant where trichloroethylene was manufactured by chlorination of acetylene followed by dehydrochlorination, 61 men who were exposed to trichloroethylene in air at a concentration of 3–94 ppm [16.1–505 mg/m^3] and 17 women exposed to 2–47 ppm [11–253 mg/m^3] had ≤ 127 mg/L (men) and ≤ 111 mg/L (women) total trichloro compounds in their urine. In a metal-plating plant where trichloroethylene was used for degreasing, 52 men were exposed to concentrations of 1–63 ppm [5.37–338 mg/m^3] and 10 women were exposed to 2–13 ppm [10.7–69.8 mg/m^3]; the urinary levels were ≤ 89 mg/L for the men and ≤ 98 mg/L for the women (Inoue *et al.*, 1989).

The Danish Labour Inspection Service conducted biological monitoring of workers exposed to trichloroethylene in various factories between 1947 and 1987. The concentrations of trichloroacetic acid in 2272 urine samples from workers in 330 factories were similar from the mid-1950s to the mid-1970s and then began to decrease. The average urinary concentrations were 82 mg/L (range, 0–750 mg/L) in 1947–51, 40 mg/L (0–1975 mg/L) in 1950–56, 32 mg/L (0–680 mg/L) in 1957–61, 55 mg/L (0–730 mg/L) in 1962–66, 53 mg/L (0–850 mg/L) in 1967–71, 35 mg/L (0–370 mg/L) in 1972–76, 30 mg/L (0–365 mg/L) in 1977–81 and 18 mg/L (0–130 mg/L) in 1982–86 (Christensen & Rasmussen, 1990).

Blood and urine samples were collected in 1990 from 10 people working in four dry cleaning shops in Croatia, where trichloroethylene was used as the cleaning solvent. The concentration of trichloroethylene in the air was 25–40 ppm [134–215 mg/m^3]. The mean blood levels of trichloroethylene were 0.38 μmol/L [50 μg/L] on Monday morning (range, 0.15–3.58 μmol/L) [20–470 μg/L] and 3.39 μmol/L [445 μg/L] on Wednesday afternoon (range, 0.46–12.71 μmol/L [60–1670 μg/L]). The mean trichloroethanol levels in blood were 3.02 μmol/L (0–10.7 μmol/L) [451 (0–1600 μg/L)] and 7.70 μmol/L (0–26.1 μmol/L) [1150 (0–3894 μg/l)] for the same period, respectively, and the results for trichloroacetic acid were 165 μmol/L (6.12–302

μmol/L) [27 (1–49 mg/L)] and 194 μmol/L (13.5–394 μmol/L) [31 (2–64 mg/L)]. The mean trichloroacetic acid level in urine was 32.5 mmol/mol creatinine (1.3–61.2) [47 (2–89) mg/g] on Monday morning and 37.2 mmol/mol creatinine (1.9–77.4) [54 (3–112) mg/g] on Wednesday afternoon. The mean trichloroethanol levels in urine were 9.7 mmol/mol creatinine (0.4–35.7) [13 (0.5–47 mg/g)] in the Monday morning sample and 54.9 mmol/mol creatinine (5.3–177.7) [73 (7–235) mg/g] in the Wednesday afternoon sample (Skender *et al.*, 1991).

A number of researchers have studied the influence of hourly and daily variations in exposure concentrations on the alveolar concentrations of trichloroethylene and on the urinary excretion of trichloroethanol and trichloroacetic acid (Ogata *et al.*, 1971; Droz & Fernández, 1978). The estimated concentrations of trichloroacetic acid in urine at the end of a workday in which workers were exposed to 270 mg/m^3 trichloroethylene for 8 h per day, five days a week, were 100 mg/g creatinine 0.5 h after exposure, 80 mg/g creatinine after 16 h and 50 mg/g creatinine after 64 h (Monster, 1984).

People exposed to 50 ppm (270 mg/m^3) trichloroethylene for 8 h per day on five days a week were estimated to have alveolar air concentrations of 10–15 ppm [53.7–80.6 mg/m^3] at the end of exposure and 0.1 ppm [0.5 mg/m^3] 64 h after exposure. The blood concentrations were estimated to range from 0.9 to 0.006 mg/L (Monster, 1984).

The airborne concentrations of trichloroethylene at a liquid–vapour degreasing operation in the United States in 1980 were 117–357 mg/m^3, with short-term sampling peaks of 413–2000 mg/m^3. Nine exposed workers had a mean pre-shift urinary concentration of total trichloroethylene metabolites of 298 μg/L; the mean post-shift concentration was 480 μg/L (Landrigan *et al.*, 1987).

Swedish producers of trichloroethylene offered an exposure control programme to customers using trichloroethylene in which free analysis of trichloroacetic acid in urine was conducted annually. On this basis, Axelson *et al.* (1994) categorized the average exposure of 1670 workers as 0–49 mg/L, 50–99 mg/L and ≥ 100 mg/L; 81% were placed in the lowest group. The analytical method used to determine trichloroacetic acid in urine indicated that 50 mg/L was approximately equivalent to an 8-h time-weighted average exposure to 20 ppm [107 mg/m^3] trichloroethylene.

In an ongoing biological monitoring study of workers in various occupations who are exposed to trichloroethylene, tetrachloroethylene or 1,1,1-trichloroethane, conducted by the Finnish Institute of Occupational Health, 11 534 samples representing 3976 workers in 600 workplaces were obtained for the three compounds between 1965 and 1983. Of these workers, 94.4% were monitored for one solvent, 5.2% for two solvents and 0.4% for three solvents. The overall median concentrations of trichloroethylene, reported as trichloroacetic acid in urine, were 63 μmol/L [10.3 mg/L] for women and 48 μmol/L [7.8 mg/L] for men. Before 1970, the mean urinary levels were 80–90 μmol/L [13.1–14.7 mg/L] for men and 60–80 μmol/L [9.8–13.1 mg/L] for women (Anttila *et al.*, 1995).

Trichloroethylene was detected in the blood of 22 of 39 subjects in Zagreb, Croatia, who had no known exposure to solvents, and trichloroacetic acid was found in all plasma and urine samples. The geometric mean concentrations of trichloroethylene were 0.023 μg/L (range, < 0.020–0.090 μg/L) in blood; those of trichloroacetic acid were 45.4 μg/L (13.5–160 μg/L) in

plasma and 24.2 μg/L (1.67–292 μg/L) in urine. The concentration of trichloroethylene in the drinking-water was 4.20 μg/L (0.69–35.9 μg/L) (Skender *et al.*, 1993).

The mean concentration of trichloroacetic acid in sera from 94 subjects who were not exposed to organic solvents in Germany was 23.8 μg/L (range, 4.8–221 μg/L), and the average level of trichloroacetic acid in 24-h urine samples was 7.6 μg (range, 0.6–261.4 μg) (Hajimiragha *et al.*, 1986).

Of the 14 million inhabitants of the Netherlands in the 1980s, 14 000 were estimated to be exposed by all routes to an average trichloroethylene concentration of 10 μg/m^3, resulting in a daily intake of 200 μg; 350 000 were exposed to 4 μg/m^3 with a daily intake of 80 μg; and 13.6 million inhabitants were exposed to 0.8 μg/m^3 for a daily intake of 16 μg (Besemer *et al.*, 1984).

The serum levels of trichloroacetic acid in inhabitants of Milan, Italy, who drank water containing > 2000 μg/L of trichloroethylene was 36.5 μg/L; that in an unexposed group was 8 μg/L (Ziglio *et al.*, 1984c). The ambient air level of trichloroethylene in Milan in 1979 was 7.6 μg/m^3 (Ziglio *et al.*, 1983).

Analysis of human tissue taken *post mortem* showed trichloroethylene concentrations of 2–32 μg/kg wet weight in body fat, 2–5.8 μg/kg in liver, < 1–3 μg/kg in kidney and ≤ 1 μg/kg in brain (McConnell *et al.*, 1975).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for trichloroethylene in a number of countries are presented in Table 10.

WHO (1993) has established a provisional guideline of 70 μg/L trichloroethylene in drinking-water.

The American Conference of Governmental Industrial Hygienists (1994) has recommended several biological exposure indices for trichloroethylene. That for trichloroacetic acid in urine at the end of the work week is 100 mg/g creatinine; that for trichloroacetic acid and trichloroethanol in urine at the end of the shift at the end of the work week is 300 mg/g creatinine; and that for free trichloroethanol in blood at the end of the shift at the end of the work week is 4 mg/L. It is noted that these indices are nonspecific, i.e. other exposures can affect the measurement, and that trichloroethylene in exhaled air and in blood can be used as an indicator of exposure but interpretation of the measurement is only semiquantitative.

Biological indices for exposure to trichloroethylene have been reported. In Finland, the action level for trichloroacetic acid in urine is 360 μmol/L [47.3 mg/L] (Aitio *et al.*, 1995); in Germany, the biological tolerance values are 5 mg/L trichloroethanol in blood and 100 mg/L trichloroacetic acid in urine (Deutsche Forschungsgemeinschaft, 1993); and in Switzerland, the biological tolerance values are 5 mg/L trichloroethanol in blood and 100 mg/g creatinine trichloroacetic acid in urine (Schweizerische Unfallversicherungsanstalt, 1994).

Table 10. Occupational exposure limits and guidelines for trichloroethylene

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1993	270	TWA
		1080	STEL
Austria	1987	260	TWA
Belgium	1993	269	TWA
		1070	STEL
Brazil	1987	420	TWA
Bulgaria	1993	269	TWA
		537	STEL
Canada	1987	75	TWA
		402	STEL (15 min)
Chile	1987	428	TWA
China	1987	535	TWA
Colombia	1993	269	TWA
		537	STEL
Czech Republic	1993	250	TWA
		1250	STEL
Denmark	1993	160	TWA
Egypt	1987	269	TWA
Finland	1993	160	TWA
		240	STEL
France	1993	405	TWA
		1080	STEL
Germany	1993	270	TWA; suspected carcinogen
Hungary	1987	10	TWA
		40	STEL
India	1987	535	TWA
		800	STEL
Indonesia	1987	535	TWA
Italy	1987	400	TWA
Japan	1993	270	TWA
Jordan	1993	269	TWA
		537	STEL
Mexico	1987	535	TWA
Netherlands	1994	190	TWA
		538	STEL (15 min)
New Zealand	1993	269	TWA
		537	STEL
Norway	1984	105	TWA; carcinogen
Philippines	1993	535	TWA
Republic of Korea	1993	269	TWA
		537	STEL
Poland	1993	50	TWA

Table 10 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation
Romania	1987	200	TWA
		300	STEL
Russian Federation	1993	269	TWA
Singapore	1993	269	TWA
		537	STEL
Sweden	1993	50	TWA
		140	STEL
Switzerland	1994	260	TWA
		1300	STEL
Thailand	1993	537	TWA
		1074	STEL
Turkey	1993	535	TWA
United Kingdom	1993	535	TWA
		805	STEL
USA			
ACGIH	1994	269	TWA
		537	STEL
NIOSH	1994	134	TWA; carcinogen
		11	Ceiling (60 min[a])
OSHA	1994	537	TWA
		1074	Ceiling
		1611	Peak
Venezuela	1987	535	TWA
		800	STEL
Viet Nam	1993	269	TWA
		537	STEL

From Cook (1987); ILO (1991); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); Schweizerische Unfallversicherungsanstalt (1994); United Kingdom Health and Safety Executive (1994); United States National Institute for Occupational Safety and Health (NIOSH) (1994c); United States Occupational Safety and Health Administration (OSHA) (1994)

TWA, time-weighted average; STEL, short-term exposure limit; ceiling, level not to be exceeded during any part of the workday; peak, acceptable maximum peak above acceptable ceiling concentration for an 8-h shift (maximum duration, 5 min in any 2 h)

[a] During use as an anaesthetic

2. Studies of Cancer in Humans

2.1 Case reports

Málek *et al.* (1979) followed-up 57 men who had worked for at least one year in dry cleaning in Prague, Czech Republic, since the 1950s. Nearly 60% of those tested had a urinary trichloroacetic acid concentration in excess of 100 mg/L, with sporadic values in the region of 1000 mg/L. The follow-up period was 5–50 years. Six men were found to have cancer: three had lung cancer, one had cancer of the tongue, one had rectal cancer and one had a bladder cancer and two rectal tumours.

Novotná *et al.* (1979) reviewed the occupational histories of all 63 subjects diagnosed with histologically confirmed carcinoma of the liver in 1972 and 1974 in Prague, Czech Republic. None of them had been employed in workshops where trichloroethylene was used. Paraf *et al.* (1990) reported a case of gall-bladder cancer in a woman aged 64 who had worked as a technician in a laboratory in France where trichloroethylene was used for degreasing metal.

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

2.2 Descriptive studies

Risks for cancer among workers in industries where there is potential exposure to trichloroethylene have been addressed in a number studies but in which exposure to this compound was not specified (e.g. Krain, 1972; Blair, 1980; Blair & Mason, 1980; Brandt-Rauf *et al.*, 1982, 1986; Brandt-Rauf & Hathaway, 1986; Malker *et al.*, 1986; Dubrow & Gute, 1987). These descriptive studies were not considered relevant in view of the availability of cohort and case–control studies.

Paddle (1983) retrieved records from the Mersey Regional Cancer Registry (United Kingdom) for 1951–77 for all 95 subjects with a diagnosis of primary liver cancer and an address near Runcorn, where there is a plant in which trichloroethylene has been manufactured since 1909. Two members of the personnel department of the company compared the records of tens of thousands of people who had worked at the Runcorn site during 1934–76 with the registry list, and the records of two potential matched persons were subsequently checked at the Department of Health and Social Security. It was concluded that none of the subjects had ever worked at the Runcorn site. [The Working Group noted that the interpretation of this result was hindered by the lack of expected numbers.]

2.3 Cohort studies

The cohort studies available to the Working Group addressed three occupational groups: dry cleaners, workers who had undergone biological monitoring for exposure to trichloroethylene and workers employed in miscellaneous manufacturing industries. The Working Group did not consider that the first group of studies (see the monograph on dry cleaning) was relevant to an evaluation of trichloroethylene *per se*, given the extensive exposure of these people to other

solvents. Workers who were biologically monitored were considered likely to have been exposed to trichloroethylene, but the proportion of workers in the third group of studies who were actually exposed to trichloroethylene varied.

2.3.1 Exposure evaluated by biological monitoring

Axelson *et al.* (1978, 1984 [abstract], 1994) studied a cohort of workers in Sweden who had been exposed to trichloroethylene. Between 1930 and 1986, only one plant in central Sweden produced trichloroethylene for the domestic market, and this producer offered its customers free surveillance of their exposed workers by analysis for trichloroacetic acid in the urine. Files containing data from such monitoring constitute the basis of the study, but some of the files had been destroyed. Axelson *et al.* (1978) originally retrieved records for 518 men, later expanded the cohort to 1424 men (Axelson *et al.*, 1984, abstract) and finally included 1727 persons drawn from 115 companies that had used the surveillance service at least once between 1955 and 1975 (Axelson *et al.*, 1994). Records were incomplete for 23 persons, four people could not be found in the population register, and 30 had emigrated. The final analysis was thus based on 1670 persons, 1421 men and 249 women, who were followed up for mortality from 1955 through 1986 and for cancer incidence from 1958 through 1987. Swedish national rates were used for the calculation of expected numbers. Exposure was assessed as the mean concentration of trichloroacetic acid in all urinary samples available for a given person: 78% of the person-years for men were accumulated in the category 0–49 mg/L, 14% in the category 50–99 mg/L and 8% in the > 100 mg/L category. A total of 253 deaths were observed [giving an overall standardized mortality ratio (SMR) of 1.0; 95% confidence interval (CI), 0.89–1.1]; and 129 incident cancer cases occurred [giving an overall standardized incidence ratio (SIR) of 1.0; 95% CI, 0.84–1.2]. Among men, a significant excess risk was found for skin cancer (SIR, 2.4; 95% CI, 1.0–4.7; eight observed). There were five cases of non-Hodgkin's lymphoma (1.6; 0.51–3.6) and four cases of liver and biliary tract cancer (1.4; 0.38–3.6). Of the incident cancer cases in men, 77 occurred in men in the lowest exposure category [SIR, 0.92], 18 in the medium category [SIR, 0.93] and 12 [SIR, 1.4] in the highest exposure category.

Anttila *et al.* (1995) studied a cohort of 3974 persons in Finland who were biologically monitored for occupational exposure to three halogenated hydrocarbons (3089 for trichloroethylene, 849 for tetrachloroethylene and 271 for 1,1,1-trichloroethane) during 1965–83. The cohort consisted of those people for whom 10 743 measurements were taken; the persons for whom a further 791 measurements were taken could not be identified. The overall median urinary concentration of trichloroacetic acid was higher for women (63 μmol/L [10.3 mg/L]) than for men (48 μmol/L [7.8 mg/L]). The cohort was followed up for incident cancer cases through 1992, and the expected numbers were calculated on the basis of Finnish national rates. There were 208 cancer cases among people monitored for exposure to trichloroethylene (SIR, 1.1; 95% CI, 0.92–1.2). A significant excess risk was seen for cervical cancer (2.4; 1.1–4.8; eight observed), and the risk was further increased for women with a mean level of exposure ≥ 100 μmol/L [≥ 16.3 mg/L] (4.4; 1.4–10; five observed); no further increase in risk was seen with increasing latency since the time the first measurement was made. The SIR for liver cancer among people with high exposure was 2.7 (0.33–9.9; two observed); a significantly increased SIR was seen with a 20-year latency since first measurement (6.1; 1.3–18; three observed). The

SIR for cancers of the lymphohaematopoietic tissues was increased among people with high exposure (2.1; 0.95–4.0; nine observed) and was further increased with the 20-year latency (3.0; 1.2–6.1; seven observed). The SIRs for stomach cancer were 0.91 (0.25–2.3; four cases) for high exposure and 3.0 (1.2–6.1; seven cases) with a 20-year latency. The SIR for prostatic cancer was 0.68 (0.08–2.4; two cases) with high exposure and 3.6 (1.5–7.0; eight cases) with a 20-year latency.

