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1,1,1-TRICHLOROETHANE AND FOUR OTHER INDUSTRIAL CHEMICALS

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

1,1,1-TRICHLOROETHANE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 71-55-6

EC/List No.: 200-756-3

*Chem. Abstr. Serv. name*: 1,1,1-trichloroethane

IUPAC systematic name: 1,1,1-trichloroethane

Synonyms: methylchloroform; trichloroethane; methyltrichloromethane; trichloromethylmethane; ethane, 1,1,1-trichloro-; α-trichloroethane; chlorothene; Solvent 111, Inhibisol, and other depositor-supplied synonyms and acronyms (NCBI, 2021).

1.1.2 Structural and molecular information

Relative molecular mass: 133.40 (IFA, 2021a)

Chemical structure:
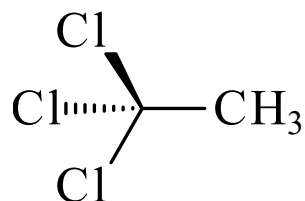
Molecular formula: $C_2H_3Cl_3$

1.1.3 Chemical and physical properties

Description: colourless liquid with a mildly sweet, ethereal, and chloroform-like odour (IFA, 2021a, NCBI, 2021)

Odour threshold: odour may be noticeable at concentrations near 100 ppm [555 mg/m³] and has been described as strong and unpleasant at 1500–2000 ppm [8.32–11.1 g/m³] (NCBI, 2021)

Boiling point: 74 °C (IFA, 2021a)

Melting point: –30 °C (NCBI, 2021)

Density: 1.34 g/cm³ at 20 °C (IFA, 2021a)

Relative vapour density: 4.61 (air = 1) (IFA, 2021a)

Vapour pressure: 133.3 hPa at 20 °C (IFA, 2021a)

Auto-ignition temperature: 490 °C (IFA, 2021a)

Lower explosion limit: 9.5 vol.% (529 g/m³) (IFA, 2021a)

Upper explosion limit: 15.5 vol.% (860 g/m³) (IFA, 2021a)

Solubility: 1 g/L at 25 °C (IFA, 2021a), < 1 g/L at 20 °C, soluble in all common organic solvents including acetone, benzene, methanol, carbon tetrachloride, and ether; very good solvent for fats, paraffins, and other organic compounds (NCBI, 2021)

Viscosity: 0.86 mPa.s at 20 °C (NCBI, 2021)

Octanol/water partition coefficient (P): log K_{ow} = 2.49 (IFA, 2021a)

Reactivity: decomposes on exposure to light and high temperatures with carbon monoxide, carbon dioxide, hydrogen chloride, chlorine, and trace amounts of phosgene, polychlorinated dioxins, and related chlorine compounds as decomposition products. Risk of explosion on contact with alkali metals, nitrogen oxides, and oxygen, and at increased pressures and heat. Readily corrodes aluminium and aluminium alloys, and moderately corrodes iron and zinc (IFA, 2021a; NCBI, 2021)

Conversion factor: 1 ppm is equivalent to 5.55 mg/m³ at 101 kPa and 20 °C (IFA, 2021a).

1.1.4 Impurities

Commercial-grade 1,1,1-trichloroethane has a purity of 90–95% and contains stabilizers at 3–8% (WHO, 1992; Doherty, 2000). Known impurities of 1,1,1-trichloroethane include trace amounts of 1,2-dichloroethane, chloroform, 1,1-dichloroethane, carbon tetrachloride, trichloroethylene, 1,1,2-trichloroethane, and vinylidene chloride (Stewart et al., 1969; NCBI, 2021).

1.2 Production and use

1.2.1 Production process

1,1,1-Trichloroethane is mainly manufactured from the catalytic hydrochlorination of ethylene to 1,2-dichloroethane, followed by thermal dehydrochlorination to vinyl chloride, conversion to 1,1-dichloroethane via catalytic hydrochlorination, and finally to 1,1,1-trichloroethane through a chlorination process (Doherty, 2000; Marshall & Pottenger, 2016). 1,1,1-Trichloroethane is also produced by the catalytic hydrochlorination of 1,1-dichloroethylene, which is derived from 1,1,2-trichloroethane, which in turn is derived from vinyl chloride or 1,2-dichloroethane via chlorination (Marshall & Pottenger, 2016). Alternatively, 1,1,1-trichloroethane and various other chlorinated ethanes and ethenes can also be produced via non-catalytic chlorination of ethane, as was the case until 1979 in the USA (US EPA, 1994a; Doherty, 2000).

1.2.2 Production volume

1,1,1-Trichloroethane is classified as a High Production Volume chemical, indicating that it is manufactured or imported in amounts greater than 1 million pounds [454 tonnes] per year (US EPA 2021b). However, production volumes of 1,1,1-trichloroethane were historically much higher and since the adoption of the Montreal Protocol on Substances that Deplete the Ozone Layer, in 1987, and the Clean Air Act, USA, in 1990, the production of 1,1,1-trichloroethane has been phased out for most non-essential uses, both in the USA and globally.

Total world production of 1,1,1-trichloroethane was 155 000 tonnes in 1970, which gradually increased and peaked at 725 000 tonnes in 1990, after which it rapidly declined to 301 000 tonnes in 1993 (Midgley & McCulloch, 1995), 184 000 tonnes in 2009, and 160 000 tonnes in 2014 (Marshall & Pottenger, 2016). Production in the USA was 245 000 tonnes in 1973 and peaked at 394 000 tonnes in 1985 (WHO, 1992), after which it declined to 450 million pounds [204 000 tonnes] in 1993 (ATSDR, 2006). In the USA, during the period 2012–2015, 163 million pounds [74 000 tonnes] to 192 million pounds [87 000 tonnes] of 1,1,1-trichloroethane were produced in the industrial sectors "industrial gas manufacturing" and "plastic material and resin manufacturing" (US EPA, 2016).

The use of and demand for 1,1,1-trichloroethane in the USA was estimated at 273 000 tonnes in 1987, with a peak at

312 000 tonnes in 1989, followed by a gradual decline in subsequent years to 282 000 tonnes in 1992 (US EPA, 1994a); total world demand for 1,1,1-trichloroethane in 1987 was 578 000 tonnes (IARC, 1999). Production and use of 1,1,1-trichloroethane was last reported in 2000–2001 in the lubricants category at 0.9–1.6 tonnes in Norway, and in 2009 at 0.6 tonnes for cleaning/washing agents in Denmark (SPIN, 2021).

In 1989, the biggest producers of 1,1,1-trichloroethane were the USA, followed by Japan, UK, Germany, France, Canada, and Brazil. All these countries, except Canada, reported continued production in 2004, albeit at much lower volumes. A similar decline was reported for the global consumption of 1,1,1-trichloroethane. The highest users of 1,1,1-trichloroethane in 1989 were the USA, Japan, European Community, Canada, Brazil, and Australia; most countries globally had zero or significantly reduced consumption levels by 2004 (UNEP, 2005).