The population studied by Anttila *et al.* (1995) included most of the workers investigated in a previous study that comprised 2117 Finnish workers in whom urinary trichloroacetic acid was measured or were reported as having been exposed to trichloroethylene during 1963–76 (Tola *et al.*, 1980). A total of 11 cancer deaths (14.3 expected) was reported.

2.3.2 *Exposure in miscellaneous manufacturing industries*

Barret *et al.* (1984) reported in an abstract a study of the death certificates of 235 workers who had been exposed to trichloroethylene and cutting oils; a total of 14 500 had been so employed in 1983. In a comparison of SMRs [method not described] for each site of cancer, the authors found a high risk for cancer of the naso- and oropharynx (SMR, 2.5 [95% CI, 1.4–4.1]; 15 deaths).

Shindell and Ulrich (1985) studied a plant in northern Illinois, United States, where trichloroethylene had been used extensively as a degreasing agent and where the workers drank water containing traces (43 ppb [μg/L]) of trichloroethylene. The plant began operation in 1957. The study included all office employees at this plant and all production employees who had worked for three months or more in this or a nearby facility between 1 January 1957 and 31 July 1983. The cohort consisted of 2646 individuals, of whom 2140 were white men, 76 were non-white men and 430 were women. The cohort was followed up until 31 July 1983; vital status was determined for all but 52 persons. National mortality rates were used to calculate the expected numbers of deaths. A total of 141 persons had died, whereas 181.6 deaths were expected [SMR, 0.78; 95% CI, 0.65–0.92]. There were nine deaths from respiratory cancer [0.74; 0.34–1.4] and 12 deaths from non-respiratory cancer [0.49; 0.25–0.85]. The employees who had the greatest opportunity for occupational exposure to trichloroethylene were assemblers, but their mortality rate generally conformed to the expected value for all types of diseases.

Garabrant *et al.* (1988) followed a cohort of 14 067 persons who had worked for at least four years for a large aircraft manufacturing company in the United States and for at least one day at the company facility in San Diego County between January 1958 and 31 December 1982. The cohort was followed up through 1982. Persons lost to follow-up were included up to the last date at which they were known to be alive. United States national rates and rates from San Diego County were used to calculate the expected numbers of deaths. Data from a relatively small case–control study nested in the cohort indicated that 37% of the jobs held in the plant entailed exposure to trichloroethylene. A total of 1804 deaths was observed (SMR, 0.75; 95% CI, 0.72–0.79), and there were 453 deaths from cancer (0.84; 0.77–0.93). None of the SMRs for individual cancer sites was significantly elevated. There were eight deaths from cancer of the biliary passages and liver (0.94; 0.40–1.9).

Spirtas *et al.* (1991) analysed a cohort of 14 457 civilian employees who had worked for at least one year at an air force base in Utah, United States, between 1 January 1952 and 31

December 1956, where they maintained and overhauled aircraft and missiles, cleaning and repairing small parts. The analysis included 12 538 white workers and 1528 workers of unknown race, who were followed up until 31 December 1982; 97% were successfully traced. At the end of follow-up, 3832 persons had died, and their death certificates were obtained from the State vital statistics office and coded by a nosologist. The expected number of deaths was based on rates for the Utah population. In the early years of operation of the base, 1939–54, cold solvents were used to clean metal parts, and these were primarily Stoddard solvent, carbon tetrachloride, trichloroethylene and alcohols. Of these, Stoddard solvent was used most frequently; however, in 1955, trichloroethylene replaced Stoddard solvent, and in 1968 1,1,1-trichloroethane replaced trichloroethylene. Trichloroethylene was the primary solvent used in vapour degreasing in the base shops from 1939 to 1979, when it was replaced by 1,1,1-trichloroethane. Of the 14 467 cohort members, 10 256 were classified as having been exposed to mixed solvents, 7282 to trichloroethylene, 6977 to Stoddard solvent and 6737 to carbon tetrachloride (Stewart *et al.*, 1991). Actual exposure levels could not be quantified, but for each combination of job and organization an index of exposure to trichloroethylene was calculated on the basis of the frequency of exposure, the frequency of peak exposure and duration of use. Cumulative exposure categories were derived by multiplying the exposure index assigned to each combination of job and organization by the time spent in this job and by adding these products. The 3832 deaths in the total cohort resulted in an overall SMR of 0.92 (95% CI, 0.90–0.95). Among white men exposed to trichloroethylene, there were 1508 deaths (0.92; 0.87–0.96), 248 of which were from cancer (0.92; 0.81–1.1). When the data for men and women exposed to trichloroethylene were combined, there were 1694 deaths from all causes [0.90; 0.86–0.95] and 281 deaths from cancer [0.88; 0.78–0.99]; there was an elevated risk for cancer of the biliary passages [2.2; 0.96–4.4]. Nonsignificantly excess risks were also seen for cancer of the bone in men (2.6; 0.54–7.7; three deaths) and for cancer of the cervix (2.2; 0.61–5.7; four deaths) and for non-Hodgkin's lymphoma (2.9; 0.78–7.3; four deaths) in women. There were two deaths from primary liver cancer [1.1; 0.12–4.0]. No evidence of a dose–response relationship was seen when the data were analysed by cumulative exposure to trichloroethylene (scored as categories of < 5, 5–25, > 25) for cancer at any site, including cancer of biliary passages, for which the SMRs were [2.5] (three deaths) for exposure to < 5, [4.3] (three deaths) for exposure to 5–25 and [1.3] (two deaths) for exposure to > 25. Both deaths from liver cancer occurred among men in the lowest category of cumulative exposure.

A retrospective cohort study of renal cancer among workers exposed to trichloroethylene in a cardboard manufacturing factory in Germany was reported by Henschler *et al.* (1995). Measurements of exposure were not available, and workers were classified as exposed or not exposed on the basis of categories of job held in the factory. The exposed group consisted of 169 men who had worked for at least one year during 1956–75; a control group consisting of 190 unexposed workers from the same factory was included for comparison. The average observation period was 34 years. Assessment of cancer occurrence was based on abdominal sonography, records of the medical, personnel and pension departments and interviews with relatives. Causes of death were obtained from hospital records or from the treating physician. During the period of follow-up, four histologically verified cases of renal-cell carcinoma and one case of urothelial cancer of the renal pelvis were seen in the exposed group, and no case was

observed in the controls ($p = 0.03$). The five cancers occurred 18–34 years after first exposure; four of the five men had been exposed for more than 13 years. The excess was confirmed in comparisons with population rates for Denmark (SIR, 8.0; 95% CI, 2.6–19) and for the former German Democratic Republic (9.7; 3.1–23). The incidences of cancers at other sites were not reported. There were 50 deaths from all causes among exposed workers and 52 among controls; 16 cases of cancer of any organ were seen in both exposed and control workers; and two deaths from renal cancer occurred in exposed workers and none in controls. In a comparison with the local population, the SMR for renal cancer in the exposed group was 3.3 (95% CI, 0.40–12). [The Working Group noted that the use of sonography suggested that the study originated from the observation of a cluster of cases of renal cancer.]

The main cohort studies are summarized in Table 11.

2.4 Case–control studies

2.4.1 Primary liver cancer

Hernberg *et al.* (1984) identified 374 cases of primary liver cancer (ICD 155.0) that had been reported to the Finnish Cancer Registry in 1979–80. The notifying hospital could not be identified in nine cases, the hospital refused contact with 38 patients, and the diagnosis was incorrect in 83 cases. For the remaining 244 cases, a questionnaire was sent to either the patient or the next-of-kin. Three deceased patients had no relatives, and in 79 instances no reply was obtained. A further check of the diagnoses revealed that only 126 of the 162 cases for which a reply was obtained were primary liver cancers. For each of the 162 cases, two controls with coronary infarct and without cancer were selected, from the hospital register for living cases and from autopsy records for dead cases. Complete replies were obtained from only 174 controls or their next-of-kin. An industrial hygienist evaluated exposure to solvents on the basis of the reported occupational histories. Eight patients had been exposed to solvents for at least one year (odds ratio, 2.3; 95% CI, 0.8–7.0). Six of the exposed patients were women, one of whom had possibly been exposed to trichloroethylene; none of the female controls had been exposed.

Hernberg *et al.* (1988) subsequently identified 618 persons reported as having primary liver cancer to the Finnish Cancer Registry in 1976–78 and 1981. Five patients alive at the start of the study were excluded, and no relative was found for 87 patients. Questionnaires were sent to relatives of the remaining 526 cases, and a response was obtained from 377. Thirty-three cases were omitted on the basis of an incorrect or unconfirmed diagnosis, leaving 344 cases in the study. Two control groups were selected: one, as in the previous study, comprised 674 patients who had died with a coronary infarct, of whom 116 had no relatives and for 385 of whom the questionnaire was returned; the second control group consisted of 720 deceased stomach cancer patients, 66 of whom had no relatives and for 476 of whom a questionnaire was returned from next-of-kin. Two industrial hygienists coded occupational histories for potential exposure to solvents. In comparison with the two control groups combined, the odds ratios for exposure to solvents were 0.6 [95% CI, 0.3–1.4] for men and 3.4 [1.1–10] for women. None of the exposed women had been a heavy or moderate alcohol drinker. One of the seven solvent-exposed female patients and none of the solvent-exposed controls had been exposed to trichloroethylene.

Table 11. Summary of data from four cohort studies of trichloroethylene

Cancer site	Axelson *et al.* (1994) 1421 men using trichloroethylene and monitored for exposure (Sweden, 1958–87)			Anttila *et al.* (1995) 3089 men and women using trichloroethylene and monitored for exposure (Finland, 1967–92)			Spirtas *et al.* (1991) 7282 men and women employed in aircraft maintenance and exposed to trichloroethylene (USA, 1953–82)			Garabrant *et al.* (1988) 14 067 men and women employed in aircraft manufacture (USA, 1958–82)		
	SIR	95% CI	Obs	SIR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs
All cancers	0.96	0.80–1.2	107	1.1	0.92–1.2	208	[0.88]	[0.78–0.99]	281	0.84	0.77–0.93	453
Oesophagus	NR			NR			[1.0]	[0.37–2.2]	6	1.1	0.62–1.9	14
Stomach	0.70	0.23–1.6	5	1.3	0.75–2.0	17	[0.78]	[0.43–1.3]	14	0.40	0.18–0.76	9
Colon	1.0	0.44–2.0	8	0.84	0.36–1.7	8	[1.0]	[0.67–1.4]	29	0.96	0.71–1.3	47
Liver and biliary tract	1.4	0.38–3.6	4	[1.9]	[0.86–3.6]	9	[1.9]	[0.91–3.5]	10	0.94	0.40–1.9	8
Primary liver cancer				2.3	0.74–5.3	5	[1.1]	[0.14–4.0]	2			
Biliary tract				1.6	0.43–4.0	4	[2.2]	[0.96–4.4]	8			
Cervix	NR			2.4	1.1–4.8	8	2.2	0.61–5.7	4	0.61[a]	0.25–1.3	7
Prostate	1.3	0.84–1.8	26	1.4	0.73–2.4	13	0.80	0.50–1.2	22	0.93	0.60–1.4	25
Kidney	1.2	0.42–2.5	6	0.87	0.32–1.9	6	[1.1]	[0.46–2.1]	8	0.93	0.48–1.6	12
Urinary bladder	1.0	0.44–2.0	8	0.82	0.27–1.9	5	[1.4]	[0.70–2.5]	11	1.3	0.74–2.0	17
Skin	2.4	1.0–4.7	8	NR			[1.0][b]	[0.38–2.3]	6	0.7[c]	0.29–1.5	7
Brain and nervous system	NR			1.1	0.50–2.1	9	[0.78]	[0.36–1.5]	9	0.78	0.42–1.3	13
Lymphohaemato-poietic system				1.5	0.92–2.3	20	[0.94]	[0.66–1.3]	37	0.78	0.56–1.1	38
Non-Hodgkin's lymphoma	[1.5][d]	0.5–3.6	5	1.8[d]	0.78–3.6	8	[1.3][d]	[0.68–2.1]	14	0.82	0.44–1.4	13
Hodgkin's disease	1.1	0.03–6.0	1	1.7	0.35–5.0	3	[0.87]	[0.24–2.2]	4	0.73	0.20–1.9	4
Leukaemia	NR			1.1	0.35–2.5	5	[0.73][e]	[0.37–1.3]	11	0.82[d]	0.47–1.3	16

SIR, standardized incidence ratio; CI, confidence interval; Obs, observed; SMR, standardized mortality ratio; NR, not reported

[a] Female genital organs

[b] Malignant melanoma

[c] Includes five cases of malignant melanoma

[d] Including ICD 202

[e] Including aleukaemia

Hardell *et al.* (1984) studied all cases of liver cancer reported to the Swedish Cancer Registry in 1974–81 in men aged 25–80 living in the Umeå region of Sweden. Six patients who were alive at the start of the study in 1981 were excluded, leaving 166 cases. The diagnosis of 114 cases was confirmed on review. Six patients had been used as controls in a previous study, relatives could not be identified for five patients, and the relatives of one patient refused participation, leaving 102 patients (78 with hepatocellular, 15 with cholangiocellular, five with mixed and four with other types of liver cancer) for whom completed questionnaires were obtained. Two deceased controls matched for age, sex, year of death and municipality were selected from the National Population Register for each case, excluding people who had died from suicide or cancer. Exposure to solvents was assessed on the basis of responses to a questionnaire. The risk ratio for all primary liver cancers (hepatocellular and/or cholangiocellular) was 1.8 (95% CI, 0.99–3.4); that for hepatocellular carcinoma was 2.1 (1.1–4.0). Two of the 22 solvent-exposed patients and one of the 27 solvent-exposed controls had been exposed to trichloroethylene.

2.4.2 *Malignant lymphoma*

Hardell *et al.* (1981) studied 169 men aged 25–85 with histologically confirmed malignant lymphoma (60 with Hodgkin's disease, 105 with non-Hodgkin's lymphoma and four with unclassified lymphomas) in the Umeå region of Sweden between 1974 and 1978. For each of the 107 living patients, two controls matched for sex, age and residence were selected from the National Population Registry. For each of the 62 deceased patients, two controls matched for sex, age, year of death and municipality were selected from the National Registry for Causes of Death, excluding people who had died from suicide or cancer. Exposure to solvents was assessed on the basis of responses to a questionnaire. Three of the 338 controls did not return the questionnaire but were considered not to have been exposed in matched analyses. The relative risk associated with exposure to styrene, trichloroethylene, tetrachloroethylene or benzene was 4.6 (95% CI, 1.9–11). Seven cases and three controls reported exposure to trichloroethylene.

2.4.3 *Hodgkin's disease*

Olsson and Brandt (1980) studied 25 men aged 20–65 who were admitted consecutively to the Department of Oncology at the University Hospital of Lund, Sweden, in 1978–79 with Hodgkin's disease. For each case, two male controls, matched for age and residence, were selected from the population register. Twelve of the patients had been exposed to organic solvents, giving a relative risk of 6.6 (95% CI, 1.8–24). Three cases and no control reported exposure to trichloroethylene.

2.4.4 *Renal-cell carcinoma*

Sharpe *et al.* (1989) identified 403 patients who had been diagnosed with renal-cell carcinoma in nine hospitals in Montréal, Canada, in 1982–87. Of these, 168 were still alive in 1987 and agreed to complete a questionnaire. For each case, one control originally suspected to have renal-cell carcinoma but for whom a non-neoplastic diagnosis was given was matched for sex, age and urologist. Ultimately, 164 patients and 161 controls provided information. Ten

patients and three controls had been exposed to degreasing solvents (odds ratio, 3.4; 95% CI, 0.92–13). Tetrachloroethylene, 1,1,1-trichloroethane, trichloroethylene and dichloromethane were reported to be the agents most widely used.

2.4.5 Cancer of the colon

Fredriksson *et al.* (1989) carried out a case–control study of patients aged 30–75 in whom adenocarcinoma of the large bowel had been diagnosed in 1980–83 in the Umeå region of Sweden. A total of 402 incident cases were identified, but only patients alive in 1984–86 were included, leaving 344 patients, of whom 312 participated. Two population controls, matched by age, sex and county, were included for each case. Data on exposure were collected by a postal questionnaire. The odds ratio for exposure to trichloroethylene was 1.5 (95% CI, 0.4–5.7) and that for exposure to trichloroethylene among dry cleaners was 7.4 (1.1–47).

2.4.6 Brain tumours

Heineman *et al.* (1994) undertook a case–control study of 741 white men who had died from astrocytic brain tumours in two states of the United States between 1978 and 1981. Next-of-kin were identified for 654 patients; 483 of these were interviewed, and a hospital diagnosis of astrocytic brain tumour was confirmed in 300 cases. Of 741 selected deceased controls, 320 were included in the study. Exposure to solvents was assessed on the basis of a job–exposure matrix; 128 case patients had been employed in jobs with potential exposure to trichloroethylene (odds ratio, 1.1; 95% CI, 0.8–1.6). None of the risk estimates for subgroups reached significance.