Atmospheric measurements of 1,1,1-trichloroethane are a stable long-term indicator of its emissions, although localized small-scale emissions may be missed (Prinn et al., 2001). Various studies conducted in the USA (Millet & Goldstein, 2004), Europe (Krol et al., 2003), and globally (Prinn et al., 2001) reported an exponential decline in atmospheric levels of 1,1,1-trichloroethane from a peak in 1992 to 2000, when levels were below those of 1978, when measurements began (Prinn et al., 2001; Reimann et al., 2005). Fig. 1.1 illustrates the decline in global atmospheric levels of 1,1,1-trichloroethane (Prinn et al., 2018).

[The Working Group noted that, while continued localized and smaller-scale use of 1,1,1-trichloroethane may be occurring, the data in Fig. 1.1 serves as a useful indicator of the large reduction in production and use of this chemical worldwide.]

The Montreal Protocol resulted in a significant decline in production of 1,1,1-trichloroethane in developed countries in the 1990s. However,

production of 1,1,1-trichloroethane for export to low- and middle-income countries (LMICs) that were signatories to the Montreal Protocol may have continued until 2012 (ATSDR, 2006). [The Working Group noted that, while the downward trend in the production of 1,1,1-trichloroethane is clear, reliable data on current production volumes, particularly in LMICs, were hard to identify.]

1.2.3 Uses

1,1,1-Trichloroethane was among the most widely used degreasing solvents in the USA in the 1970s and 1980s. Before the 1950s, 1,1,1-trichloroethane was reported to be a contaminant in the production of chlorinated hydrocarbons, as a rubber solvent, and in a list of dyes. 1,1,1-Trichloroethane was commercially applied in the 1950s–1960s as a cold-cleaning solvent for some metals and as an aerosol propellant for products, e.g. hair spray. In the 1970s, 1,1,1-trichloroethane was primarily used for cold cleaning, vapour degreasing, and ultrasonic cleaning of metal parts. Between 1975 and 1985, cold cleaning and vapour degreasing accounted for 63% of 1,1,1-trichloroethane produced in the USA, with the remainder spread over the manufacture of copolymers (20.5%), exports (11.8%), and miscellaneous purposes (5.1%) (Doherty, 2000). In 1995, the major use of 1,1,1-trichloroethane was as an intermediate in the production of hydrochlorofluorocarbons (~60%), followed by vapour degreasing and cold cleaning (25%), as a solvent for adhesives (5%), in coatings and inks (3%), textiles (2%), and in miscellaneous applications including electronics (5%) (ATSDR, 2006). In 1995, the Montreal Protocol banned all nonessential uses of 1,1,1-trichloroethane by 2002 (Marshall & Pottenger, 2016; UNEP, 2021) [the Working Group noted that, other than the use as an intermediate, most of the uses cited above (ATSDR, 2006) are probably nonessential uses]. Essential uses – defined by the Montreal Protocol

Fig. 1.1 Concentrations of 1,1,1-trichloroethane (CH₃CCl₃) in the lower atmosphere, as measured by the Advanced Global Atmospheric Gases Experiment at stations around the world, 1978–2020
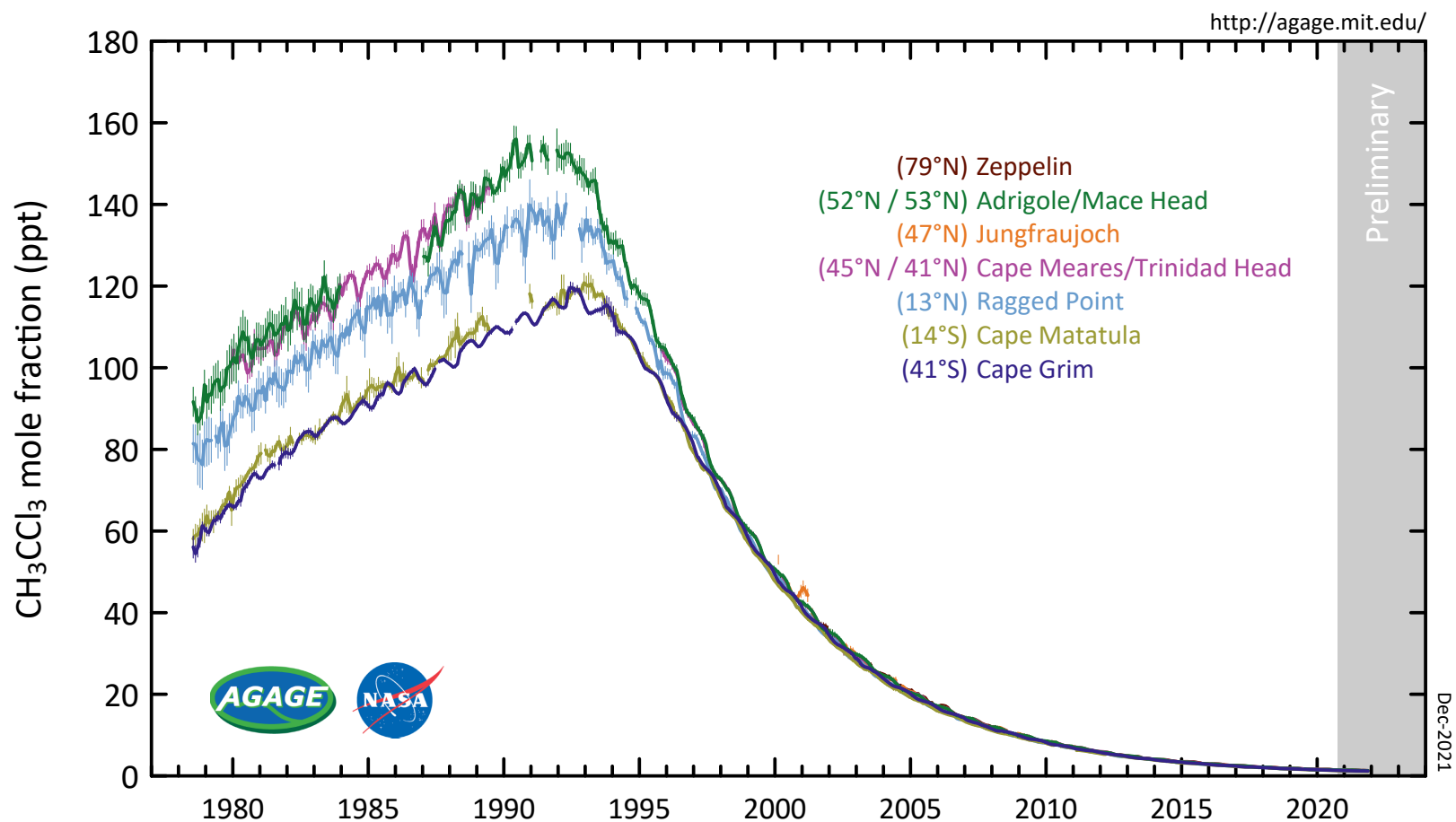
Abundances are given as pollution-free monthly mean mole fractions in parts per trillion. The Advanced Global Atmospheric Gases Experiment (AGAGE) has been measuring the composition of the global atmosphere continuously since 1978.
From © Prinn et al. (2018). This work is distributed under the Creative Commons Attribution 4.0 License. Adapted from Rigby et al. (2017). CC BY-NC-ND.

as those "necessary for the health and safety or for the critical functioning of society" – such as for medical devices and aviation safety testing, may have continued (ATSDR, 2006). By the early 2000s, 1,1,1-trichloroethane was almost entirely used as a precursor for hydrofluorocarbons (ATSDR, 2006). Toxic release inventory (TRI) data from 2009 to 2020 show that 46.8% of toxic releases were reported by the hazardous-waste industry sectors and 49.1% by the chemical industry (US EPA, 2021c). Other nonessential uses of 1,1,1-trichloroethane may also have occurred after 2000 to consume stockpiles of the chemical accumulated earlier. In LMICs, some current use of 1,1,1-trichloroethane that would not be considered essential under the Montreal Protocol is still evident; for example, one online chemical supplier in India lists this chemical for use as a "fumigant herbicide" (Ottokemi, 2021). [The Working Group noted that, aside from the obvious reduction in the widespread use of 1,1,1-trichloroethane since its prohibition, reliable data on current use patterns, particularly in LMICs, were not available.]

1.3 Detection and quantification

1,1,1-Trichloroethane is quantified in air, water, soil, consumer products, and various biological samples (including breath, blood, and urine) by a variety of analytical methods that use chromatography for separation of the constituents plus various detectors (ATSDR, 2006). Representative methods in different matrices are summarized in Table 1.1.

1.3.1 Air

Several standard methods for workplace evaluations of 1,1,1-trichloroethane in air samples include sample collection on coconut shell/activated charcoal tube, or in an adsorption tube filled with Chromosorb 106, and analysis by gas chromatography with flame ionization detection (GC-FID) following National Institute for Occupational Safety and Health (NIOSH) Method 1003 or the German Deutsche Gesetzliche Unfallversicherung (DGUV) information 213-565 Method 02 or 03 (NIOSH, 2003; DGUV, 2017a, b). Another standard method includes the collection of 1,1,1-trichloroethane in evacuated stainless-steel canisters, followed by preconcentration, and separation and analysis by gas chromatography-mass spectrometry (GC-MS) according to United States Environmental Protection Agency (US EPA) Method TO-15A (US EPA, 2019). A variation of this method includes the collection and preconcentration of samples in a sorbent tube filled with activated charcoal and analysis by GC-MS (Russell & Shadoff, 1977).

1.3.2 Water

Water and wastewater samples are analysed by bubbling an inert gas through a sample to transfer the volatile sample components to a vapour phase, followed by trapping the purged vapour onto sorbent material, and finally desorbing and transferring the purgeables onto a gas chromatography (GC) column for separation. The sample can be quantified for 1,1,1-trichloroethane using a variety of detectors including electrolytic conductivity or microcoulometric detector using US EPA Method 601 (US EPA, 1994b) or mass spectrometry using US EPA Method 624 for wastewater samples (US EPA, 1984). Similarly, 1,1,1-trichloroethane in drinking-water samples is measured by purging and trapping the volatile sample components, then separating with GC-MS using US EPA Method 524.2 (US EPA, 1995; Zoccolillo et al., 2005). Groves et al. (2006) describe the development of a field-portable instrument for the quantification of 1,1,1-trichloroethane in drinking-water samples, based on measuring changes in the mass and viscoelastic properties of an array of polymer-coated surface-acoustic-wave microsensors,

Table 1.1 Representative methods for the detection and quantification of 1,1,1-trichloroethane and its metabolites (trichloroethanol and trichloroacetic acid) in various matrices

Sample matrix (method number)	Sample preparation	Analytical technique	LOD (unless otherwise stated)	Reference
Workplace air				
Air (NIOSH Method 1003)	Coconut shell charcoal tube and extraction in carbon disulfide; sample target volume 3 L	GC-FID	1.0 µg/sample	NIOSH (2003)
Air (German DGUV Information 213-565 Method 02)	Activated charcoal tube and extraction in carbon disulfide	GC-FID	0.6 ng/sample (LOQ) [0.18 ng/sample (LOD)]	DGUV (2017a)
Air (German DGUV Information 213-565 Method 03)	Sorbent tube with Chromosorb 106 followed by thermal desorption	GC-FID/MSD	0.85 µg/sample (LOQ)	DGUV (2017b)
Air (US EPA Method TO-15A)	Collection in evacuated stainless-steel canisters with flow controllers and preconcentration before injection	GC-MS	1 pptv	US EPA (2019)
Ambient air				
Air	Stainless steel tubes packed with Porapak N porous polymer and thermal desorption	GC-ECD/MS	NR	Russell & Shadoff (1977)
Water and wastewater				
Water (US EPA Method 601 for municipal and industrial discharges)	Purge and trap onto adsorbent followed by rapid heating	GC-ECD*	0.03 µg/L	US EPA (1994b)
Water (US EPA Method 624 for wastewater)	Purge and trap onto adsorbent followed by thermal desorption	GC-MS	3.8 µg/L	US EPA (1984)
Water (US EPA Method 524.2 for surface water, ground water, and drinking-water)	Purge and trap onto adsorbent followed by thermal desorption	GC-MS	0.08 µg/L	US EPA (1995)
Soil, sediment, consumer products				
Liquid or solid beverages, and grains	Extraction in isooctane	GC-ECD GC-HECD	3 ppb [µg/L] (LOQ) 7 ppb [µg/L] (LOQ)	Daft (1987)
Table-ready foods and various grains	Purged in 100 °C bath with nitrogen gas, collected on Tenax TA and XAD-4 resin trap, and eluted with hexane	GC-ECD/ HECD	0.3 ppb [µg/kg] (LOQ)	Heikes & Hopper (1986); Heikes (1987)
PVC containers used for food packaging, foodstuffs	PVC sample dissolved in *N,N*-dimethyl-formamide followed by headspace analysis	GC-MS (PVC) GC-ECD (foods)	1 ppm [mg/kg] (LOQ) 0.002–0.01 ppm [mg/kg]	Gilbert et al. (1978)
Pharmaceutical products	*N,N*-Dimethylformamide as dispersive and 1,2-dibromoethane as extraction solvents	GC-FID	0.05 µg/g in solid sample; 5 µg/L in solution	Farajzadeh et al. (2012)
	Dispersive liquid–liquid microextraction	GC-MS	1.5 µg/mL in solution	Heydari & Azizi (2015)

Table 1.1 (continued)