2.4.7 Childhood leukaemia

Lowengart *et al.* (1987) identified 216 children aged 10 years or less from the Los Angeles County (United States) Cancer Surveillance Program in whom acute leukaemia had been diagnosed in 1980–84. Permission for contact with families was obtained for 202 patients; 159 mothers were interviewed, and information about the fathers was obtained for 154 cases. The mothers of the patients were asked to name a control child from among their child's friends. A total of 136 control mothers were interviewed; information about the fathers was obtained for 130 controls. Data on occupational exposure were obtained by telephone interview. The odds ratios associated with father's exposure to trichloroethylene were 2.0 ($p = 0.16$) for exposure one year before pregnancy, 2.0 ($p = 0.16$) for exposure during pregnancy and 2.7 ($p = 0.07$; 95% CI, 0.64–16) for exposure after delivery. The results of this study were also reported in an abstract (Peters *et al.*, 1984).

2.4.8 Childhood brain tumours

Peters *et al.* (1981) studied the occupations of the parents of 92 children under the age of 10 with brain tumours and of 92 matched controls in Los Angeles County, United States. Interviews with the fathers showed that those of 12 children with brain tumours and those of two controls had worked in the aircraft industry; the fathers of only two children with brain tumours reported exposure to trichloroethylene. The results of this study were also reported in an abstract (Peters *et al.*, 1984).

2.4.9 *Multiple sites*

Siemiatycki (1991) studied men aged 35–70 in Montréal, Canada, during 1979–85. A total of 3730 people with cancers at 21 sites and 533 population controls were interviewed about their occupations in detail, and their exposure to 293 agents or mixtures was then estimated by a group of chemists. The estimated prevalence of exposure to trichloroethylene was 2%. Both case–case and case–control comparisons were conducted. After control for confounding, increased odds ratios were found in the case–case comparison for cancer of the rectum (1.9 [95% CI, 0.9–3.9] and for skin melanoma (2.6 [1.2–5.8]) in relation to presumed exposure to trichloroethylene; for 'substantial' exposure (at least five years of exposure at a presumably medium or high concentration and frequency), elevated odds ratios were reported for prostatic cancer (1.8 [0.7–4.7]) and for skin melanoma (2.3 [0.8–7.0]), while the risk for rectal cancer was no longer elevated (0.8 [0.2–2.8]). The increased risk for skin melanoma was restricted to French Canadians; in the latter group, the risk for lung adenocarcinoma was also elevated (odds ratio for any exposure, 2.6 [0.8–8.4]; odds ratio for substantial exposure, 4.5 [1.1–18]). The risk was not increased for cancers of the bladder (0.6 [0.3–1.4]) or kidney (0.8 [0.3–2.1]) or for non-Hodgkin's lymphoma (1.1 [0.5–2.4]).

2.5 Studies of drinking-water

Cancer occurrence in populations exposed to drinking-water contaminated with various concentrations of trichloroethylene has been compared in a number of studies. The interpretation of some of these studies is complicated by several methodological problems:

(i) information on the concentration of trichloroethylene in water was obtained subsequently to or contemporaneously with the period over which cancer occurrence was measured, although cancer rates should be correlated with exposure before occurrence of the disease;

(ii) exposure was generally measured at the community level and does not necessarily reflect the exposure of individuals;

(iii) the problem of migration in and out of the populations under study was not addressed; and

(iv) the possible confounding effects of other characteristics of the populations being compared (socioeconomic, industrial and cultural factors) were not taken into account.

Isacson *et al.* (1985) tabulated the average annual age-adjusted incidence rates of cancers of the bladder, breast, colon, lung, prostate or rectum per 100 000 population in towns in Iowa, United States, in 1969–81 by the level of detectable volatile organic compounds in finished groundwater supplies. The levels of trichloroethylene were < 0.15 µg/L in one group of areas and ≥ 0.15 µg/L in another. There were virtually no differences in the incidences between these two groups.

Lagakos *et al.* (1986) studied childhood leukaemia in a community in Massachusetts, United States, where water from two wells was contaminated with trichloroethylene. Measurements made in 1979 showed a concentration of 267 ppb [µg/L] trichloroethylene in the well water. Twenty cases of childhood leukaemia were diagnosed in the community in 1964–83, and these were associated with a significantly higher estimated cumulative exposure to water from

the two contaminated wells than a random sample of children from the community (observed cumulative exposure, 21.1; expected cumulative exposure, 10.6; $p = 0.03$).

A study conducted in New Jersey, United States, during 1979–87 included 75 towns (Cohn *et al.*, 1994), of which 27 were included in a study reported by Fagliano *et al.* (1990). Trichloroethylene concentrations were measured during 1984–85, and an average level was assigned to each town. The highest level assigned was 67 μg/L. The water supply of six towns contained > 5 μg/L trichloroethylene (average, 23.4 μg/L). Women in these towns had a significantly higher total incidence of leukaemia than the inhabitants of towns where the concentration of trichloroethylene in drinking-water was < 0.1 μg/L (relative risk, 1.4; 95% CI, 1.1–1.9); no such effect was seen for men (1.1, 0.84–1.4). The risk among women was particularly elevated for acute lymphocytic leukaemia, chronic lymphocytic leukaemia and chronic myelogenous leukaemia. The risk for acute lymphocytic leukaemia in childhood was also significantly increased, in girls but not in boys. Increased risks for non-Hodgkin's lymphoma were apparent in towns in the highest category of trichloroethylene contamination (0.2; 0.94–1.5 for men and 1.4; 1.1–1.7 for women) and was particularly elevated for high-grade lymphomas.

Studies were conducted in two counties in Arizona, United States, to address the possible association between consumption of drinking-water from trichloroethylene-contaminated wells and childhood leukaemia (Maricopa County, Flood *et al.*, 1990) or all childhood neoplasms and testicular cancer (Pima County, Arizona Department of Health Services, 1990). In Maricopa County, two wells that were occasionally used to supplement the water supply were found to contain 8.9 and 29. 0 ppb [μg/L] trichloroethylene in 1982; they were then taken out of service. The concentrations of trichloroethylene in contaminated wells in Pima County were 1–239 μg/L, with levels as high as 4600 μg/L in wells at an Air Force facility in the area. No association was found between cancer at any of the sites examined and residence in the counties with contaminated wells, as opposed to residence in other areas of the county. The incidence rates in both Maricopa and Pima counties were comparable to those in other areas included in the United States SEER programme.

Vartiainen *et al.* (1993) collected 24-h urine samples from 95 and 21 inhabitants of two Finnish villages where the groundwater was contaminated with trichloroethylene (≤ 212 μg/L) and tetrachloroethylene (≤ 180 μg/L). The average excretion of trichloroethylene by inhabitants of the two villages was 0.55 and 0.45 μg/day, and that of two control groups was 0.36 and 0.32 μg/day; the corresponding figures for excretion of dichloroacetic acid were 0.78 and 1.3 μg/day *versus* 1.3 and 1.3 μg/day, and those for the excretion of trichloroacetic acid were 19 and 7.9 μg/day *versus* 2.0 and 4.0 μg/day. With the possible exception of non-Hodgkin's lymphoma, which occurred in a marginal excess in one of the villages (SIR, 1.4; 95% CI, 1.0–2.0; 31 cases) but not in the other (0.6; 0.3–1.1; 14 cases), neither overall cancer incidence nor the incidence of liver cancer or lymphohaematopoietic cancers was increased in the two villages.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F1 mice, five weeks of age, were administered trichloroethylene (purity, > 99%; containing 0.19% epoxybutane and 0.09% epichlorohydrin [see IARC, 1987c] as stabilizers) in corn oil by gavage on five days a week for 78 weeks. The time-weighted average doses of trichloroethylene were 1169 and 2339 mg/kg bw per day for males and 869 and 1739 mg/kg bw per day for females. All surviving animals were killed 90 weeks after the start of treatment and submitted to complete necropsy and histopathological evaluation. Groups of 20 male and 20 female vehicle controls were included. The numbers of survivors at the end of the study were 8/20 male vehicle controls, 36/50 males at the low dose and 22/48 males at the high dose; and 20/20 female vehicle controls, 42/50 females at the low dose and 39/47 females at the high dose. The survival-adjusted (Cox and Tarone test) incidences of hepatocellular carcinomas were increased in animals of each sex in relation to dose; males: 1/20 in vehicle controls, 26/50 ($p = 0.004$) at the low dose, 31/48 ($p < 0.001$) at the high dose; females: 0/20 in vehicle controls, 4/50 at the low dose, 11/47 ($p = 0.008$) at the high dose. One male at the high dose developed a forestomach papilloma (United States National Cancer Institute, 1976).

In a subsequent study, groups of 50 male and 50 female B6C3F1 mice, eight weeks of age, were administered 1000 mg/kg bw trichloroethylene (purity, > 99.9%; containing no epichlorohydrin) in corn oil by gavage on five days a week for up to 103 weeks. Groups of 50 mice of each sex served as vehicle controls. Survival of treated males was significantly reduced ($p = 0.004$) in comparison with controls; at the end of the experiment, 33 control and 16 treated males and 32 control and 23 treated females were still alive. Histopathological evaluation revealed increased incidences (incidental tumour test) of hepatocellular tumours in treated animals. In males, hepatocellular adenomas occurred in 7/48 controls and 14/50 ($p = 0.048$) treated animals; hepatocellular carcinomas were found in 8/48 controls and 31/50 ($p < 0.001$) treated animals; and the combined numbers of animals bearing hepatocellular adenomas and/or carcinomas were 14/48 controls and 39/50 ($p < 0.001$) treated animals. In females, hepatocellular adenomas were seen in 4/48 control and 16/49 ($p = 0.001$) treated animals; hepatocellular carcinomas occurred in 2/48 control and 13/49 ($p = 0.002$) treated animals; and the combined numbers of animals bearing hepatocellular adenomas and/or carcinomas were 6/48 controls and 22/49 ($p < 0.001$) treated animals. There was no significant treatment-related increase in the incidence of tumours at other sites. Toxic nephrosis (cytomegaly) was seen in 90% of treated males and in 98% of treated females (United States National Toxicology Program, 1990).

Two groups of 30 male and 30 female ICR:Ha Swiss mice, six to eight weeks of age, were each administered 0 or 0.5 mg trichloroethylene [purity unspecified] by gavage in 0.1 ml trioctanoin once a week for at least 74 weeks. Only sections of lung, liver and stomach were taken for histopathological examination. The incidence of forestomach tumours was reported not to be increased; findings were not given for other sites (Van Duuren *et al.*, 1979). [The Working Group noted the low dose used and the inadequate conduct and reporting of the study.]

3.1.2 *Rat*

Groups of 50 male and 50 female Osborne-Mendel rats, six weeks of age, were administered trichloroethylene (purity, > 99%; containing 0.19% epoxybutane and 0.09% epichlorohydrin as stabilizers) in corn oil by gavage on five days a week for 78 weeks. The time-weighted average doses of trichloroethylene were 549 (low dose) and 1097 mg/kg bw per day (high dose) for animals of each sex. All surviving animals were killed 110 weeks after the start of treatment and were submitted to complete necropsy. Groups of 20 male and 20 female vehicle controls were included. Large proportions of treated and control rats died during the experiment; the numbers of animals alive at the end of the study were 3/20 male vehicle controls, 8/50 males at the low dose and 3/50 males at the high dose; of the females, there were 8/20 vehicle controls, 13/48 at the low dose and 13/50 at the high dose. There was no significant difference in tumour incidence at any site between treated and control rats (United States National Cancer Institute, 1976). [The Working Group noted the high rates of early mortality in both control and treated rats and the limited duration of treatment.]

In a subsequent study, groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were administered 0, 500 or 1000 mg/kg bw trichloroethylene (purity, > 99.9%; containing no epichlorohydrin) in corn oil by gavage on five days a week for up to 103 weeks. A group of 50 male and 50 female rats were used as untreated controls. Survival of low-dose and high-dose males was significantly reduced ($p < 0.005$) in comparison with vehicle controls; the numbers of survivors at the end of the experiment were 35 male vehicle controls, 20 at the low dose and 16 at the high dose; and 37 female vehicle controls, 33 at the low dose and 26 at the high dose. An increased incidence of renal tubular-cell adenocarcinomas was seen in males: 0/49 untreated controls, 0/48 vehicle controls, 0/49 at the low dose and 3/49 at the high dose ($p = 0.028$; incidental tumour test). Two males at the low dose had renal tubular-cell adenomas. The incidence of tumours in female rats was not increased at any site. Toxic nephrosis of the kidney occurred in 96/98 treated males and in all of the treated females but not in vehicle control rats of either sex (United States National Toxicology Program, 1990). [The Working Group noted the uncommon occurrence of renal tubular-cell tumours in untreated Fischer 344/N rats.]

Groups of 50 males and 50 females of four strains (ACI, August, Marshall and Osborne-Mendel), 6.5–8 weeks of age, were administered 0, 500 or 1000 mg/kg bw trichloroethylene (purity, > 99.9%) in corn oil by gavage on five days a week for 103 weeks. Additional groups of 50 rats of each sex and strain served as untreated controls. Survival was reduced significantly in low-dose and high-dose males and high-dose females of the ACI strain, in both treated groups of males and females of the Marshall strain, and in high-dose female Osborne-Mendel rats. The numbers of survivors at the end of the study were: ACI males – 36 untreated controls, 37 vehicle controls, 19 at the low dose, 11 at the high dose; ACI females – 36 untreated controls, 33 vehicle controls, 20 at the low dose, 17 at the high dose; August males – 24 untreated controls, 21 vehicle controls, 13 at the low dose, 15 at the high dose; August females – 26 untreated controls, 23 vehicle controls, 26 at the low dose, 24 at the high dose; Marshall males – 32 untreated controls, 26 vehicle controls, 12 at the low dose, 6 at the high dose; Marshall females – 31 untreated controls, 30 vehicle controls, 12 at the low dose, 10 at the high dose; Osborne-Mendel males – 18 untreated controls, 22 vehicle controls, 17 at the low dose, 14 at the high dose; Osborne-Mendel females – 19 untreated controls, 18 vehicle controls, 10 at the low dose, 7 at the

high dose. Many early deaths occurred accidentally. The incidence of renal cytomegaly was > 80% in all treated males and females, and toxic nephropathy (described as dilated tubules lined by elongated and flattened epithelial cells) occurred at rates of 17–80% in the treated groups; however, there was no difference in kidney toxicity between males and females of any strain. Neither of these two renal lesions was seen in untreated or vehicle controls. The incidences of renal tubular-cell hyperplasia and tubular-cell adenoma were increased in male Osborne-Mendel rats at the low dose: hyperplasia – 0/50 untreated controls, 0/50 vehicle controls, 5/50 at the low dose, 3/50 at the high dose; adenoma – 0/50 untreated controls, 0/50 vehicle controls, 6/50 (p = 0.007; survival-adjusted incidental tumour test) at the low dose, 1/50 at the high dose. One renal tubular-cell adenocarcinoma occurred in a male at the high dose. The incidences of interstitial-cell tumours of the testis were increased in Marshall rats exposed to trichloroethylene: 16/46 untreated controls, 17/46 vehicle controls, 21/48 ($p < 0.001$; survival-adjusted incidental tumour test) at the low dose, 32/48 ($p < 0.001$) at the high dose. No significant increase in tumour incidence was reported for ACI or August rats (United States National Toxicology Program, 1988). [The Working Group noted the poor survival among all strains and the fact that five of the six renal adenomas in male Osborne-Mendel rats at the low dose occurred among the 17 rats alive at the end of the study.]

Groups of 30 male and 30 female Sprague-Dawley rats, 12–13 weeks of age, were administered 0, 50 or 250 mg/kg bw trichloroethylene (purity, 99.9%; containing no epoxide) in olive oil by gavage on four to five days per week for 52 weeks and observed for life. Data on survival were not provided, but the authors reported a nonsignificant increase in mortality among treated females. Renal tubular-cell cytokaryomegaly was observed only in male rats at the high dose (46.7% [14/30]; $p < 0.01$). A nonsignificant increase in the incidence of leukaemias was observed in males: none in controls, 6.7% [2/30] at the low dose and 10.0% [3/30] at the high dose (Maltoni *et al.*, 1986). [The Working Group noted the short period of exposure.]

3.2 Inhalation

3.2.1 Mouse

Groups of 30 male and 30 female NMRI mice [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at a concentration of 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) for 6 h per day on five days per week for 18 months. The experiment was terminated after 30 months. At the end of exposure (75 weeks), there was no difference in the probability of survival among the females; in males, the probability of survival was reduced from 83% in controls to 63% in low-dose and 56% in high-dose groups. Histopathological examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours indicated increased age-adjusted incidences of lymphomas in treated female mice: 9/29 controls, 17/30 at the low dose ($p < 0.001$) and 18/28 ($p = 0.01$) at the high dose (Henschler *et al.*, 1980).