Sample matrix (method number)	Sample preparation	Analytical technique	LOD (unless otherwise stated)	Reference
Raw landfill leachates	HS-SPME	HS-SPME-GC-MS	0.05 ng/mL	Flórez Menéndez et al. (2004)
		HS-GC-MS	0.1 ng/mL	
Biological samples				
Exhaled air	Stainless-steel devise with charcoal cloth and desorbed in carbon disulfide	GC-FID	3.8 µg/mL (LOQ) [1.15 µg/mL (LOD)]	Glaser & Arnold (1989)
Blood and exhaled air, TCOH and TCA	Headspace analysis for blood Collection to Tedlar bag during 1 minute and direct injection of exhaled air sample	GC-ECD	0.06 mg/L TCOH in blood ; 0.03 mg/L TCA in blood; 0.01 µg/L TCOH in exhaled air	Monster & Boersma (1975)
Exhaled air	Collection of alveolar breath i.e. end-expired air into silanized glass tubes; direct injection	GC-ECD	0.08 ng/L	Stein et al. (1996)
Blood	Headspace analysis	GC-FID and ECD	0.1 mg/L	Ramsey & Flanagan (1982)
		GC-MS	0.1 mg/L (LOQ)	Dills et al. (1991)
Urine	Headspace analysis	GC-MSD	NR	Ghittori et al. (1987)
Urine and blood	Headspace analysis	GC-MSD	1 µg/L	Imbriani et al. (1988)
Blood and urine, TCA, TCOH, and trichloro-compounds	Multiple extraction steps	GC-ECD	< 1 mg/L (LOQ)	Ogata & Saeki (1974); Humbert & Fernández (1976)
Blood (1,1,1-trichloroethane) and urine (TCA)	Modified purge and trap with dynamic headspace analysis	GC-MS	0.8 µg/L (LOQ), blood 0.009 µg/mL (LOQ), TCA in urine	Johns et al. (2005)

DGUV, Deutsche Gesetzliche Unfallversicherung (German Social Accident Insurance); ECD, electron capture detection; ECD*, electrolytic conductivity detection; FID, flame ionization detector; GC, gas chromatography; HECD, Hall electroconductivity detector; HS, static headspace; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; MSD, mass selective detector; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; ppm, parts per million; ppt, parts per trillion; pptv, parts per trillion by volume; PVC, polyvinyl chloride; SPME, solid-phase microextraction; TCA, trichloroacetic acid; TCOH, trichloroethanol; US EPA, United States Environmental Protection Agency.

that occur when a substance of interest is absorbed.

1.3.3 Soil, sediment, consumer products, and food

Various methods for the detection and quantification of 1,1,1-trichloroethane in food products, soil, and various other media have been reported. Trace levels of 1,1,1-trichloroethane in beverages and grains treated with fumigants were measured by gas chromatography with electron capture detection and Hall electroconductivity detector (GC-ECD/HECD) in isooctane extract (Daft, 1987). GC-ECD/HECD was also used to quantify 1,1,1-trichloroethane in table-ready foods and various grains after purging samples in a 100 °C bath with nitrogen gas, collecting on a Tenax TA and XAD-4 resin trap, and eluting with hexane (Heikes & Hopper, 1986; Heikes, 1987). 1,1,1-Trichloroethane in polyvinyl chloride containers used in food packaging as well as in the food itself has been quantified using GC-MS (Gilbert et al., 1978). Dispersive liquid–liquid microextraction (DLLME) combined with GC-FID or GC-MS detection was used to quantify 1,1,1-trichloroethane and other residual solvents in pharmaceutical products (Farajzadeh et al., 2012; Heydari & Azizi, 2015). Two extraction and preconcentration procedures – static headspace and solid-phase microextraction – combined with GC-MS were used to quantify 1,1,1-trichloroethane in raw landfill leachates (Flórez Menéndez et al., 2004).

1.3.4 Biological specimens

1,1,1-Trichloroethane and its metabolites, trichloroethanol and trichloroacetic acid, have been quantified in blood, end-exhaled air (not trichloroacetic acid), and urine samples from exposed humans (Monster, 1986; ATSDR, 2006); this is described in detail in Section 4.1.

After inhalation, 1,1,1-trichloroethane is poorly metabolized, and a large fraction (up to 90%) of the absorbed dose is rapidly excreted unaltered in exhaled air (ATSDR, 2006) where it can be measured by methods based on GC-FID (Glaser & Arnold, 1989) or electron capture detection (ECD) (Monster & Boersma, 1975; Stein et al., 1996). Various combinations of sample collection and detection are used for the quantification of 1,1,1-trichloroethane in exhaled air samples (ATSDR, 2006). A direct reading method based on colorimetry has also been described (Droz et al., 1988). In general, unchanged 1,1,1-trichloroethane is measurable in blood and exhaled air within 5–15 minutes of exposure, whereas metabolites such as trichloroacetic acid are detected in the urine 64 hours after exposure (Monster, 1986; ATSDR, 2006). Real-time direct measurement of 1,1,1-trichloroethane in exhaled air was achieved in a laboratory study where the exhaled air was directly channelled from the participants's face mask through a glow discharge ionization source to an ion trap mass spectrometer for quantification (Giardino et al., 1999). The parent compound can also be analysed in blood via headspace analysis and detection using GC with both FID and ECD (Ramsey & Flanagan, 1982) or mass spectrometry (Dills et al., 1991). Urine samples have also been analysed using GC with mass selective detector (Ghittori et al., 1987; Imbriani et al., 1988). Additionally, the sum of the free and conjugated trichloroethanol (i.e. total trichloroethanol) in blood and urine have also been described as human biomarkers of exposure. A method that includes acidic hydrolysis for sample preparation and that is based on GC and ECD has been reported (Ogata & Saeki, 1974; Humbert & Fernández, 1976). A similar method has been used for trichloroacetic acid in urine, an additional human biomarker of 1,1,1-trichloroethane. Trichloroacetic acid in urine and 1,1,1-trichloroethane in blood have also been quantified using a headspace GC-MS method (Johns et al., 2005). [In contrast to total

trichloroethanol in blood and urine for which sampling time is critical for exposure assessment (end of shift at end of work week), timing (end of work week) is less critical for trichloroacetic acid in urine.]

Airborne exposure levels of 1,1,1-trichloroethane are shown to be well correlated with levels in exhaled air, blood, and urine (ACGIH, 2001; ATSDR, 2006). Therefore, 1,1,1-trichloroethane level in exhaled air, blood, and urine is the primary biomarker of exposure, with established biological limit values reported in Section 1.5.2 (ACGIH, 2001; DFG, 2020).

1.4 Occurrence and exposure

There are no natural sources of 1,1,1-trichloroethane. The main sources of emission into the environment are anthropogenic, from air emissions, release to surface water and soil, and leachates from landfills and wastewater during the production and use of industrial and consumer products. [The Working Group noted that most of the studies reviewed in this section evaluated exposures during the period of peak use and production of 1,1,1-trichloroethane (i.e. from the 1970s to the early 1990s). Few studies were identified that evaluated occurrence and exposure after the year 2000, when a decline in production and use occurred. Therefore, the Working Group does not expect the levels described to reflect current exposures (e.g. see Fig. 1.1 in Section 1.2 in relation to atmospheric emissions).]

1.4.1 Environmental occurrence

Once in the atmosphere, 1,1,1-trichloroethane is slowly eliminated through reaction with hydroxyl radicals, while an estimated 15% migrates to the stratosphere where it depletes ozone (ATSDR, 2006). Owing to its long half-life, 1,1,1-trichloroethane can migrate far from its original source, while its moderate solubility in water means that it evaporates from surface water and soil into the atmosphere, and easily leaches out of landfills and soil. Depending on the sample-collection location, 1,1,1-trichloroethane has been detected at varying levels in urban, rural, indoor and personal air; surface, ground, drinking-water and rainwater; soil and sediment; and waste (ATSDR, 2006).

(a) Air

The worldwide average atmospheric concentration of 1,1,1-trichloroethane increased from about 0.06 ppb [0.33 µg/m^3] in 1974 to about 0.15 ppb [0.83 µg/m^3] in 1991 and then declined rapidly thereafter as production and use declined (Midgley & McCulloch, 1995). In remote areas, 1,1,1-trichloroethane concentrations in the air increased during 1975–1980 from 87 to 156 ppt [0.48 to 0.87 µg/m^3] in the Pacific north-western region of the USA and from 45 to 102 ppt [0.25 to 0.57 µg/m^3] in Antarctica (Rasmussen et al., 1981).

1,1,1-Trichloroethane has been measured in air samples from all over the USA. 1,1,1-Trichloroethane concentrations were typically 0.1–1 ppb [0.55–5.55 µg/m^3] in urban areas and < 0.2 ppb [< 1.11 µg/m^3] in rural areas but could reach 1000 ppb [5.55 mg/m^3] in large urban areas and near waste sites (ATSDR, 2006). Urban 24-hour average air concentrations ranged from 0.13 to 28.4 ppb [0.72 to 158 µg/m^3] in 1987–1990 in various cities in California, USA (Hisham & Grosjean, 1991). Measurements collected at 20 landfill sites for non-hazardous municipal trash indicated 24-hour air concentrations of 1,1,1-trichloroethane as high as 3.6 ppm [20 mg/m^3] (Wood & Porter, 1987). Overnight indoor and outdoor concentrations of 1,1,1-trichloroethane measured between 1980 and 1984 during various seasons in residential areas at five geographical locations in the USA were variable, being influenced by numerous factors; estimated median and maximum indoor concentrations were 1.5–24 µg/m^3 and 14–880 µg/m^3, while estimated

median and maximum outdoor concentrations were 0.6–29 μg/m³ and 7.6–190 μg/m³, respectively ([Pellizzari et al., 1986]). A National Human Exposure Assessment Survey (NHEXAS) conducted in six midwestern states in the USA in 1995–1997 measured an average indoor concentration of 1,1,1-trichloroethane of 6.29 μg/m³, with a maximum of 186.4 μg/m³ ([Bonanno et al., 2001]).

Outside the USA, 1,1,1-trichloroethane was measured in the atmosphere in Italy in 1987–1989, with a median concentration of 3.72 μg/m³ in Turin (a city) and 1.48 μg/m³ in Cuorgnè (a rural site) ([Gilli et al., 1992]). Additionally, median concentrations of 1,1,1-trichloroethane in Turin were 9 and 2.67 μg/m³ indoors, 8.55 and 2.44 μg/m³ outdoors, and 12.1 and 3.03 μg/m³ in personal samples collected during winter and summer, respectively. A study conducted by an organochlorine-manufacturing company in the United Kingdom (UK) reported the highest concentration of 1,1,1-trichloroethane (16 ppb [89 μg/m³]) in the air near the manufacturing facility in Runcorn (an industrial town located between the cities of Liverpool and Manchester). Concentrations decreased as distance from the facility increased, from 6.2–11 ppb [34–61 μg/m³] in Runcorn Heath, < 0.1–6 ppb [< 0.56–33 μg/m³] in a Liverpool/Manchester suburban area, and to even lower levels further away ([Pearson & McConnell, 1975]). Atmospheric air samples collected from multiple urban and rural locations in western Europe in 1972–1976 indicated 1,1,1-trichloroethane concentrations ranging from 0.03 to 1.01 ppb [0.17–5.6 μg/m³] at rural locations in the UK, < 0.02–0.13 ppb [0.11–0.72 μg/m³] at urban locations in the Netherlands, not detected (ND) to 6.55 ppb [ND to 36.4 μg/m³] at urban locations in Germany, ND to 0.39 ppb [ND to 2.2 μg/m³] in Brussels, Belgium, and < 0.84–2.01 ppb [< 4.7–11.2 μg/m³] in Lyon, France ([Correia et al., 1977]). Average concentrations of 1,1,1-trichloroethane in the air in rural Hokkaido, Japan, in 1979–1980 ranged from 0.54 to 0.65 μg/m³ ([WHO, 1992]).

(b)   Water

1,1,1-Trichloroethane has been measured in a variety of water sources, from surface water and groundwater to rain runoff at sites near sources of emission. Concentrations were < 1 ppb [< 1 μg/L] in surface water at a distance from emission sources such as industrial or waste sites, 0–18 ppb [0–18 μg/L] in groundwater samples, 0.01–3.5 ppb [0.01–3.5 μg/L] in drinking-water from surface water or groundwater, and up to 11 000 ppb [11 mg/L] in groundwater near or at sources of emission, as reported in numerous studies in cities throughout the USA ([ATSDR, 2006]). Between 1981 and 1983, 5000 samples of drinking-water were collected from 400 respondents in New Jersey, North Carolina, and North Dakota, USA. The mean and maximum concentrations of 1,1,1-trichloroethane ranged from 0.03 to 0.6 μg/m³ and from 0.05 to 5.3 μg/m³, respectively ([Wallace et al., 1987b]). 1,1,1-Trichloroethane concentrations in 945 samples collected from water supplies using groundwater sources across USA states in 1981–1982 ranged from non-quantifiable (< 0.2 μg/L) to 21 μg/L ([Westrick et al., 1984]). Drinking-water samples collected from 100 cities in Germany contained 1,1,1-trichloroethane at concentrations ranging from < 0.1 to 1.7 μg/L ([Bauer, 1981]; [WHO, 1992]). The combined concentration of 1,1,1-trichloroethane plus carbon tetrachloride was found to be 3 ppb [3 μg/L] in municipal surface-water supplies of the cities of Liverpool, Manchester, and Chester in the UK ([Pearson & McConnell, 1975]).

(c)   Soil and sediment

Limited data have been reported on the contamination of soil with 1,1,1-trichloroethane, partly because 1,1,1-trichloroethane rapidly evaporates or leaches out. In the USA, grab samples taken from sludge at a solvent-recovery plant measured 1,1,1-trichloroethane concentrations

in the range of 23 000 to 120 000 ppb [µg/L]. 1,1,1-Trichloroethane concentrations averaged 0.4 ppb [µg/kg] in samples taken from river sediments passing through an industrial area in Japan and were non-detectable in samples taken from a river going through non-industrial areas. In the USA, 1,1,1-trichloroethane was found in nearly half of the hazardous waste sites that are on the National Priorities List, which is a list of sites with hazardous waste of serious concern and are targeted by the US EPA for clean-up (ATSDR, 2006).