Groups of 49–50 female ICR mice, seven weeks of age, were exposed to air containing trichloroethylene (purity, 99.8%; containing 0.13% carbon tetrachloride and > 0.02% benzene and epichlorohydrin) at concentrations of 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m^3) for 7 h per day on five days per week for up to 104 weeks. There were no significant differences in

survival between the control and exposed groups. Complete necropsy was carried out on all animals. Histopathological evaluation revealed a significant increase (Fisher's exact test) in the incidence of lung adenocarcinomas: 1/49 controls, 3/50 at the low dose, 8/50 ($p < 0.05$) at the middle dose and 7/46 ($p < 0.05$) at the high dose. [The Working Group found a significant dose–response trend: $p = 0.034$, Cochran-Mantel-Haenszel test.] The incidences of adenomas and adenocarcinomas of the lung combined in the groups at the middle (13/50) and high doses (11/46) were not significantly increased in comparison with controls (6/49). The average number of lung tumours was, however, increased in mice at the middle and high doses in comparison with controls: 0.12 in controls, 0.10 at the low dose, 0.46 at the middle dose and 0.39 at the high dose (Fukuda *et al.*, 1983).

Groups of 90 male and 90 female Swiss mice, 11 weeks of age, and groups of 90 male and 90 female B6C3F1 mice, 12 weeks of age, were exposed to air containing trichloroethylene (purity, 99.9%; containing no epoxide) at concentrations of 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3) for 7 h per day on five days a week for 78 weeks and were then observed for life. Data on survival were not provided, but the authors reported that mortality was higher ($p < 0.05$) in treated male B6C3F1 mice than in controls. Dose-related increases in the incidences of lung and liver tumours were observed in male Swiss mice [Fisher's exact test or Cochran-Armitage linear trend test]. The percentages of male Swiss mice bearing a malignant pulmonary tumour were: control, 11.1% [10/90]; low-dose, 12.2% [11/90]; mid-dose, 25.5% [23/90] ($p < 0.05$); and high-dose, 30.0% [27/90] ($p < 0.01$); the percentages of male mice bearing a hepatoma were: control, 4.4% [4/90]; low-dose, 2.2% [2/90]; mid-dose, 8.9% [8/90]; and high-dose, 14.4% [13/90] ($p < 0.05$). In B6C3F1 mice, a dose-related increase in the incidence of lung tumours was observed in females: control, 4.4% [4/90]; low-dose, 6.7% [6/90]; mid-dose, 7.8% [7/90]; and high-dose, 16.7% [15/90] ($p < 0.05$) (Maltoni *et al.*, 1986, 1988).

3.2.2 Rat

Groups of 30 male and 30 female Wistar rats [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at concentrations of 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) for 6 h per day on five days per week for 18 months. The experiment was terminated after 36 months. No differences in survival were reported; the probability of survival in each group at the end of the experiment was: 46.7% of male controls, 23.3% of males at the low dose, 36.7% of males at the high dose, 16.7% of female controls, 13.3% of females at the low dose and 16.7% of females at the high dose. Histopathological and gross examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours revealed no increase in tumour incidence (Henschler *et al.*, 1980).

Groups of 49–51 female Sprague-Dawley rats, seven weeks of age, were exposed to air containing trichloroethylene (purity, 99.8%) at concentrations of 0, 50, 150 or 450 ppm (0, 270, 810 or 2430 mg/m^3) for 7 h per day on five days per week for 104 weeks. Survival was significantly higher in the exposed groups than in controls: about 75% of the rats in the three treated groups and 50% of controls were alive at 100 weeks. Gross and histopathological examination revealed no difference in the incidence of tumours between the control and exposed groups (Fukuda *et al.*, 1983).

Groups of 130–145 male and female Sprague-Dawley rats, 12 weeks of age, were exposed to air containing trichloroethylene (purity, 99.9%; containing no epoxide) at a concentration of 0, 100, 300 or 600 ppm (0, 540, 1620 or 3240 mg/m^3) for 7 h per day on five days per week for 104 weeks. All animals were observed for their lifetime. Data on survival were not provided, but the authors reported no excess mortality in any of the exposed groups. A significant, dose-related increase in the incidence of Leydig cell (interstitial) tumours of the testis was observed [$p < 0.001$; Cochran-Mantel-Haenszel test]; the percentages of male rats bearing these tumours were 4.4% [6/135] of controls, 12.3% [16/130] at the low dose [$p < 0.05$; Fisher's exact test], 23.1% [30/130] at the middle dose [$p < 0.01$; Fisher's exact test] and 23.8% [31/130] at the high dose [$p < 0.01$; Fisher's exact test]. Four renal tubular adenocarcinomas (3.1%) were observed in the high-dose male rats; no such tumours were observed in the lower dose groups, in controls or in the historical control database for Sprague-Dawley rats at the study laboratory. Cytokaryomegaly of renal tubular cells was also observed: in none of the control or low-dose rats, in 16.9% at the middle dose and in 77.7% at the high dose (Maltoni *et al.*, 1986, 1988).

3.2.3 Hamster

Groups of 30 male and 30 female Syrian hamsters [age unspecified] were exposed to air containing trichloroethylene (purity, > 99.9%; stabilized with 0.0015% triethanolamine) at concentrations of 0, 100 or 500 ppm (0, 540 or 2700 mg/m^3) for 6 h per day on five days per week for 18 months. The experiment was terminated after 30 months. The probability of survival was similar in exposed and control groups. Histopathological examination of spleen, liver, kidney, lung, heart, stomach, central nervous system and all tumours revealed no significant increase in tumour incidence (Henschler *et al.*, 1980).

3.3 Topical application

Mouse: In a study of two-stage carcinogenesis on mouse skin, single doses of 1.0 mg trichloroethylene [purity unspecified] in 0.1 ml of acetone were applied to the shaven dorsal skin of 30 female ICR:Ha Swiss mice aged six to eight weeks; 14 days later, topical applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 2.5 μg in 0.1 ml of acetone, three times per week) were begun, for at least 49 weeks. Nine skin papillomas were found in 4/30 treated mice, and 10 papillomas were found in 9/120 TPA-treated controls. Trichloroethylene was also administered by repeated topical application (three times per week) to groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, for 83 weeks at a dose of 1.0 mg per mouse. No tumours were observed at the site of application (Van Duuren *et al.*, 1979).

3.4 Subcutaneous injection

Mouse: Groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, were given subcutaneous injections of 0.5 mg trichloroethylene [purity unspecified] in 0.05 ml trioctanoin once a week for at least 74 weeks, or received the vehicle alone. No tumours were observed at the injection site in either group (Van Duuren *et al.*, 1979).

3.5 Administration with known carcinogens

Mouse: Five groups of 50 male and 50 female ICR:Ha Swiss mice, five weeks of age, were administered either industrial-grade trichloroethylene (purity, 99.4%; containing 0.11% epichlorohydrin and 0.20% 1,2-epoxybutane) in corn oil by gavage, purified trichloroethylene (purity, > 99.9%) in corn oil by gavage, purified trichloroethylene with added epichlorohydrin (0.8%), purified trichloroethylene with added 1,2-epoxybutane (0.8 %) or purified trichloroethylene with 0.25% epichlorohydrin plus 0.25% 1,2-epoxybutane, on five days per week for 18 months. The doses of trichloroethylene that were administered were 2.4 g/kg bw for males and 1.8 g/kg bw for females. Groups of 50 mice of each sex given corn oil served as vehicle controls. The treatment period was followed by a six-month observation period. The probabilities of survival were significantly reduced ($p < 0.001$) in all groups of treated males in comparison with controls; in females, the probabilities of survival were reduced ($p < 0.05$) in the group receiving purified trichloroethylene and in that receiving purified trichloroethylene plus epichlorohydrin ($p < 0.001$). At the end of the study, there were no more than two survivors in any treatment group. Complete necropsies were performed on all animals. The incidence of squamous-cell carcinomas of the forestomach was increased in several of the treatment groups over that in controls (0/50 for males and females); males: purified trichloroethylene, 0/50; industrial-grade trichloroethylene, 0/49; purified trichloroethylene plus epichlorohydrin, 5/49 ($p < 0.001$); purified trichloroethylene plus 1,2-epoxybutane, 3/49 ($p = 0.029$); and purified trichloroethylene plus epichlorohydrin and 1,2-epoxybutane, 2/49 ($p = 0.036$); females: controls, 0/50; purified trichloroethylene, 0/50; industrial-grade trichloroethylene, 3/50; purified trichloroethylene plus epichlorohydrin, 9/50 ($p < 0.001$); purified trichloroethylene plus 1,2-epoxybutane, 1/48; and purified trichloroethylene plus epichlorohydrin and 1,2-epoxybutane, 9/50 ($p < 0.001$). No significant increase in the incidences of tumours at other sites was reported. The authors attributed the increased incidence of forestomach cancers to the direct alkylating effects of epichlorohydrin and 1,2-epoxybutane (Henschler *et al.*, 1984). [The Working Group noted that the incidences of hepatocellular tumours (adenomas and carcinomas combined) in male mice were: controls, 3/50; purified trichloroethylene, 6/50; and industrial-grade trichloroethylene, 9/50; and that no survival-adjusted analysis of tumour incidence was performed.]

Groups of 23–33 male B6C3F1 mice, 15 days of age, were given a single intraperitoneal injection of *N*-ethylnitrosourea in 0.1 mol/L sodium acetate at doses of 0, 2.5 or 10 mg/kg bw. When the mice were four weeks of age, a 61-week treatment period was begun with 0, 3 or 40 mg/L trichloroethylene (purity, > 99%) in the drinking-water. The highest concentration of trichloroethylene was equivalent to a daily dose of 6 mg/kg bw. The incidences of hepatocellular adenomas and carcinomas were not increased in mice that received trichloroethylene alone in comparison with vehicle controls, and trichloroethylene did not promote liver tumours in mice initiated with *N*-ethylnitrosourea (Herren-Freund *et al.*, 1987). [The Working Group noted the low dose of trichloroethylene used.]

3.6 Carcinogenicity of metabolites

Studies of the carcinogenicity of the known metabolites of trichloroethylene, dichloroacetic acid, trichloroacetic acid and chloral hydrate, are summarized in separate monographs in this volume.

3.6.1 Mouse

A single dose of 1.0 mg of trichloroethylene oxide, a putative metabolite [purity unspecified], in 0.1 ml of acetone was applied to the dorsal skin of 30 female ICR:Ha Swiss mice, six to eight weeks of age; 14 days later, topical applications of TPA (2.5 μg in 0.1 ml of acetone, three times per week) were begun and continued for more than 61 weeks. The incidence of tumours at the site of application was not increased in the group treated with trichloroethylene plus TPA (three mice each had a single papilloma) in comparison with mice receiving TPA alone (10 papillomas in 9/120 mice) (Van Duuren *et al.*, 1979).

Trichloroethylene oxide was administered to a group of 30 female ICR:Ha Swiss mice, six to eight weeks of age, by repeated skin application for 82 weeks (2.5 mg/mouse in 0.1 ml acetone three times weekly); 30 mice served as vehicle controls. No tumour was observed at the site of application in either group. Further groups of 30 female ICR:Ha Swiss mice, six to eight weeks of age, were given 0 or 500 μg/mouse trichloroethylene oxide in 0.05 ml tricaprylin once a week for up to 80 weeks. One fibrosarcoma occurred at the injection site in treated animals (Van Duuren *et al.*, 1983).

1,2-Dichlorovinyl cysteine, a minor metabolite [purity unspecified], was administered at a concentration of 0, 10 or 50 mg/L in drinking-water to three groups of 30 Swiss-Webster mice [age and sex unspecified] for 14 weeks, beginning one day after administration of *N*-nitrosodimethylamine (NDMA) (six intraperitoneal injections of 5.0 mg/kg bw administered every other day). The average daily doses of 1,2-dichlorovinyl cysteine were 2.4 and 12.6 mg/kg bw, respectively. Renal tumours occurred after 50 weeks in 2/16 mice receiving NDMA alone, 2/15 receiving NDMA plus the low dose of 1,2-dichlorovinyl cysteine and 3/16 receiving NDMA plus the high dose of 1,2-dichlorovinyl cysteine [not significant]. Multiple renal tumours were found in 7/40 mice treated with NDMA plus 1,2-dichlorovinyl cysteine, whereas none were found in 21 mice treated with NDMA alone [$p = 0.043$; Fisher's exact test] (Meadows *et al.*, 1988).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

The biotransformation and the kinetics of trichloroethylene have been described in many studies of workers and of volunteers. Pulmonary uptake of trichloroethylene is rapid, the rate of

uptake being dependent on the rate of respiration, and uptake increases about twofold with exercise (Monster *et al.*, 1976). Distribution to the tissues has not been described, but the concentrations of trichloroethylene should be proportional to the duration and concentration of exposure, and the distribution is probably similar to that in animals. The blood:air partition coefficient for trichloroethylene in human volunteers was about 15 (Monster *et al.*, 1979), and the fat:air partition coefficient was about 700 (Sherwood, 1976; Steward *et al.*, 1973); there is therefore a tendency for deposition in fat from blood, the fat:blood partition coefficient being about 50 (700/15).

After inhalation, 40–70% of an administered dose of trichloroethylene is metabolized, the unmetabolized fraction being cleared by exhalation. Metabolism was proportional to the concentration of trichloroethylene in air up to 315 mg/m^3 for 3 h (Ikeda & Imamura, 1973; Monster *et al.*, 1976; Ikeda, 1977; Nomiyama & Nomiyama, 1977). No saturation of biotransformation has been detected with concentrations up to 380 ppm [1976 mg/m^3].

Trichloroethanol, its glucuronide and trichloroacetic acid are major metabolites in urine, and chloral hydrate is a transient metabolite in blood (Cole *et al.*, 1975). After controlled exposure of males to 200 ppm (1040 mg/m^3) trichloroethylene for 6 h, oxalic acid and *N*-(hydroxyacetyl)aminoethanol were detected as minor metabolites (Dekant *et al.*, 1984). Traces of *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-L-cysteine were present in the urine of workers exposed to unknown concentrations of trichloroethylene in air (Birner *et al.*, 1993). Trichloroethanol and its glucuronide are rapidly eliminated in urine, with half-lives of about 10 h, and trichloroacetic acid is eliminated slowly, with a half-life of about 52 h (range, 35–70 h) (Müller *et al.*, 1972, 1974). Repeated exposure of volunteers to 50 ppm (260 mg/m^3) trichloroethylene for 4 h per day on five consecutive days resulted in slightly higher concentrations of trichloroethylene and trichloroethanol in blood than after a single exposure to 40 ppm (208 mg/m^3) for 4 h (Ertle *et al.*, 1972). Urinary excretion of trichloroethanol by five male volunteers exposed to 70 ppm [364 mg/m^3] for 4 h per day for five days stabilized rapidly and remained constant until the end of the exposure, whereas urinary excretion of trichloroacetic acid continued to rise (Monster *et al.*, 1979).

4.1.2 Experimental systems

The biotransformation of trichloroethylene has been reviewed (Bonse & Henschler, 1976; Kimbrough *et al.*, 1985; Dekant, 1986; Bruckner *et al.*, 1989; Davidson & Beliles, 1991).

The absorption, distribution, metabolism and excretion of trichloroethylene at doses outside the range of those tested experimentally have been predicted from a number of physiologically based pharmacokinetic models constructed from the existing experimental data (Dallas *et al.*, 1991; Fisher *et al.*, 1991; Allen & Fischer, 1993).

The absorption and excretion of trichloroethylene have been studied in rats and mice. The compound is rapidly absorbed from the gastrointestinal tract and through the lungs; skin absorption after exposure to the vapour is negligible. In male Sprague-Dawley rats exposed to 50 ppm [260 mg/m^3] or 500 ppm [2600 mg/m^3] trichloroethylene for 2 h through a miniaturized one-way breathing valve (Dallas *et al.*, 1991), the uptake decreased from > 95% at the beginning of exposure to a relatively constant, almost steady-state level of 70%. The concentrations of trichloroethylene in exhaled breath towards the end of the exposure period were 34.6 ± 1.1 ppm

[185 ± 6 mg/m^3] after exposure to 50 ppm and 340.8 ± 10.6 ppm [1830 ± 60 mg/m^3] after exposure to 500 ppm. This direct proportionality was not reflected in the arterial blood concentrations, where the 10-fold increase in dose resulted in a 25- to 30-fold increase in blood levels and only an 8.7-fold increase in total absorbed dose.

The blood:air partition coefficient is about 14 in mice (Fisher *et al.*, 1991) and about 18 in rats (Andersen *et al.*, 1987; Fisher *et al.*, 1989). The corresponding fat:blood values are about 36 and 27, and the liver:blood partition coefficients are about 1.8 and 1.3. At the end of 4-h exposures of Fischer 344 rats to 529 ppm [2751 mg/m^3] (males) and 600 ppm [3120 mg/m^3] (females), the concentrations of trichloroethylene in blood were about 35.5 μg/ml (males) and 25.8 μg/ml (females). The concentrations of trichloroethylene in the blood of B6C3F1 mice were much lower: the highest mean blood concentrations seen during exposure of males to 110–748 ppm [572–3890 mg/m^3] and females to 42–889 ppm [218–4623 mg/m^3] were 7.3 μg/ml after exposure to 748 ppm [3890 mg/m^3] (males) and 6.3 μg/ml after exposure to 368 ppm [1914 mg/m^3] (females) (Fisher *et al.*, 1991).

The distribution of trichloroethylene in mice after a 10-min inhalation (approximate dose, 280 mg/kg bw) was studied by whole-body autoradiography of animals killed at intervals over 8 h. Trichloroethylene was distributed throughout the body into well-perfused organs; after 30 min, redistribution to adipose tissues had occurred (Bergman, 1983a).