1.4.2 Dietary exposure

1,1,1-Trichloroethane was measured in a variety of food products ranging from meats and dairy to cereals, baked products, nuts, fruit, and vegetables. Some of the highest concentrations were reported in seafood products such as clams and oysters, and some dairy products such as butter, ice cream, and cheese in samples obtained in the USA (ATSDR, 2006). 1,1,1-Trichloroethane was detected in 138 out of 231 food items tested from the market basket collection by the United States Food and Drug Administration (US FDA), and the levels in these food products were highly variable, with 3–35 ng/g [ppb] in cereals, 1–9 ng/g in raw, canned or cooked vegetables, 2–40 ng/g in baked goods, 10–228 ng/g in nuts/nut products, 1–520 ng/g in dairy products, 15 ng/g in a chocolate candy, 2–76 ng/g in meat dishes, 6 ng/g in one infant/toddler blend, 2–32 ng/g in raw, canned, or dried fruits, and 2–3 ng/g in clear beverages (Daft, 1988). A Canadian study reported 1,1,1-trichloroethane concentrations ranging from ND (limit of detection, approximately 0.01 µg/g for both detectors) to 0.39 µg/g (electron capture detector) or 0.47 µg/g (Coulson electrolytic conductivity detector) in several samples of breakfast cereal (Page & Charbonneau, 1977).

1.4.3 Consumer products

1,1,1-Trichloroethane was extensively used as a functional ingredient in many household products, including adhesives and adhesive cleaners, lubricants, general-purpose liquid cleaners and spray degreasers, various automotive products, oven cleaners, spot removers, shoe polish, glues, typewriter correction fluid, fabric finishes, and some fumigation products for grains (ATSDR, 2006). A survey of 1159 household products purchased in shops in six cities in the USA in the late 1980s measured 1,1,1-trichloroethane in 18.6% of the products, with average concentrations (w/w%) varying from 36.4% in automotive products, 30.2% in household cleaners and polishes, 12.7% in paint-related products, 66.5% in fabric- and leather-treatment products, 21.2% in cleaners for electronic equipment, 43.3% in oils, greases, and lubricants, 38.3% in adhesive-related products, and 57.1% in miscellaneous products (Sack et al., 1992). In the USA, average concentrations of 1,1,1-trichloroethane in emissions from household products and building material were 696 µg/m^3 for cleaning agents and pesticides, 4.9 µg/m^3 for painted sheetrock, 13 µg/m^3 from glued wallpaper, and 22 µg/m^3 from glued carpet; 1,1,1-trichloroethane was present in 8 of the 15 products tested (Wallace et al., 1987a). 1,1,1-Trichloroethane was also used as a solvent in some cosmetic products, such as aerosol hair-colour spray, a manicuring product, and a personal hygiene product (Hooker, 2008). A study on concentrations of volatile organic compounds in 666 sanitary products obtained from retail stores in the Republic of Korea reported that all measurements of 1,1,1-trichloroethane were below the lower limit of quantification [limit unspecified] (Kim et al., 2019). Some pharmaceutical products, such as aerosol drug products intended for inhalation, contained 1,1,1-trichloroethane, but these products were withdrawn from the market by the US FDA in 1973 at which time a new drug application was required for all

such products (US FDA, 1973). [The Working Group noted that, due to the adoption of the Montreal Protocol and subsequent drop in production and use of 1,1,1-trichloroethane, many of the abovementioned occurrences may no longer be applicable.]

1.4.4 Occupational exposure

[The Working Group noted that most of the studies reviewed in this section evaluated occupational exposures during the pre-Montreal Protocol era.]

The NIOSH National Occupational Exposure Survey (NOES) of 1981–1983 estimated that approximately 2 528 300 workers were potentially exposed to 1,1,1-trichloroethane in 42 broad industry activities in the USA (NIOSH, 1990). In 1982, 101 510 000 workers were employed in the USA (Silvestri et al., 1983); thus 2.5% of the working population of the USA in 1982 was potentially occupationally exposed to 1,1,1-trichloroethane. Qualitative information on jobs with the potential for occupational exposure to 1,1,1-trichloroethane was available from several epidemiological studies investigating health outcomes. Degreasing was the primary operation identified by several epidemiological studies (Anttila et al., 1995; Gold et al., 2011; Purdue et al., 2017; Callahan et al., 2018). Exposure in metal plating and coating work was also prevalent (Hadkhale et al., 2017; Talibov et al., 2017). Printing was identified in two case reports in Japan (Kubo et al., 2014a; Kumagai, 2014). 1,1,1-Trichloroethane was also noted as a component in cleaning fluids (Anttila et al., 1995; Zarchy, 1996) and glues (Anttila et al., 1995; Gold et al., 2011). Occupations reported in epidemiological studies as having exposure to 1,1,1-trichloroethane were airplane maintenance workers (Stewart et al., 1991; Gold et al., 2011); automobile workers (Gold et al., 2011); upholsterers; smelters; shoe lasters and sole fitters; machine and engine mechanics (Talibov

et al., 2017); mechanics and repairmen; metal-machining occupations; occupations related to fabricating, assembling, installing and repair of electrical, electronic and related equipment; metal shaping and forming occupations, except machining; and occupations in the physical sciences (Christensen et al., 2013). [The Working Group noted that some of these occupations overlap.]

The potential for high exposure existed in 1,1,1-trichloroethane manufacture, industrial organic chemistry, and five broad industry-activity groups that used the largest amount of 1,1,1-trichloroethane for cleaning, including furniture and fixtures, fabricated metal products, electric and electronic equipment, transportation equipment, and miscellaneous manufacturing industries. Smaller amounts were used for cleaning in food and kindred products, primary metals, nonelectric machinery, instruments and clocks, and in non-manufacturing industries such as maintenance facilities (railroad, bus, aircraft and truck), automotive and electric-tool repair shops, automobile dealers, and service stations (US EPA, 1994a).

Exposure to 1,1,1-trichloroethane also occurred in industries where it was used as a raw material to manufacture paints and inks, aerosol products (e.g. hair sprays), adhesive products (e.g. holding adhesives), other chemical products (e.g. chlorofluorocarbons used as refrigerants), and textile products (e.g. spotting fluid) (US EPA, 1994a). The report noted that downstream application and use of these products could have caused exposures during, for example, the application of surface-coating products in the paper and paperboard industries, in wood and flatwood product plants, in printing and publishing facilities, and in the production of adhesives and sealants. Other end uses included use as a coolant and lubricant in cutting oils, a component in plastic film cleaners, and a carrier solvent for silicone paper coatings and protective coatings (US EPA, 1994a).

In these diverse workplaces, 1,1,1-trichloroethane is absorbed via all routes, but inhalation is the major route of exposure, while exposure via the skin contributes < 0.1% to the absorbed dose (Riihimäki & Pfäffli, 1978; ACGIH, 2001).