The urinary excretion of trichloroacetic acid by rats exposed to 55 ppm [286 mg/m^3] trichloroethylene for 8 h per day for 14 weeks reached a maximum after two days and remained constant until the end of the exposure, whereas urinary excretion of trichloroethanol increased steadily over the first 10 weeks of the study (Kimmerle & Eben, 1973).

Mice have consistently higher rates of biotransformation than rats (Fisher *et al.*, 1991). The metabolism of trichloroethylene in rats can be described by Michaelis-Menten kinetics and is saturated after exposure by inhalation to more than 500–600 ppm (2600–3120 mg/m^3). Saturation of metabolism in rats at 500 ppm was also seen in the experiments of Dallas *et al.* (1991), described above. The atmospheric concentration at which elimination shifts from first-order to zero-order kinetics was found to be 65 ppm [338 mg/m^3] in rats in a closed exposure system (Filser & Bolt, 1979). Metabolic saturation occurs after oral administration of > 200–500 mg/kg bw trichloroethylene to rats; in mice, the rate of biotransformation is linear up to a dose of 2000 ppm (10 400 mg/m^3) by inhalation and up to 2000 mg/kg bw by oral administration (Stott *et al.*, 1982; Buben & O'Flaherty, 1985; Green & Prout, 1985; Prout *et al.*, 1985).

Mice have been shown to biotransform 2.6 times more trichloroethylene on a body weight basis than rats after exposure by inhalation to 600 ppm (3120 mg/m^3) (Dekant *et al.*, 1986a). Trichloroacetic acid concentrations in blood reached significantly higher values in B6C3F1 mice than in Fischer 344 rats at the end of a 4-h exposure by inhalation. The peak concentrations were 23.3 μg/ml in male rats and 39.6 μg/ml in female rats exposed to 505 ppm [2626 mg/m^3] and 600 ppm [3120 mg/m^3], respectively, while the values for mice were 129.6 μg/ml in males exposed to 748 ppm [3890 mg/m^3] and 94.3 μg/ml in females exposed to 889 ppm [4623 mg/m^3] (Fisher *et al.*, 1991). After exposure to low doses, the rate of metabolism in mice and rats is similar, and about 90% of an oral dose of 2 or 10 mg/kg bw trichloroethylene was eliminated as metabolites within 72 h by female Wistar and NMRI mice (Dekant *et al.*, 1986b). After an oral dose of 2000

mg/kg bw, 78% of the dose was exhaled as unchanged trichloroethylene by rats but only 14% by mice (Prout *et al.*, 1985).

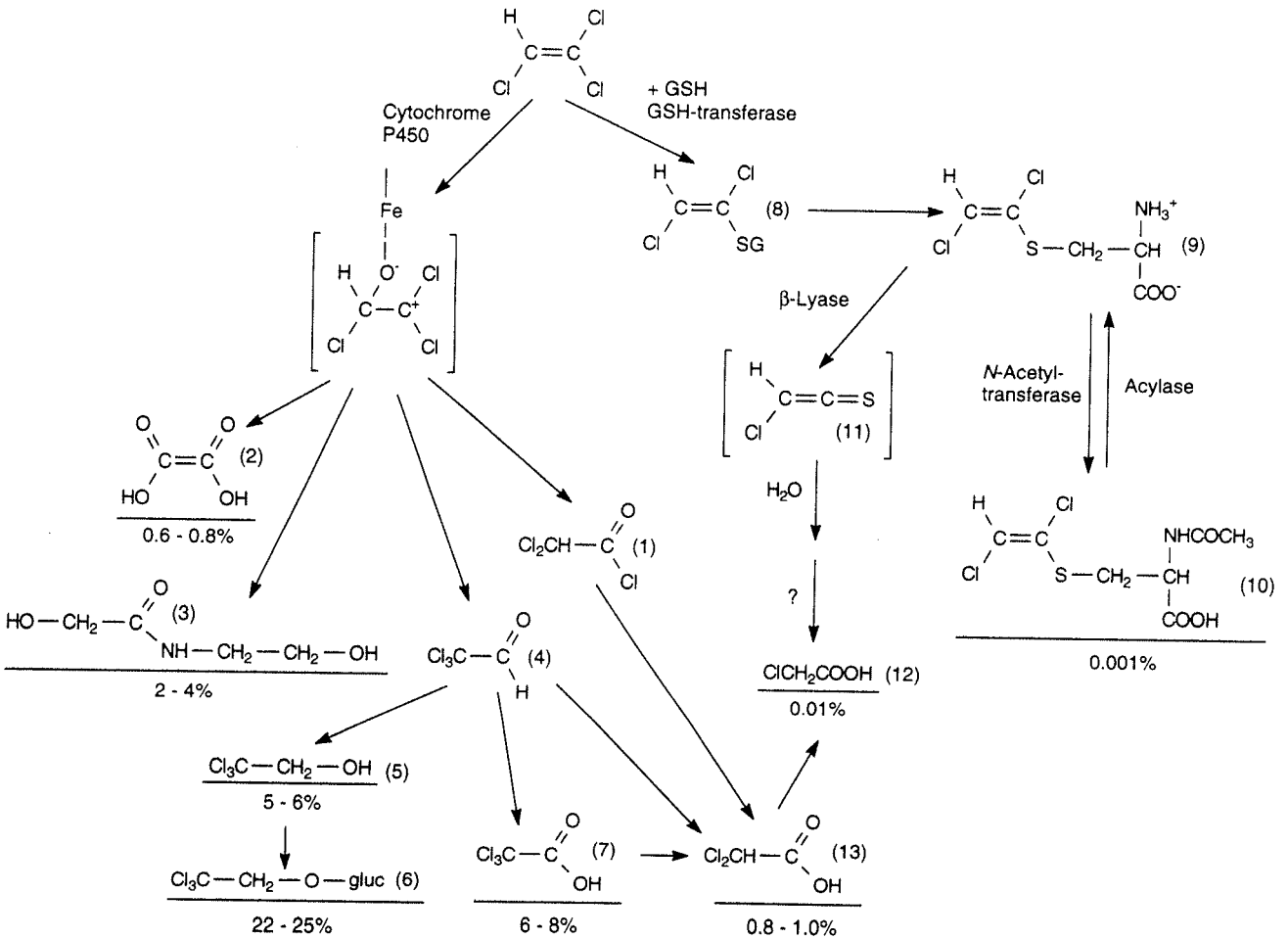
As a result of the higher biotransformation rate in mice, their blood levels of trichloroethanol and trichloroacetic acid were four- and sixfold higher than those in rats, and peak concentrations were reached within 2 h in mice and up to 10 h in rats. In mice, the high levels of trichloroacetate in blood persisted for over 30 h (Prout *et al.*, 1985). After dosing by gavage with 1.5 mmol/kg bw (200 mg/kg bw) trichloroethylene, the peak blood concentrations of trichloroacetic acid and the area under the integrated time–concentration curve were higher in mice (216 nmol/ml [35 μg/ml] and 2.5 μmol-h/ml) [408 μg-h/ml] than in rats (81 nmol/ml [13 μg/ml] and 1.5 μmol-h/ml [245 μg-h/ml]) (Larson & Bull, 1992a). The highest concentration of trichloroacetic acid that was found in the blood of rats after oral administration of trichloroethylene in corn oil was equivalent to about 50 mg/kg bw of trichloroacetic acid (Elcombe, 1985). Blood concentrations of the chloroacetic acids resulting from their administration to mice and rats are described in the relevant monographs in this volume.

Several excretory metabolites have been identified in mice and rats (see Figure 1). Most of the metabolites in urine can be accounted for by cytochrome P450-catalysed oxidation reactions of trichloroethylene to chloral hydrate. Trichlorethanol and its glucuronide are formed by reduction of chloral hydrate; trichloroacetic acid is formed by oxidation of this intermediate (Butler, 1949; Daniel, 1963; Kimmerle & Eben, 1973). The glucuronide of trichloroacetic acid has been identified in the urine of non-human primates treated by intramuscular injection with trichloroethylene (Müller *et al.*, 1982). The mechanism of formation of dichloroacetic acid has been postulated as a rearrangement of 1,1,2-trichlorooxirane and subsequent hydrolysis (Hathway, 1980), but it may also be formed by biotransformation of chloral hydrate or trichloroacetic acid (Larson & Bull, 1992b). Oxalic acid may be formed as a urinary metabolite of trichloroethylene as an end-product of 1,1,2-trichlorooxirane, by enzymatic or non-enzymatic cleavage of the epoxide followed by spontaneous elimination of two equivalents of hydrochloric acid, reaction with water and oxidation (Dekant *et al.*, 1984). Oxalic acid may also be formed by oxidation of dichloroacetic acid (Larson & Bull, 1992a,b). The formation of *N*-(hydroxyacetyl)-aminoethanol is proposed to proceed by the reaction of trichloroethylene-derived oxidative intermediates with ethanol amine or with phosphatidylethanol amine and enzymic breakdown of the acylated lipids (Dekant *et al.*, 1984).

Traces of metabolites indicative of conjugation of trichloroethylene with glutathione are also excreted in urine after high oral doses of trichloroethylene. The presence of *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine and *N*-acetyl-*S*-(2,2-dichlorovinyl)-L-cysteine indicates trichloroethylene conjugation with glutathione followed by catabolism and acetylation by the enzymes of the mercapturic acid pathway (Dekant *et al.*, 1986a; Commandeur & Vermeulen, 1990; Dekant *et al.*, 1990). Chloroacetic acid is another trace metabolite of trichloroethylene in rats (Green & Prout, 1985); it may be formed by hydrolysis of the intermediate electrophile, chlorothioketene, which is a cysteine conjugate β-lyase-catalysed cleavage product of *S*-(1,2-dichlorovinyl)-L-cysteine (Dekant *et al.*, 1986c, 1988). Monochloroacetate may be formed by reduction of dichloroacetic acid (Larson & Bull, 1992b).

Species and strain differences in the biotransformation of trichloroethylene have been reported. Higher peak blood levels of dichloroacetic acid were reported in B6C3F1 mice

Figure 1. Proposed biotransformation of trichloroethylene to urinary metabolites in rats



Modified from Dekant *et al.* (1984); Dekant (1986)

Identified urinary metabolites are underlined; percentages are those of an oral dose of 200 mg/kg bw excreted as individual metabolites

1, Dichloroacetyl chloride; 2, oxalic acid; 3, *N*-(hydroxyacetyl)aminoethanol; 4, chloral; 5, trichloroethanol; 6, trichloroethanol glucuronide; 7, trichloroacetic acid; 8, dichlorovinylglutathione; 9, *S*-1,2-dichlorovinylcysteine; 10, *S*-1,2-dichlorovinyl-*N*-acetylcysteine; 12, monochloroacetic acid; 13, dichloroacetic acid

(35 nmol/ml [4.5 μg/ml]) dosed with 1.5 mmol/kg bw (200 mg/kg bw) trichloroethylene orally than in rats (< 4 nmol/ml [< 0.5 μg/ml]) receiving 23 mmol/kg bw (3000 mg/kg bw) (Larson & Bull, 1992a). These differences are not, however, reflected in the urinary excretion of dichloroacetic acid (Green & Prout, 1985; Dekant *et al.*, 1986b): In both mice and rats, the blood levels of dichloroacetic acid are at least one order of magnitude lower than those of trichloroacetic acid (Larson & Bull, 1992a). Strain differences among mice in the metabolism of trichloroethylene to trichloroacetic acid are also apparent: In Swiss and B6C3F1 mice, trichloroacetic acid in urine accounts for 7–12% of an oral dose of trichloroethylene; in NMRI mice, trichloroacetic acid is only a trace metabolite of trichloroethylene (Dekant *et al.*, 1986b).

The elimination rates of the major trichloroethylene metabolites differ markedly. Trichloroethanol and chloral hydrate are cleared from the blood with a half-life of 1–2 h, whereas high concentrations of trichloroacetic acid are present for up to 30 h and are cleared only slowly (Kimmerle & Eben, 1973). The amounts of trichloroethylene that are cleared by exhalation depend on the administered dose.

No changes in metabolite profiles were observed after exposure of rats to 55 ppm (286 mg/m^3) trichloroethylene by inhalation for 14 weeks (Kimmerle & Eben, 1973). Daily administration by gavage of 1000 mg/kg bw trichloroethylene to male B6C3F1 mice for 180 days did not induce the overall metabolism of trichloroethylene (Green & Prout, 1985).

Cytochrome P450 activity in mouse lung Clara cells was reduced following exposure to 100 ppm [537 mg/m^3] trichloroethylene for 6 h; the activities of glutathione *S*-transferases were unaffected. Studies with isolated mouse lung Clara cells showed oxidative metabolism of trichloroethylene, leading to accumulation of chloral in the cells, which were presumably unable to metabolize chloral further to trichloroethanol, as occurs in the liver (Odum *et al.*, 1992).

The metabolism of trichloroethylene in liver microsomes from mice and rats has been studied by determining changes in trichloroethylene concentrations in the headspace of incubation vials containing liver subfractions. The apparent Michaelis-Menten constant (K_m) and the maximal metabolic velocity (V_{max}) in microsomal fractions were 4.2 μmol/L and 8.0 mmol/mg protein per 10 min, respectively, for substrate concentrations of 0.3–34 μmol/L (Kim *et al.*, 1994). Chloral hydrate was found consistently as an end-product of trichloroethylene biotransformation. The formation of chloral hydrate and the cofactor requirements suggest that a cytochrome P450 (probably 2E1) catalyses the formation of chloral hydrate from trichloroethylene (Byington & Leibman, 1965; Leibman & McAllister, 1967; Leibman, 1968; Costa *et al.*, 1980; Guengerich *et al.*, 1991). Other cytochrome P450 enzymes may also catalyse the oxidation of trichloroethylene but have a lower affinity (Nakajima *et al.*, 1990, 1992).

An epoxide (1,2,2-trichlorooxirane) was postulated as an intermediate during the oxidation of trichloroethylene to chloral hydrate (Bonse *et al.*, 1975; Greim *et al.*, 1975; Bonse & Henschler, 1976; Henschler, 1977; Henschler & Bonse, 1977; Hathway, 1980); however, later studies on the biotransformation of trichloroethylene and other chlorinated olefins and knowledge of the mechanisms of oxidation by cytochrome P450 enzymes suggest a stepwise oxidation of trichloroethylene to chloral hydrate, in which the epoxide is not an obligatory intermediate (Miller & Guengerich, 1982; Liebler & Guengerich, 1983; Miller & Guengerich, 1983). Mouse liver microsomes had a threefold higher capacity for the oxidative biotransformation of trichloroethylene than rat liver microsomes (Miller & Guengerich, 1982).

Incubation of trichloroethylene with liver microsomes and liver cytosol from rats in the absence of cofactors for oxidative biotransformation by cytochrome P450 and in the presence of glutathione resulted in the formation of *S*-(1,2-dichlorovinyl)glutathione at low rates (Dekant *et al.*, 1990).

4.1.3 Comparison of humans and animals

A quantitative comparison of the metabolism of trichloroethylene in humans and rats and mice by application of physiologically based pharmacokinetic models suggests that humans have a lower rate of metabolism (14.9 mg/kg bw per h) than B6C3F1 mice (23.2 mg/kg bw per h in females and 32.7 mg/kg bw per h in males) but a slightly higher rate than Fischer 344 rats (11 mg/kg bw per h) (Allen & Fisher, 1993). In the absence of comparative studies, the role of saturable metabolism in humans cannot be assessed; however, in the occupationally and environmentally relevant range of exposures, the metabolism of trichloroethylene after exposure by inhalation seems to be similar in humans and rats. Qualitatively, the pathways of biotransformation in humans and animals are identical, and most metabolites identified in experimental animals have also been found in humans; however, whereas the urinary excretion of trichloroacetic acid remains constant in rats exposed repeatedly to trichloroethylene, the quantity increases steadily in humans over five days. The opposite trend is observed for trichloroethanol, the urinary excretion increasing in rats and remaining constant in humans. The kinetics of the biotransformation of trichloroethylene to trichloroacetic acid in isolated hepatocytes was markedly species dependent: The V_{max}/K_m values ('intrinsic clearance') in mouse, rat and human hepatocytes were 3.8×10^{-6}, 1.2×10^{-7} and 3.25×10^{-8} L/min per 10^6 cells, respectively (Elcombe, 1985).

4.2 Toxic effects

4.2.1 Humans

The acute toxicity of trichloroethylene in humans is characterized mainly by depression of the central nervous system: In 288 cases of acute intoxication with trichloroethylene, effects on the central nervous system were the major toxic manifestations. Liver toxicity was seen in only five individuals, and there was no renal damage (McCarthy & Jones, 1983).

Chronic exposure to trichloroethylene has been reported to be hepatotoxic, and trichloroethylene has also been implicated in the so-called 'psycho-organic syndrome' (McCarthy & Jones, 1983). There was no direct evidence for renal toxicity in humans exposed chronically to low levels of trichloroethylene (50 mg/m^3) (Seldén *et al.*, 1993).

4.2.2 Experimental systems

The oral LD_{50} values for trichloroethylene are 7183 mg/kg bw in rats (Smyth *et al.*, 1969) and 2400–2850 mg/kg bw in mice (Aviado *et al.*, 1976; Tucker *et al.*, 1982). The LC_{50} in rats was 26 300 ppm [136 760 mg/m^3] for a 1-h exposure (Vernot *et al.*, 1977) and 12 500 ppm [65 000 mg/m^3] for a 4 h-exposure (Siegel *et al.*, 1971).