NIOSH conducted numerous workplace assessments for 1,1,1-trichloroethane through the Health Hazard Evaluation Program (HHE) and Industrywide Studies (IWS) in the USA (Hein et al., 2010). The 1441 measurements of exposure for 1,1,1-trichloroethane were compiled from 89 HHE reports, 9 IWS reports, and 2 studies published between 1970 and 1996. The assessments were conducted across a wide range of industries, and 1,1,1-trichloroethane exposures ranged from 0.0004 to 1500 ppm, [0.002 to 8300 mg/m^3] with a median concentration of 0.95 ppm [5.3 mg/m^3], and 2.1% of the measurements exceeded the threshold limit value (TLV) established by the American Conference of Governmental Industrial Hygienists (ACGIH) in 2001 (ACGIH, 2001). 1,1,1-Trichloroethane exposure summaries by industry activity group, obtained only from HHE reports (NIOSH, 2016) for which five or more personal samples were available for the industry activity group are reported in Table S1.2 (Annex 1, Supplementary material for 1,1,1-trichloroethane, Section 1, Exposure Characterization, available from: https://publications.iarc.fr/611). Exposures above 100 ppm [555 mg/m^3] occurred in many industries, including electrical parts, rubber products, glass products, iron and steel, plastic products, fabricated metals, books and binders, electronics, aircraft, printed material, and ship repair. Low exposures were measured for bituminous coal, textile, some plastics and paper and miscellaneous chemicals. [The Working Group noted that 1,1,1-trichloroethane exposure may not have been of interest in some of these investigations and was measured as part of a panel of analytes. Furthermore, the NIOSH HHEs can often identify emerging issues or trends in exposures, and the review by Hein et al. (2010) did not identify an HHE for 1,1,1-trichloroethane after 2000, probably because its use was restricted by the Montreal Protocol.]

Similar results were reported by ATSDR (2006) in a table summarizing 1,1,1-trichloroethane exposures, which identified high exposures in cleaning and degreasing of fabricated metals, manufacture of electronics components, mixing commercial resins, and spray painting and gluing. Published literature in 1973–1996 reported personal exposures to 1,1,1-trichloroethane in the range of 83 to 367 ppm [460 to 2950 mg/m^3] in a brake repair shop during simulation (Gitelman & Dement, 1996), 14 to 2490 mg/m^3 among degreasing workers (Tay et al., 1995), as high as 214 mg/m^3 in foam manufacturing (Boeniger, 1991), means of ND to 838 ppm [ND to 4650 mg/m^3] for various jobs in textile manufacturing (Kramer et al., 1978), and lower levels during a visit to dry cleaners (median, 675 μg/m^3), in the paper industry (range, ND to 4.5 μg/m^3), and working in a laboratory (median, 24–86 μg/m^3), albeit based on very few measurements (Wallace et al., 1989; Rosenberg et al., 1991). A more recent study in university students using solvents during printmaking quantified average personal exposure to 1,1,1-trichloroethane as 40.5 μg/m^3 (Ryan et al., 2002). In two national databases on occupational exposure in France and the USA, more than 95% of the available measurements for 1,1,1-trichloroethane were made before 2000. The few measurements made after 2000 were mostly non-detectable (USA) or corresponded to uses possibly deemed essential (i.e. manufacture of medical and dental instruments and supplies, France). [The Working Group noted that few workplace exposure data after the mid-1990s were available, and few other data were available from outside the USA. This is probably due to the restricted use of 1,1,1-trichloroethane since the adoption of the Montreal Protocol (see Section 1.2.2).]

An assessment of intensity of exposure to chlorinated solvents, including 1,1,1-trichloroethane, was conducted for several epidemiological studies (Neta et al., 2012; Ruder et al., 2013; Purdue et al., 2017; Callahan et al., 2018). Published measurement data ($n = 947$) were linked to a set of exposure determinants and applied in a regression model to identify significant exposure determinants (Hein et al., 2010). Significant determinants of 1,1,1-trichloroethane were: active application of energy to a solvent (e.g. stirring, mixing, and agitation) and aerosolization as the primary or secondary mechanisms of release; location (outdoors and outdoors/indoors versus only indoors); local exhaust ventilation (present and effective versus absent or present but ineffective); proximity (near and near/far versus far (≥ 0.9 m) only); and the presence of industrial mechanical dilution (versus not present).

Few studies have conducted biomonitoring of 1,1,1-trichloroethane or its urinary metabolites in the workplace. In a study on aircraft-maintenance workers at an Air Force base in the USA, 1,1,1-trichloroethane concentrations in air ranged from ND to 4.7 ppm [ND to 26.1 mg/m³, the Working Groups noted that the definition of ND was not provided], 0.1 to 51.0 ppb [0.56 to 283 µg/m³] in breath, and ND in blood, while levels of trichloroacetic acid in the urine were ND to 0.0024 mg/mL (Lemasters et al., 1999a). A study in workers in printing companies in Japan reported average air concentrations of 1,1,1-trichloroethane of 4.3, 24.6, and 53.4 ppm [23.9, 136.5, and 296.4 mg/m³] at three plants, which corresponded to urinary concentrations of trichloroethanol of 1.2, 5.5, and 9.9 mg/L, trichloroacetic acid of 0.6, 2.4, and 3.6 mg/L, and total trichloro-compounds of 2.0, 8.2, and 13.9 mg/L, respectively (Seki et al., 1975). In Germany, the average blood concentration of 1,1,1-trichloroethane was 633 µg/L in 3 priming workers, whereas levels were undetectable in 4 other priming workers and 28 varnishing workers (Angerer & Wulf, 1985). [The Working Group

noted that several additional occupational biomonitoring studies have been conducted with the objective of evaluating the relations between exposure to 1,1,1-trichloroethane and its biological markers in various media (e.g. Monster, 1986; Ghittori et al., 1987; Mizunuma et al., 1995). As such, these studies reported correlation or regression coefficients between various metrics and not summary values for 1,1,1-trichloroethane or its biological markers.]

1.4.5 Exposure of the general population

The general population was probably exposed to low levels of 1,1,1-trichloroethane between the 1970s and the 1990s because of the widespread use of 1,1,1-trichloroethane in a variety of consumer and household products, background concentrations in air, water, and food, and the potential for occupational exposure. Blood concentrations of 1,1,1-trichloroethane in a sample of the general public drawn from participants in the Third National Health and Nutrition Examination Survey (NHANES III) in 1988–1994 ranged from below the limit of detection (0.086 µg/L) to 14 mg/L, with a geometric mean of 0.16 µg/L (Wu et al., 2006); a different sample of non-occupationally exposed participants drawn from NHANES III had a mean of 0.34 µg/L and a median of 0.13 µg/L (Ashley et al., 1994). [The Working Group noted that the studies by Wu et al. (2006) and Ashley et al. (1994) drew different samples from the 1988–1994 NHANES III data and reported different summary metrics. Wu et al. (2006) reported a geometric mean, whereas Ashley et al. (1994) reported the mean and the median. In a lognormal distribution, the geometric mean is closer to the median, and both are lower than the mean.] As a result of prohibition of the production and use of 1,1,1-trichloroethane after the 1990s, exposure of the general public has diminished, as indicated by the NHANES survey results from 2003–2010 and 2011–2016, none of which detected 1,1,1-trichloroethane in blood

samples from participating adults (CDC, 2021a, b). Blood concentrations of 1,1,1-trichloroethane in children from two poor, minority neighbourhoods in Minneapolis, USA, in 2000–2001, were mostly below the limit of detection, with 0–2% being above the limit of detection for the four sampling campaigns, and a mean of 0.03 ng/mL (Sexton et al., 2005). [The Working Group did not identify data on exposure of the general population outside the USA.]