The major toxic effects in animals are depression of central nervous function and sensitization of cardiac function to adrenalin. After acute exposure of Fischer 344 rats to high doses

of trichloroethylene, liver damage was observed, characterized by increased activities of serum glutamic–oxaloacetic acid and glutamic–pyruvic transaminases. Administration of high doses of trichloroethylene after pretreatment with phenobarbital also induced renal damage (Chakrabarti & Tuchweber, 1988). High oral doses of trichloroethylene (> 2000 mg/kg bw) damaged Clara cells in mouse lung (Scott *et al.*, 1988; Forkert & Birch, 1989), and dose-dependent damage to mouse Clara cells was observed after single exposures to 200–1000 ppm [1040–5200 mg/m^3] by inhalation for 6 h; no effect was seen at 20 ppm [104 mg/m^3]. The effect seems to be species-specific, since inhalation of 1000 ppm [5200 mg/m^3] trichloroethylene for 6 h had no toxic effects on the rat lung (Odum *et al.*, 1992).

In male Sprague-Dawley rats injected once intraperitoneally with trichloroethylene at 1 mmol/kg bw [131 mg/kg bw], the activities of serum bile acids, particularly cholic and taurocholic acids, were increased 4 and 8 h after dosing. These times reflect those at which high levels of trichloroethylene and trichloroethanol appear in serum and liver. The selected dose did not induce hepatotoxic effects, and it was suggested that the changes in bile acid activity were due to perturbation of a physiological process (Bai & Stacey, 1993; Hamdan & Stacey, 1993).

Studies on the longer-term toxicity of trichloroethylene in rats and mice exposed orally and by inhalation showed consistent increases in relative liver weight and associated histopathological and biochemical changes. The effects described in kidney included increased relative weights in mice exposed continuously to > 75 ppm (> 390 mg/m^3) trichloroethylene for 30 days and renal dysfunction in the absence of marked histopathological changes in rats exposed to > 50 ppm [> 260 mg/m^3] for 12 weeks (Kjellstrand *et al.*, 1981a,b; Stott *et al.*, 1982; Tucker *et al.*, 1982; Kjellstrand *et al.*, 1983a,b; Elcombe *et al.*, 1985; Nomiyama *et al.*, 1986).

Oral administration of 500–1500 mg/kg bw trichloroethylene for 10 consecutive days increased the weight of the liver and the synthesis of DNA and decreased hepatic DNA concentrations in B6C3F1 and Alderley Park mice (Elcombe *et al.*, 1985). Increased hepatic DNA synthesis and mitosis, but no unscheduled DNA synthesis (see section 4.4.2), have been reported in mice dosed with trichloroethylene by gavage or inhalation (Stott *et al.*, 1982; Dees & Travis, 1993).

Trichloroethylene has been shown to induce hepatic peroxisome proliferation in mice, causing substantial increases in cyanide-insensitive palmitoyl coenzyme-A oxidase activity and peroxisomal volume density. The minimal daily dose of trichloroethylene reported to induce this effect in mice is 100 mg/kg bw over 10 days (Elcombe, 1985). Increased hepatic cyanide-insensitive palmitoyl coenzyme A oxidase activity has been reported in Fischer 344 rats treated by gavage with much higher doses of trichloroethylene (1200 mg/kg bw for 14 days, 130%; 1000 mg/kg bw for 10 days, 180% increase) (Goldsworthy & Popp, 1987; Melnick *et al.*, 1987). Increases of 786% and 625% in the activity of this enzyme were reported in B6C3F1 mice treated with 1000 mg/kg bw per day for 10 days (Elcombe *et al.*, 1985; Goldsworthy & Popp, 1987).

Trichloroethylene has been shown to induce a small increase in cyanide-insensitive palmitoyl coenzyme A oxidation activity in the kidneys of both mice and rats after oral dosing with 1000 mg/kg bw per day for 10 days. Greater effects were observed in mice than in rats (Goldsworthy & Popp, 1987).

Two metabolites of trichloroethylene, dichloroacetic acid and trichloroacetic acid (see monographs, this volume), have also been shown to induce peroxisome proliferation in mice and rats (Elcombe, 1985; Goldsworthy & Popp, 1987; DeAngelo *et al.*, 1989). Trichloroacetic acid induced peroxisome proliferation in the kidney of mice, but not rats (Goldsworthy & Popp, 1987).

Trichloroethylene has been reported to inhibit the activity of the natural immune system (natural killer, natural cytotoxic and natural P815 killer cells) in Sprague-Dawley rats and B6C3F1 mice (Wright *et al.*, 1991). The inhibition was particularly evident in the liver after administration *in vivo* and in both liver and spleen after exposure *in vitro*. The background activities of natural immune activities had previously been reported to be higher in species and strains with lower background incidences of liver tumours (Wright & Stacey, 1991). More recently, trichloroethylene has been shown to inhibit aspects of the natural immune system in cells isolated from human liver (Wright *et al.*, 1994). Inhibition of natural immunity may therefore enhance the likelihood of tumour development.

Nuclear magnetic resonance was used to show that trichloroethylene interacts non-specifically with lipid molecules and that, in phosphatidylcholine bilayers, interaction occurs predominantly with the interfacial region rather than the hydrocarbon interior (Bhakuni & Roy, 1994).

4.3 Reproductive and prenatal effects

4.3.1 Humans

(a) Endocrine and gonadal effects

Out of a group of 99 metal workers in Aarhus (Denmark), 15 men who degreased parts with trichloroethylene for more than 20 h per week were asked to deliver a semen specimen (Rasmussen *et al.*, 1988). Twelve were included in the analysis and compared with 14 un-exposed physicians. There was no difference between the two groups in terms of sperm count or morphology, but the exposed group had a small, non-significant increase in the prevalence of mature spermatozoa containing two fluorescent Y bodies, which may indicate Y-chromosomal nondisjunction.

(b) Fertility

Taskinen *et al.* (1989) conducted a nested case–control study of 120 cases of spontaneous abortion and 251 controls on the basis of a file of 6000 Finnish workers who had been biologically monitored for exposure to solvents. Information about their marriages and their wives' pregnancies and spontaneous abortions were obtained from national registries; data on paternal occupational exposure to solvents were collected by means of a questionnaire sent to workers and covered the period of spermatogenesis. The likelihood of exposure was defined in three categories: unexposed, potentially exposed (i.e. use of solvents was possible but no exposure was reported or measured) and probably exposed (i.e. exposure was measured or reported). No association was found between paternal occupational exposure to trichloroethylene and spontaneous abortion (crude odds ratio, 1.0; 95% CI, 0.6–2.0).

(c) Pregnancy

Pregnancies occurring among 3265 women biologically monitored for exposure to solvents in 1965–83 were identified from a Finnish database (Lindbohm *et al.*, 1990). Only one pregnancy per woman was included, resulting in a total of 120 cases of spontaneous abortion; 336 age-matched controls were randomly selected among women who had only normal births during the study period. Data on workplace, occupational exposure, medical history, alcohol and smoking habits were obtained from a postal questionnaire, to which 85.5% of subjects responded. For each potential exposure, women were classified, without knowledge of their case or control status, into one of three categories: unexposed, potentially exposed (i.e. work tasks might have involved use of solvents, but exposure was not reported or measured) or exposed (i.e. exposure was measured or reported). The analysis addressed 73 women who had had a spontaneous abortion and 167 controls who reported a pregnancy of interest and detailed information on occupational exposures during pregnancy. The odds ratio for spontaneous abortion, adjusted for previous spontaneous abortions, parity, smoking, use of alcohol and exposure to other solvents, was 0.6 (95% CI, 0.2–2.3) for exposure to trichloroethylene.

The 852 women for whom a spontaneous abortion was certified in one of the 11 hospital laboratories in Santa Clara County, CA (United States) were compared with 1618 controls randomly selected among County residents who had had a live birth and frequency matched by date of last menstrual period and hospital (Windham *et al.*, 1991). All participants were contacted by telephone and asked about occupational use of 18 solvents or products during the first 20 weeks of pregnancy. An excess risk for spontaneous abortion was observed for those women who reported exposure to trichloroethylene (crude odds ratio, 3.1; 95% CI, 0.92–10.4) [adjusted odds ratio not calculated]; four of the seven women who reported exposure to trichloroethylene had also used tetrachloroethylene. The odds ratio increased for women who reported more 'intense' exposure, primarily on the basis of detection of odour (odds ratio, 3.9; $p = 0.04$). Odds ratios adjusted for maternal age, race, education, prior fetal loss, smoking, average number of hours worked and quality of response were nonsignificant when the whole group of halogenated solvents was considered (odds ratio for any use, 1.0; 95% CI, 0.65–1.6; odds ratio for use > 10 h per week, 1.5, 95%CI, 0.73–3.0).

Information on 7316 pregnancies was obtained from the hospital discharge register for 9186 women identified as working in Finnish laboratories (Taskinen *et al.*, 1994).The pregnancies resulted in 5663 births, 687 spontaneous abortions and 966 induced abortions, and a case–referent study was conducted within the cohort. Questionnaires were posted requesting confirmation of the study pregnancy and data on exposures; the response rate was 78%. The 206 women with only one registered spontaneous abortion and 329 controls randomly selected among women who had given birth to a normal infant were included in the analysis of spontaneous abortion. The analysis of congenital malformations involved 36 cases and 105 referents. Seven women who had had a spontaneous abortion and nine controls reported exposure to trichloroethylene, giving an odds ratio of 1.6 (95% CI, 0.5–4.8), adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control and febrile disease during pregnancy. The odds ratios associated with exposure to halogenated solvents as a group were 0.6 (0.4–1.1) for exposure on one to two days per week and 1.8 (0.9–3.7) for exposure on three to five days per week. The odds ratio for congenital malformations

associated with exposure to halogenated solvents was 0.8 (0.2–2.5), adjusted for alcohol consumption, parity, previous miscarriages and failed birth control.

In 1981, the groundwater in a small area in the southwestern part of the city of Tucson, Arizona (United States), was found to be contaminated with trichloroethylene and, to a lesser extent, with dichloroethylene and chromium (Goldberg *et al.*, 1990). The parents of 707 children with congenital heart disease who had conceived their child and spent the beginning of the pregnancy (one month before and the first trimester) in the Tucson valley between 1969 and 1987 were interviewed. The prevalence of congenital heart disease among children born to mothers who had been exposed (0.68%) was higher than that of mothers who lived outside the area (0.26%; $p < 0.001$). The ratio decreased to near unity for new arrivals in the contaminated area after closure of the well.

4.3.2 Experimental systems

Trichloroethylene and its metabolites appear to cross the placenta readily in many species (Helliwell & Hutton, 1949, 1950; Lanham, 1970; Withey & Karpinski, 1985; Ghantous *et al.*, 1986). In mice, inhalation of trichloroethylene resulted in accumulation of its metabolite, trichloroacetic acid (see also Land *et al.*, 1981), in amniotic fluid (Ghantous *et al.*, 1986).

A significant increase in the percentage of abnormal spermatozoa was observed in mice exposed to 0.2% trichloroethylene for 4 h per day for five days over that in controls and in mice exposed to 0.02% trichloroethylene (Land *et al.*, 1981). No sperm toxicity was induced in male Long-Evans rats exposed by gavage to up to 1000 mg/kg bw, trichloroethylene on five days per week for six weeks (Zenick *et al.*, 1984). Mating of untreated female NMRI mice with male mice that had been exposed to up to 450 ppm [2417 mg/m^3] trichloroethylene by inhalation for 24 h did not influence fertilization or pre- or post-implantation rates and did not induce dominant lethal mutation (Slacik-Erben *et al.*, 1980). No modification of mating performance or female fertility was observed in groups of female Long-Evans rats exposed to trichloroethylene by gavage for two weeks before mating at doses up to 1000 mg/kg bw, which was a toxic dose (Manson *et al.*, 1984). Administration of trichloroethylene in the diet of mice and rats at concentrations equivalent to doses of up to 300 mg/kg bw per day for two generations resulted in marginal effects on testicular weight and on survival of pups of both the F_1 and F_2 generations at the highest dose. No other signs of reproductive toxicity were observed (United States National Toxicology Program, 1985, 1986).

Female Long-Evans rats were exposed by inhalation to 1800 ± 200 ppm [9666 ± 1074 mg/m^3] trichloroethylene for two weeks before and/or during gestation. Post-natal body weight was decreased in the offspring of mothers that had been exposed before gestation. Significant increases in the incidence of skeletal and soft-tissue anomalies, indicative of developmental delay in maturation rather than teratogenesis, were observed in the group exposed during pregnancy alone (Dorfmueller *et al.*, 1979). A significant increase in the incidence of cardiac malformations was reported in newborn Sprague-Dawley rats after maternal exposure to trichloroethylene in drinking-water (1.5 or 1100 ppm [mg/L]) for seven days before and throughout gestation. [The actual dose could not be calculated from the available data.] No signs of maternal toxicity or other signs of fetal toxicity were observed (Dawson *et al.*, 1993). No increase in the frequency of birth defects has been reported in most other studies of rat or mouse dams exposed

by various routes to various concentrations of trichloroethylene, except for a predictable impairment of fetal growth associated with maternally toxic doses (Schwetz *et al.*, 1975; Leong *et al.*, 1975; Healy & Wilcox, 1978; Hardin *et al.*, 1981; Cosby & Dukelow, 1992).

The male offspring of female rats exposed to trichloroethylene in the drinking-water at up to 1250 mg/L before and during gestation and postpartum up to day 21 had enhanced locomotor activity and exploratory behaviour (Taylor *et al.*, 1985). Impairment of myelinization of the central nervous system and decreased glucose uptake by whole brain and cerebellum were observed in the offspring of rats exposed to 312 or 625 mg/L trichloroethylene in the drinking-water before and during gestation and postpartum (Noland-Gerbee *et al.*, 1986; Isaacson & Taylor, 1989). The specific gravity of brain tissue was reduced in the offspring of mice exposed to 150 ppm [806 mg/m^3] trichloroethylene by inhalation four weeks before and during gestation (Westergren *et al.*, 1984).

4.4 Genetic and related effects

4.4.1 Humans

Cytogenetic damage in lymphocytes: In a study of 28 male degreasers exposed to trichloroethylene, nine were reported to have > 13% hypodiploid cells in cultured peripheral lymphocytes (Konietzko *et al.*, 1978). These men had been exposed to a higher mean maximal concentration of trichloroethylene (206 ppm [1106 mg/m^3]) than those considered to have normal rates of hypodiploidy (116 ppm [623 mg/m^3]). A correlation ($r = 0.46$; $p < 0.05$) was also seen between the hypodiploidy rate and the average daily or average maximal exposure to trichloroethylene. The mean rate of hypodiploid cells was 10.9% (SD, 4.5; $n = 27$, excluding one man with karyotype 47, XY, +mar), in comparison with 6.5% (SD, 3.2) among 10 male controls. The exposed workers also had a fivefold higher mean rate of chromosomal breaks per 100 mitoses (3.1; SD, 3.7; $n = 27$) than the controls (0.6; SD, 0.7; $n = 10$), but these data were not commented upon. The effects of age and cigarette smoking could not be judged from the report. [The Working Group noted that the hypodiploidy rate among controls was very high.]

In a study of 22 workers who had constantly used trichloroethylene in their [unspecified] jobs for an average of 9.7 years (range, 0.7–34) and 22 controls matched for age, sex and smoking habits, no increase in the frequency of sister chromatid exchange was seen in peripheral lymphocyte (Nagaya *et al.*, 1989). Spot urine samples collected at the same time as the blood samples from the exposed workers showed a concentration of 19.1–1066.4 mg/L (mean, 183.6 mg/L) total trichloro compounds. Smoking increased the frequency of sister chromatid exchange.

A group of 15 workers involved in metal degreasing with trichloroethylene for more than 20 h per week in a half-open vapour plant had a significantly greater frequency of chromosomal aberrations, excluding gaps and hyperdiploid cells, in cultured lymphocytes than 669 controls; seven of the degreasers were also painters. The mean urinary concentration of trichloroacetate was fairly low: 3.7 mg/L (range, 0.02–26.9), and the mean number of cumulative working years was 4.6 (range, 0.8–22.0) (Rasmussen *et al.*, 1988). The effects of smoking and age could not be judged from the paper. The authors considered the reference group 'not ideal' but reported that the distribution of confounding factors was no different from that in the average population.

Sperm counts and the frequencies of abnormal sperm heads and of sperm with two fluorescent Y bodies were not significantly different in the 12 workers and 14 controls from whom semen samples containing sperm were taken.

Sister chromatid exchange was analysed in 22 male and 16 female workers in trichloroethylene synthesis and degreasing and in 26 control male and 25 female subjects who worked filling tanks with hydrogen, nitrogen and oxygen or as lathe operators (Seiji *et al.*, 1990). No effect of the occupational exposure was seen among nonsmokers, but the eight exposed smokers (all males) had a significantly higher mean frequency of sister chromatid exchange per cell (7.06) than seven male smoking controls (5.10). Sister chromatid exchange was also studied in nine male and 10 female tetrachloroethylene synthesis workers who had been exposed to an 8-h time-weighted geometric mean concentration of 8 ppm [43.0 mg/m^3] trichloroethylene (75th percentile, 49 ppm [263 mg/m^3]; maximum, 521 ppm [2798 mg/m^3]) and 17 ppm [115 mg/m^3] tetrachloroethylene (75th percentile, 28 ppm [190 mg/m^3]; maximum, 567 ppm [3844 mg/m^3]). They were compared with a control group of nine men and nine women and an extended control group consisting of 21 men and 23 women. Occupational exposure was reported to have affected the frequency of sister chromatid exchange in exposed male smokers, on the basis of a comparison of the frequency in these five men (7.33) with that in six nonsmoking male controls in the small (5.72; $p < 0.05$) and nine controls in the extended (5.48; $p < 0.01$) groups; the mean frequency of sister chromatid exchange in exposed male smokers was also higher than that in the 12 male smokers in the extended control group (5.7). No significant differences were reported between exposed and unexposed smokers. [Comparison of exposed smokers and unexposed nonsmokers may not be justified, especially as smoking usually induces sister chromatid exchange, although in this study such an effect could not be shown.]

4.4.2 *Experimental systems* (see also Tables 12 and 13 and Appendices 1 and 2)

The genetic toxicology of trichloroethylene has been reviewed (Baden & Simmon, 1980; Fabricant & Chalmers, 1980; Vainio *et al.*, 1985; Crebelli & Carere, 1989; Candura & Faustman, 1991; Jackson *et al.*, 1993; European Centre for Ecotoxicology and Toxicology of Chemicals, 1994). The mechanisms of the possible genotoxicity of trichloroethylene were discussed by Henschler (1987).

(a) DNA binding

Trichloroethylene was reported to bind to DNA *in vitro* after metabolic activation; the binding was enhanced by the addition of glutathione and reduced by addition of SKF-525-A, an inhibitor of mixed-function oxidases. High-performance liquid chromatography indicated a possible DNA adduct, which could not be identified (Mazzullo *et al.*, 1992). DNA binding could not be demonstrated *in vivo* in several tissues of mice in one study (Bergman, 1983b) or in the liver of rats in another study (Parchman & Magee, 1982); however, the latter authors noted incorporation of label into normal nucleosides. A low level of covalent interaction was reported with the DNA of rat and mouse liver, kidney, lungs and stomach (estimated at 0.15 adducts per 10^6 nucleotides; Mazzullo *et al.*, 1992) and of mouse liver (maximum, 0.62 alkylations per 10^6 nucleotides; Stott *et al.*, 1982).

Table 12. Genetic and related effects of trichloroethylene without mutagenic stabilizers

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	–	–	7325[c]	Mersch-Sundermann *et al.* (1989)
SAF, *Salmonella typhimurium* BAL13, forward mutation (*ara* test)	–	–	190	Roldán-Arjona *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	160 vapour[c]	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	160 vapour[c]	Baden *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	420 (8% vapour) 16h	Bartsch *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	18 vapour	Crebelli *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	260 vapour[d]	Shimada *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167[c]	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	1050 vapour	McGregor *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	526 vapour[c]	Baden *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	0	50[c]	Kringstad *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	–	50 vapour[d]	Shimada *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167[c]	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167[c]	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167[c]	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	1050 vapour	McGregor *et al.* (1989)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	+	2600	Bronzetti *et al.* (1978)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	+	1300	Bronzetti *et al.* (1978)
ANG, *Aspergillus nidulans*, diploid *yA2/+* strain 35x17, quiescent conidia, mitotic crossing-over	–	0	3660	Crebelli *et al.* (1985)
ANG, *Aspergillus nidulans*, diploid *yA2/+* strain 35x17, growth-mediated assay, mitotic crossing-over	–	0	90 vapour	Crebelli *et al.* (1985)
SZF, *Schizosaccharomyces pombe* P1, stationary phase, forward mutation	–	–	3280	Rossi *et al.* (1983)
SZF, *Schizosaccharomyces pombe* P1, growing cells, forward mutation	–	–	13 140	Rossi *et al.* (1983)
ANF, *Aspergillus nidulans*, haploid strain 35, quiescent conidia, forward mutation (methionine suppressor)	–	0	100 vapour	Crebelli *et al.* (1985)
ANF, *Aspergillus nidulans*, haploid strain 35, 'growth-mediated assay', forward mutation (methionine suppressor)	+	0	13 vapour	Crebelli *et al.* (1985)

Table 12 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ANN, *Aspergillus nidulans*, diploid *yA2/+* strain 35×17, quiescent conidia, nondisjunctional diploids	–	0	3660	Crebelli *et al.* (1985)
ANN, *Aspergillus nidulans*, diploid *yA2/+* strain 35×17, quiescent conidia, haploids	–	0	3660	Crebelli *et al.* (1985)
ANN, *Aspergillus nidulans*, diploid *yA2/+* strain 35×17, 'growth-mediated assay', nondisjunctional diploids	+	0	40 vapour	Crebelli *et al.* (1985)
ANN, *Aspergillus nidulans*, diploid *yA2/+* strain 35×17, 'growth-mediated assay', haploids	+	0	90 vapour	Crebelli *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–		2500[c] injection	Foureman *et al.* (1994)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	?		5000 feeding[c]	Foureman *et al.* (1994)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	130 vapour[d]	Shimada *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	+	146[e]	Caspary *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	(+)	(+)	401[c]	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	–	–	14 900[c]	Galloway *et al.* (1987)
TRR, Cell transformation, RLV/Fischer rat F1706 embryo cells *in vitro*	+	0	144	Price *et al.* (1978)
GIH, Gene mutation, human lymphoblastoid TK6 cells *in vitro*	–	–	600	Caspary *et al.* (1988)
ICR, Inhibition of intercellular communication, B6C3F1 mouse hepatocytes *in vitro*	+	0	1.3	Klaunig *et al.* (1989)
ICR, Inhibition of intercellular communication, F344 rat hepatocytes *in vitro*	–	0	13	Klaunig *et al.* (1989)
HMM, Host-mediated assay, gene conversion in *Saccharomyces cerevisiae* D4 recovered from CD-1 mouse liver, lungs and kidneys	+		400 po × 1[f]	Bronzetti *et al.* (1978)
HMM, Host-mediated assay, gene conversion in *Saccharomyces cerevisiae* D7 recovered from CD-1 mouse liver and kidneys	+		400 po × 1	Bronzetti *et al.* (1978)
HMM, Host-mediated assay, gene conversion in *Saccharomyces cerevisiae* D7 recovered from CD-1 mouse lungs	–		400 po × 1	Bronzetti *et al.* (1978)
HMM, Host-mediated assay, reverse mutation in *Saccharomyces cerevisiae* D7 from CD-1 mouse liver, lungs and kidneys	+		400 po × 1	Bronzetti *et al.* (1978)
HMM, Host-mediated assay, forward mutation in *Schizosaccharomyces pombe* P1, CD-1 × C57Bl hybrid mouse	–		2000 iv or ip × 1	Rossi *et al.* (1983)
DVA, DNA single-strand breaks, mouse liver *in vivo*	–		2000 ip × 1	Parchman & Magee (1982)
DVA, DNA single-strand breaks (alkaline unwinding) in liver and kidney of male NMRI mice *in vivo*	+[f]		790 ip × 1	Walles (1986)

Table 12 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DVA, DNA single-strand breaks (alkaline unwinding), mouse liver *in vivo*	+		1500 po × 1[c]	Nelson & Bull (1988)
DVA, DNA single-strand breaks (alkaline unwinding), rat liver *in vivo*	+		3000 po × 1[c]	Nelson & Bull (1988)
MST, Mouse spot test *in vivo*	–		350 ip × 1	Fahrig (1977)
UVM, Unscheduled DNA synthesis, CD-1 mouse primary hepatocytes *in vivo*	–		1000 po × 1	Doolittle *et al.* (1987)
MVM, Micronucleus induction, mouse bone-marrow erythrocytes *in vivo*	+		750 po × 2	Duprat & Gradiski (1980)
MVM, Micronucleus induction, B6C3F1 mouse bone-marrow erythrocytes *in vivo*	–		2500 ip × 3[c]	Shelby *et al.* (1993)
MVM, Micronucleus induction, mouse spermatocytes *in vivo* (spermatids examined) *in vivo*	–		565 inh 6 h/d × 5	Allen *et al.* (1994)
MVM, Micronucleus induction, mouse splenocytes *in vivo*	–		9800 inh 6 h	Kligerman *et al.* (1994)
MVR, Micronucleus induction, rat bone-marrow erythrocytes *in vivo*	+		5 inh 6 h	Kligerman *et al.* (1994)
MVR, Micronucleus induction, rat bone-marrow erythrocytes *in vivo*	–		960 inh 6 h × 4	Kligerman *et al.* (1994)
MVR, Micronucleus induction, rat peripheral lymphocytes *in vivo*	–		8800 inh 6 h	Kligerman *et al.* (1994)
MVR, Micronucleus induction, rat peripheral lymphocytes *in vivo*	–		960 inh 6 h × 4	Kligerman *et al.* (1994)
SVA, Sister chromatid exchange, rat peripheral lymphocytes *in vivo*	–		8800 inh 6 h	Kligerman *et al.* (1994)
SVA, Sister chromatid exchange, rat peripheral lymphocytes *in vivo*	–		960 inh 6 h × 4	Kligerman *et al.* (1994)
SVA, Sister chromatid exchange, mouse splenocytes *in vivo*	–		9800 inh 6 h	Kligerman *et al.* (1994)
CLA, Chromosomal aberrations, rat peripheral lymphcytes *in vivo*	–		8800 inh 6 h	Kligerman *et al.* (1994)
CLA, Chromosomal aberrations, rat peripheral lymphcytes *in vivo*	–		960 inh 6 h × 4	Kligerman *et al.* (1994)
CVA, Chromosomal aberrations, mouse splenocytes *in vivo*	–		9800 inh 6 h	Kligerman *et al.* (1994)
DLM, Dominant lethal mutation, male NMRI-Han/BGA mice *in vivo*	–		3400 inh 24 h[c]	Slacik-Erben *et al.* (1980)
BID, Binding (covalent) to salmon sperm DNA *in vitro*	–	+	270	Banerjee & Van Duuren (1978)
BID, Binding (covalent) to calf thymus DNA *in vitro*	–	+	340[c]	Bergman (1983b)
BID, Binding (covalent) to calf thymus DNA *in vitro*	0	+	13	Miller & Guengerich (1983)
BID, Binding (covalent) to DNA of isolated rat hepatocytes *in vitro*	+	0	13	Miller & Guengerich (1983)
BID, Binding (covalent) to DNA of isolated mouse hepatocytes *in vitro*	+	0	13	Miller & Guengerich (1983)
BID, Binding (covalent) to calf thymus DNA *in vitro*	0	+	131	DiRenzo *et al.* (1982)
BVP, Binding (covalent) to RNA of NMRI mouse spleen, lung, liver, kidney, pancreas, testis and brain *in vivo*	–[g]		67 ip × 5[c]	Bergman (1983b)

Table 12 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Binding (covalent) to DNA of NMRI mouse spleen, pancreas, lung, testis, kidney and brain *in vivo*	–[k]		67 ip × 5	Bergman (1983b)
BVD, Binding (covalent) to DNA of NMRI mouse liver *in vivo*	?		67 ip × 5	Bergman (1983b)
BVD, Binding (covalent) to DNA of B6C3F1 mouse liver *in vivo*	?		1200 po × 1	Stott *et al.* (1982)
BVD, Binding (covalent) to DNA of B6C3F1 mouse liver *in vivo*	?		250 ip × 1	Parchman & Magee (1982)
BVD, Binding (covalent) to DNA of rat liver *in vivo*	?		1000 ip × 1	Parchman & Magee (1982)
Dichloroacetyl chloride				
PRB, λ Prophage induction, *Escherichia coli* WP2	–	–	10 000	DeMarini *et al.* (1994)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	3	DeMarini *et al.* (1994)

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

[b] LED, lowest effective dose; HID, highest effective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; ip, intraperitoneally; po, orally

[c] 99% purity or greater

[d] 0.001% stabilizers

[e] Also positive by gavage at 150 mg/kg for 5 days a week, 22 times with 400 mg/kg on the last day

[f] No DNA strand breaks in lungs of mice treated with 1300 mg/kg ip × 1

[k] Metabolic incoporation of ^{14}C into nucleotides was observed.

Table 13. Genetic and related effects of trichloroethylene containing mutagenic stabilizers or for which information on purity was not sufficiently clear

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	–	–	0.00	von der Hude *et al.* (1988)
***, Mutatox assay, derepression of luminescence operon, *Photobacterium phosphorium*	–	0	0.00	Elmore & Fitzgerald (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	14 650	Henschler *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	525 vapour	Waskell (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	260 vapour[c]	Shimada *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.00	Milman *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	130 vapour	McGregor *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	50 vapour[c]	Shimada *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.00	Milman *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	33 vapour	McGregor *et al.* (1989)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	525 vapour	Waskell (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.00	Milman *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	65 vapour	McGregor *et al.* (1989)
ECK, *Escherichia coli* K12, forward mutation	–	–	434	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*arg*$^+$)	–	+	434	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*gal*$^+$)	–	–	434	Greim *et al.* (1975)
ECK, *Escherichia coli* K12, reverse mutation (*nad*$^+$)	–	–	434	Greim *et al.* (1975)
SCG, *Saccharomyces cerevisiae* D7, log-phase cultures, gene conversion	0	+	1970	Callen *et al.* (1980)
SCG, *Saccharomyces cerevisiae* D7, log-phase and stationary cultures, gene conversion	–	–	2900	Koch *et al.* (1988)
SCG, *Saccharomyces cerevisiae* XV185-14C, reverse mutation (*lys*1-1, *his*1-7, *hom*3-10)	0	+	1460	Shahin & Von Borstel (1977)
SCR, *Saccharomyces cerevisiae* D7, log-phase cultures, reverse mutation	0	+	1970	Callen *et al.* (1980)
SCH, *Saccharomyces cerevisiae* D7, log-phase cultures, mitotic recombinants or otherwise genetically altered colonies (*ade*2)	0	+	1970	Callen *et al.* (1980)

Table 13 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCR, *Saccharomyces cerevisiae* D7, log-phase and stationary cultures, reverse mutation	–	(+)	2900	Koch *et al.* (1988)
SZF, *Schizosaccharomyces pombe* P1, stationary phase, forward mutation	–	–	3280	Rossi *et al.* (1983)
SZF, *Schizosaccharomyces pombe* P1, growing cells, forward mutation	–	–	13 140	Rossi *et al.* (1983)
SCN, *Saccharomyces cerevisiae* D61.M, growing cells, aneuploidy	0	+	725	Koch *et al.* (1988)
TSM, *Tradescantia* species, mutation	+	0	0.0003	Schairer & Sautkulis (1982)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	130 vapour	Shimada *et al.* (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	0.00	Milman *et al.* (1988)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	0	1445	Williams *et al.* (1989)
UIA, Unscheduled DNA synthesis, B6C3F1 mouse primary hepatocytes *in vitro*	+	0	0.00	Milman *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	0	–	9	White *et al.* (1979)
CIC, Chromosomal aberrations, Chinese hamster lung (CHL) cells *in vitro*	–	–	1000	Sofuni *et al.* (1985)
TBM, BALB/c–3T3 mouse cells, cell transformation *in vitro*	(+)	0	250	Tu *et al.* (1985)
TFS, Syrian hamster embryo cells, morphological transformation *in vitro*	(+)	0	25	Amacher & Zelljadt (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	(+)	0	178	Gu *et al.* (1981)
HMM, Host-mediated assay, forward mutation in *Schizosaccharomyces pombe* P1 recovered from CD-1 mouse kidneys and lungs	–	0	2000 po × 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, forward mutation in *Schizosaccharomyces pombe* P1 recovered from CD-1 mouse liver	(+)	0	2000 po × 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, *Schizosaccharomyces pombe* P1, forward mutation, in CD-1 mouse peritoneum	(+)	0	1000 po × 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, *Schizosaccharomyces pombe* P1, forward mutation, in Spraque-Dawley rat peritoneum	–	0	1000 po × 1	Loprieno & Abbondandolo (1980)
HMM, Host-mediated assay, forward mutation in *Schizosaccharomyces pombe* P1, CD-1 × 7BL hybrid mouse	–	0	2000 iv or ip × 1	Rossi *et al.* (1983)
UPR, Unscheduled DNA synthesis, Fischer-344 male rat hepatocytes *in vivo*	–		1000 po × 1	Mirsalis *et al.* (1989)
UVM, Unscheduled DNA synthesis, male and female B6C3F1 mouse hepatocytes *in vivo*	–		1000 po × 1	Mirsalis *et al.* (1989)

Table 13 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CBA, Chromosomal aberrations, CD-1 mouse bone marrow cells *in vivo*	–		1000 po × 1	Loprieno & Abbondandolo (1980)
CBA, Chromosomal aberrations, mouse bone marrow cells *in vivo*	–		1200 po × 1	Sbrana *et al.* (1985) (abstract)
CBA, Chromosomal aberrations, mouse bone marrow cells *in vivo*	–		795 inh 7 h × 50[c]	Sbrana *et al.* (1985) (abstract)
MVM, Micronucleus induction, mouse bone marrow erythrocytes *in vivo*	+		1200 po × 1	Sbrana *et al.* (1985) (abstract)
MVM, Micronucleus induction, mouse bone marrow erythrocytes *in vivo*	+		460 ip × 1	Hrelia *et al.* (1995)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	(+)		0.00	Gu *et al.* (1981)
BID, Binding (covalent) to calf thymus DNA *in vitro*	0	+	3.2	Mazzullo *et al.* (1992)
BVD, Binding (covalent to DNA of BALB/c mouse liver, kidney, lung and stomach *in vivo*	(+)		0.76 ip × 1	Mazzullo *et al.* (1992)
BVD, Binding (covalent) to DNA of Wistar rat liver, kidney, lung and stomach *in vivo*	(+)		0.76 ip × 1	Mazzullo *et al.* (1992)
***, Enzyme-altered foci in male Osborne-Mendel rat liver *in vivo*, promotion protocol, with and without NDEA as an initiator	–		1300 mg/kg, 5 d/week, 7 weeks	Milman *et al.* (1988)
***, Enzyme-altered foci in male Osborne-Mendel rat liver *in vivo*, initiation protocol, phenobarbital as promoter	–		1300 mg/kg	Milman *et al.* (1988)
***, S-Phase induction, male and female B6C3F1 mouse hepatocytes *in vivo*	+		200 mg/kg	Mirsalis *et al.* (1989)

NDEA, *N*-nitrosodiethylamine

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

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

[c]5 days/week, 10 weeks

***, Not included on profile

(b) Mutation and allied effects

The stabilizers often used in commercial preparations of trichloroethylene, such as epichlorohydrin and 1,2-epoxybutane, are mutagenic, rendering problematic the interpretation of positive results in assays for the mutagenicity of trichloroethylene *per se* (McGregor *et al.*, 1989). Humans are exposed mostly, if not exclusively, to preparations containing stabilizers.

Apart from two reports in which trichloroethylene weakly induced mutation in *Salmonella typhimurium* TA1535, purified trichloroethylene did not induce gene mutation in various strains of *Salmonella* in the absence of metabolic activation; however, trichloroethylene containing directly mutagenic epoxide stabilizers did. Purified trichloroethylene also did not usually induce mutation in *Salmonella* in the presence of exogenous metabolic activation systems, except in two tests with *S. typhimurium* TA100.

Trichloroethylene (pure or of unspecified purity) gave negative results in the SOS chromotest in *Escherichia coli* with and without metabolic activation and in the Mutatox assay in the absence of metabolic activation. In the presence of metabolic activation, analytical-grade trichloroethylene induced *arg*$^+$ reverse mutations, but not forward mutations or *gal*$^+$ or *nad*$^+$ reversions, in *E. coli*.

Trichloroethylene (pure or of unspecified purity) induced gene conversion in *Saccharomyces cerevisiae* in two of three studies and induced reverse mutation in all four studies available in the presence of a metabolic activation system. In a single study, pure trichloroethylene or trichloroethylene containing stabilizers did not induce forward mutation in *Schizosaccharomyces pombe*. Pure trichloroethylene induced forward mutation in one study of growing cultures of *Aspergillus nidulans*, which are capable of some metabolic activation reactions, whereas no such effect was seen in quiescent conidia. Trichloroethylene (of unspecified purity) induced aneuploidy in *S. cerevisiae* in the presence of growth-mediated metabolic activation, and the pure compound induced aneuploidy in *A. nidulans*. In a single study, trichloroethylene (of unspecified purity) induced gene mutation in *Tradescantia*. Pure trichloroethylene did not cause recessive lethal mutations in *Drosophila melanogaster* after injection, and equivocal results were obtained after feeding.

Unscheduled DNA synthesis *in vitro* was reported in four studies, one with mouse and three with rat hepatocytes. Positive results were obtained with trichloroethylene (of unspecified purity) in mouse cells and in one study of rat cells, while negative results were obtained in the other two studies of rat primary hepatocytes, in one of which trichloroethylene of high and of unspecified purity were compared. Pure trichloroethylene induced gene mutation in mouse lymphoma L5178Y cells in the presence of exogenous metabolic activation. In a single study, pure trichloroethylene weakly induced sister chromatid exchange in Chinese hamster cells *in vitro* with and without metabolic activation. Pure trichloroethylene did not increase the frequency of chromosomal aberrations in Chinese hamster cells *in vitro*. In three different assays, trichloroethylene (of unspecified purity) weakly induced cell transformation in mouse, Syrian hamster and (pure trichloroethylene) rat cells *in vitro*, without exogenous metabolic activation. Pure trichloroethylene inhibited intercellular communication in mouse hepatocytes but not in rat hepatocytes *in vitro*.

A 95% pure formulation weakly induced sister chromatid exchange in the absence of metabolic activation in one study. No induction of gene mutation was seen in human lymphoblastoid cells exposed to pure trichloroethylene.

In a host-mediated assay, gene conversion and reverse mutation were induced in *S. cerevisiae* recovered from the liver, lungs and kidneys of mice treated orally with pure trichloroethylene. Forward mutation was weakly induced by trichloroethylene of unspecified purity in *Schizosaccharomyces pombe* cells injected into the peritoneum of mice in one of two studies; no effect was seen in the only study available in rats. *S. pombe* cells recovered from mice after intravenous injection showed no forward mutation in one study; a positive result was seen in another study in mouse liver, but not in kidneys or lungs, after treatment with trichloroethylene of unspecified purity.

Pure trichloroethylene induced DNA single-strand breaks/alkaline-labile sites *in vivo* in mouse liver and kidney and in rat liver. Unscheduled DNA synthesis was not augmented in mouse or rat hepatocytes after treatment with trichloroethylene (pure or of unspecified purity) *in vivo*, and pure trichloroethylene did not induce a significant response in a mouse spot test. Trichloroethylene did not induce chromosomal aberrations in mouse bone marrow *in vivo*. Micronuclei were reported to be induced by trichloroethylene (pure or of unknown purity) in mouse bone-marrow polychromatic erythrocytes in two studies (one was reported in an abstract), while two other studies showed no such effect. A significant increase ($p = 0.028$) observed in one of the latter studies was considered to be due to an exceptionally low control value. Micronuclei were not induced in mouse spermatocytes. In a study in which mice and rats were exposed by inhalation to reagent-grade trichloroethylene (purity, > 99%), micronuclei were induced in the bone-marrow cells of rats but not of mice; neither micronuclei, chromosomal aberrations nor sister chromatid exchange were induced in the peripheral lymphocytes of rats or the splenocytes of mice (Kligerman *et al.*, 1994). In a single study, pure trichloroethylene did not induce dominant lethal mutation in mice. Trichloroethylene increased the frequency of S-phase in mouse hepatocytes *in vivo* but did not produce enzyme-altered foci in rat liver.

(c) Genetic effects of trichloroethylene metabolites

The genetic toxicology of dichloroacetic and trichloroacetic acids is reviewed in the relevant monographs in this volume. Dichloroacetyl chloride, a presumed metabolite of trichloroethylene, did not induce prophage in *E. coli*, but was weakly mutagenic in *S. typhimurium* TA100 in the absence of metabolic activation in one study.

The minor urinary metabolite, *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine, was mutagenic in *S. typhimurium* TA2638 in the presence of kidney cytosol, which allows deacetylation to the corresponding cysteine conjugate (Vamvakas *et al.*, 1987). The presumed intermediate metabolite, *S*-(1,2-dichlorovinyl)-L-cysteine, was mutagenic to *S. typhimurium* TA100 and TA2638 in the presence and absence of metabolic activation (Green & Odum, 1985; Dekant *et al.*, 1986c). *S*-(1,2-Dichlorovinyl)glutathione, the precursor of the cysteine conjugate, was also mutagenic to *S. typhimurium* TA2638 in the presence of rat kidney microsomes, which allow degradation to the cysteine conjugate (Vamvakas *et al.*, 1988). Both the cysteine and the glutathione conjugate induced a low rate of unscheduled DNA synthesis in a cultured pig kidney cell line (Vamvakas *et al.*, 1989). In the same cell line, *S*-(1,2-dichlorovinyl)-L-cysteine induced

DNA double-strand breaks and expression of the proto-oncogenes c-*fos* and c-*myc* (Vamvakas *et al.*, 1992; Vamvakas & Köster, 1993; Vamvakas *et al.*, 1993). DNA single-strand breaks were observed in mouse kidney and double-strand breaks in rat kidney after intraperitoneal injection of *S*-(1,2-dichlorovinyl)-L-cysteine (Jaffe *et al.*, 1985; McLaren *et al.*, 1994).

^{35}*S*-(1,2-Dichlorovinyl)-L-cysteine metabolites bound to isolated DNA *in vitro* (Bhattacharya & Schulze, 1972).

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

A group of 110 male B6C3F1 mice, eight weeks of age, were given trichloroethylene in corn oil orally by gavage at a dose of 1700 mg/kg bw per day on five days per week for up to 76 weeks. There were two concurrent control groups, each consisting of 50 male mice: one was untreated and the other received corn oil at a dose of 10 ml/kg bw. Ten control mice in each group were killed at 76 weeks, and the remainder were killed at 96, 103 and 134 weeks [numbers not stated]. At death, liver tumours 0.5 cm in diameter were taken for histological examination and for analysis of oncogenes. At the time of the terminal kill, there were 24 untreated controls, 32 vehicle controls and 75 animals treated with trichloroethylene. The numbers of hepatocellular adenomas per mouse in animals in these three groups were 0.9 ± 0.06 (8%), 0.13 ± 0.06 (13%) and 1.27 ± 0.14 (67%); the corresponding numbers of hepatocellular carcinomas were 0.09 ± 0.06 (8%), 0.12 ± 0.06 (12%) and 0.57 ± 0.10 (39%), respectively. The authors noted numerous foci of cellular alteration (presumed preneoplastic lesions) in the livers of treated mice but only rare foci in the livers of controls. No neoplasms related to treatment were found at other sites. The frequency of mutations in codon 61 of H-*ras* was not significantly different in 76 hepatocellular tumours from trichloroethylene-treated mice and in those from the 74 combined historical and concurrent controls (51% *versus* 69%). The spectra of these mutations, however, showed a significant decrease in AAA and an increase in CTA in the tumours from treated mice in comparison with those from controls. Other H-*ras* and K-*ras* mutations each contributed 4% to the total in the treated mice, whereas their frequency appeared to be very low in the concurrent controls and none were seen in the historical controls. The authors interpreted these findings as suggesting that exposure to trichloroethylene provides the environment for a selective growth advantage for spontaneous CTA mutations in codon 61 of H-*ras* (Anna *et al.*, 1994).

5. Summary and Evaluation

5.1 Exposure data

Trichloroethylene, a chlorinated solvent, has been produced commercially since the 1920s in many countries by chlorination of ethylene or acetylene. Its use in vapour degreasing began in the 1920s. In the 1930s, it was introduced for use in dry cleaning, but it has had limited use in that way since the 1950s. Currently, 80–90% of trichloroethylene worldwide is used for degreasing metals. Use for all applications in western Europe, Japan and the United States in 1990 was about 225 thousand tonnes.

Trichloroethylene has been detected in air, water, soil, food and animal tissues. The most heavily exposed people are those working in the degreasing of metals, who are exposed by inhalation.

5.2 Human carcinogenicity data

Three cohort studies were considered to be particularly relevant for the evaluation of trichloroethylene. Two of these studies, conducted in Sweden and Finland, involved people who had been monitored for exposure to trichloroethylene by measurement of trichloroacetic acid in urine. The levels in samples from most of the people in the two cohorts indicated relatively low levels of exposure. The third study, from the United States, covered workers exposed to trichloroethylene during maintenance of military aircraft and missiles, some of whom were also exposed to other solvents.

A fourth cohort study included all workers in an aircraft manufacturing company in the United States. This study was considered less relevant, as only one-third of the jobs in the plant entailed exposure to trichloroethylene and the exposures of the workers could not be classified.

In none of the available cohort studies was it possible to control for potential confounding factors, such as those associated with social class with regard to cervical cancer and smoking in respect of urinary bladder cancer.

Case–control studies have been conducted to investigate a number of cancer sites, including a multisite study from Montréal, Canada, in which other cancer cases were used as controls. Most of these studies do not provide risk estimates for exposure to trichloroethylene separately but only for groups of chemicals.

The results of the three most informative cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected. The risk for these cancers was not elevated in the fourth, less informative cohort study. Results for liver cancer were given separately in the study from Finland and for the maintenance workers in the study in the United States. A total of seven cases were observed, whereas 4.00 were expected. Three case–control studies of primary liver cancer indicated elevated relative risks for people exposed to solvents, but only a few of the subjects in each study reported exposure to trichloroethylene.

With regard to non-Hodgkin's lymphoma, the results of the three most informative cohort studies were consistent; the data indicated a modest excess relative risk, with 27 cases observed and 18.9 expected. The risk for non-Hodgkin's lymphoma was not increased in the fourth, less informative study. In a case–control study covering all malignant lymphomas, an elevated odds ratio for exposure to trichloroethylene was indicated on the basis of seven exposed cases. The risk for non-Hodgkin's lymphoma was not increased among people assumed to have been exposed to trichloroethylene in the study in Montréal.

A twofold risk for cervical cancer was observed in two cohort studies.

The occurrence of cancer of the kidney was not elevated in the cohort studies; however, a study of German workers exposed to trichloroethylene revealed five cases of renal cancer whereas no case was found in an unexposed comparison group. The study may, however, have been initiated after the observation of a cluster. A case–control study and the multisite cancer

study, both from Montréal, Canada, provided discordant results with regard to cancer of the kidney.

The incidence of urinary bladder cancer was not increased in the two cohort studies from Sweden and Finland, whereas slightly increased numbers of deaths were seen in the two United States cohorts. The incidence of urinary bladder cancer was not increased in people assumed to be exposed to trichloroethylene in the Montréal study.

Data on cancer incidence or mortality have been reported from five areas in which groundwater was contaminated with trichloroethylene. A weak association between contamination and the incidence of leukaemia was indicated in two of these studies, from Massachusetts and New Jersey, United States. The cohort studies of trichloroethylene-exposed workers did not indicate an association with the occurrence of leukaemia. Two studies, from Finland and New Jersey, suggested a marginal increase in the occurrence of non-Hodgkin's lymphoma in areas with contaminated groundwater.

Overall, the most important observations are the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for non-Hodgkin's lymphoma in all three of the most informative cohort studies. Two of these studies reported data for primary liver cancer separately. Finally, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated groundwater is noted.

5.3 Animal carcinogenicity data

Trichloroethylene, with and without stabilizers, was tested for carcinogenicity by oral administration in two adequate experiments in mice. The studies showed significant increases in the incidences of benign and malignant liver tumours. Of seven studies in which trichloroethylene was given orally to rats, most were inconclusive because of reduced survival or a too short treatment. In two of the studies, the incidence of uncommonly occurring renal-cell tumours was significantly increased in male rats, and in one study an increased incidence of interstitial-cell testicular tumours was seen.

Trichloroethylene was tested for carcinogenicity by inhalation in four experiments in mice. One study showed an increased incidence of lymphomas, one study showed increased incidences of liver tumours, and three studies showed increased incidences of lung tumours. One of three experiments in which rats were exposed by inhalation showed an increased incidence of interstitial testicular tumours and a marginal increase in that of renal-cell tumours in males. No increase in tumour incidence was observed in one study in hamsters exposed by inhalation.

In limited studies, trichloroethylene and its proposed metabolite trichloroethylene oxide did not increase the incidence of skin tumours or local sarcomas in mice when administered by topical application or subcutaneous injection.

5.4 Other relevant data

In rodents, trichloroethylene is rapidly absorbed from the gastrointestinal tract and through the lungs, whereas absorption of the vapour through the skin is negligible. The major pathway is oxidative metabolism leading to the formation of chloroacetic acids. Mice showed consistently

higher rates of oxidative biotransformation than rats. A minor pathway in rodents and humans involves the formation of mercapturic acids.

The acute toxicity of trichloroethylene in rodents and humans is low. After high doses of trichloroethylene are administered repeatedly to rodents, damage is seen in liver and kidney (in mice and rats) and in lung (in mice only). Repeated exposure of humans in the workplace appears to have no marked toxic effects on the kidney or liver. Trichloroethylene is a more potent peroxisome proliferator in the livers of mice than of rats.

The available studies show no consistent effect of trichloroethylene on the human reproductive system. Trichloroethylene is metabolized to trichloroacetic acid in the placenta or fetus of many species. There is little evidence of toxic effects in developing rats or mice.

Studies of structural chromosomal aberrations, aneuploidy and sister chromatid exchange in peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive.

Pure trichloroethylene did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange or unscheduled DNA synthesis in rodents, whereas an increased induction of micronuclei and DNA single-strand breaks/alkaline labile sites was observed.

In single studies with human cells *in vitro*, trichloroethylene of low purity slightly increased the frequencies of sister chromatid exchange and unscheduled DNA synthesis. Pure trichloroethylene did not induce gene mutation in human cells. In mammalian cells *in vitro*, pure trichloroethylene induced cell transformation, sister chromatid exchange and gene mutation, but not chromosomal aberrations. In fungi, trichloroethylene (pure or of unspecified purity) induced aneuploidy, gene mutation and mitotic recombination and induced gene conversion in the presence of metabolic activation.

Gene mutation or DNA damage was usually not induced in prokaryotes by pure trichloroethylene, while preparations containing epoxide stabilizers were mutagenic. Sulfur-containing metabolites formed by a minor trichloroethylene biotransformation pathway were genotoxic in bacteria and cultured renal cells.

5.5 Evaluation[1]

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

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

Overall evaluation[2]

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

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

(i) Although the hypothesis linking the formation of mouse liver tumours with peroxisome proliferation is plausible, trichloroethylene also induced tumours at other sites in mice and rats.

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

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

(ii) Several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin's lymphoma.

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