1.5 Regulations and guidelines

1.5.1 Exposure limits and guidelines

(a) Occupational exposure limits

Australia, Switzerland, and Turkey have established the same airborne exposure limits as the European Union and its Member States, that is, 555 mg/m³ (100 ppm) for the 8-hour time-weighted average (TWA), and 1110 mg/m³ (200 ppm) for 15-minute short-term measurements. Singapore and the provinces of Ontario and Quebec in Canada all use the same limits as the ACGIH TLV of 1910 mg/m³ (350 ppm) for the 8-hour TWA, and 2460 mg/m³ (450 ppm) for 15-minute short-term measurements. The Republic of Korea has an 8-hour TWA of 1900 mg/m³ (350 ppm) and a short-term limit of 2450 mg/m³ (450 ppm). In Denmark, Sweden, and Norway, 8-hour TWAs are 275, 300, and 270 mg/m³, respectively (50 ppm), and short-term limits are 550 mg/m³ (100 ppm) in Denmark and 1100 mg/m³ (200 ppm) in Sweden, while none has been established in Norway (IFA, 2021b). In the USA, NIOSH has established an "immediately dangerous to life and health" limit of 700 ppm [3800 mg/m³], and a 15-minute ceiling recommended exposure limit of 1900 mg/m³ (350 ppm) based on data on acute toxicity by inhalation in humans (NIOSH, 2021). Table 1.3 summarizes the occupational exposure limits for 1,1,1-trichloroethane in selected countries (IFA, 2021b).

(b) Environmental exposure limits

WHO has calculated a health-based value of 2 mg/L drinking-water for 1,1,1-trichloroethane but did not consider it necessary to derive a formal guideline value for 1,1,1-trichloroethane in drinking-water (WHO, 2017). In the USA, a maximum concentration level of 0.2 mg/L was established for 1,1,1-trichloroethane in the public water supply by the US EPA in 1989 under the Safe Drinking-water Act, and the same limit was set by the US FDA for bottled drinking-water (Doherty, 2000; Hooker, 2008; US EPA, 2021a). The Agency for Toxic Substances and Disease Registry (ATSDR) has derived minimal risk levels (MRLs), which are the daily human exposures to 1,1,1-trichloroethane that are likely to be without an appreciable risk of adverse effects over specified time periods. The derived inhalation MRLs are 2 ppm [11.1 mg/m³] for an acute exposure duration of less than 14 days and 0.7 ppm [3.9 mg/m³] for an intermediate exposure duration of 15–364 days. The derived oral MRL is 20 mg/kg per day for an intermediate exposure duration of 15–364 days (ATSDR, 2006).

According to the harmonized classification and labelling system implemented in the European Union (Classification, Labelling and Packaging of Substances and Mixtures, Regulation (EC) No. 1272/2008), 1,1,1-trichloroethane has the following classification: acute toxicity, category 4; ozone, category 1 (ECHA, 2021). Employers are obliged under this regulation to minimize worker exposure to 1,1,1-trichloroethane and must arrange for medical surveillance of exposed workers (European Council, 1998).

1.5.2 Reference values for biological monitoring of exposure

The ACGIH has established various biological exposure indices (BEI) for 1,1,1-trichloroethane in different biological media (ACGIH, 2001). A BEI of 20 ppm [109 mg/m³] was established

Table 1.3 Occupational exposure limits for 1,1,1-trichloroethane in various countries

Country	8-hour TWA (mg/m³)	Short-term (15 minutes) (mg/m³)	Reference
China	900	–	IFA (2021b)
Denmark	275	550	IFA (2021b)
European Union[a]	555	1110	IFA (2021b)
Germany	550	550	IFA (2021b)
Israel	1100	1910	IFA (2021b)
Japan	1100	–	IFA (2021b)
New Zealand	680	680	IFA (2021b)
Norway	270	–	IFA (2021b)
Poland	300	–	IFA (2021b)
Republic of Korea	1900	2450	IFA (2021b)
Sweden	300	1100	IFA (2021b)
United Kingdom	1110	2220	IFA (2021b)
USA – ACGIH[b]	1910	2460	ACGIH (2001)
USA – NIOSH	–	1910 (ceiling)	NIOSH (2021)
USA – OSHA	1900	–	NIOSH (2021)

ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; TWA, time-weighted average.

[a] The same occupational exposure limits are also required in Australia, Austria, Belgium, Finland, France, Hungary, Ireland, Italy, Latvia, the Netherlands, Romania, Spain, Switzerland, and Turkey.

[b] The same occupational exposure limits are also required in the provinces of Ontario and Quebec in Canada, and in Singapore.

for 1,1,1-trichloroethane in samples of exhaled air taken before the last shift of the work week (ACGIH, 2020). A BEI of 700 μg/L was established for 1,1,1-trichloroethane in urine samples taken at the end of the work shift after 2–3 days of exposure (ACGIH, 2020). The ACGIH does not have a BEI for 1,1,1-trichloroethane in blood. Previously, the ACGIH had established a BEI of 40 ppm [220 mg/ m³] for 1,1,1-trichloroethane in end-exhaled air collected before the last shift of the work week, 10 mg/L for trichloroacetic acid in urine collected at the end of the work week, 30 mg/L for total trichloroethanol in urine collected at end of shift at the end of the work week (ACGIH, 2001), and 1 mg/L for total trichloroethanol in blood collected at end of shift at the end of the work week (ACGIH, 2012). The German Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) has established a biological tolerance value (BAT) of 275 μg/L for 1,1,1-trichloroethane in blood taken at the beginning of shift after multiple work shifts of exposure (Bolt et al., 2019; DFG, 2020). [The Working Group noted that information on biological reference values outside of the USA and Germany was not available.]

1.6 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

Two cohort studies, five nested case–control studies, 16 case–control studies, three case reports, and two mechanistic studies relevant to human cancer were available to the Working Group. Details on the selected domains of the exposure assessment review for these studies are

summarized in Table S1.4 and Table S1.5 (Annex 1, Supplementary material for 1,1,1-trichloroethane, Section 1, Exposure Characterization, available from: https://publications.iarc.fr/611).

1.6.1 Exposure assessment methods in epidemiological studies of cancer and mechanistic studies in humans

The exposure assessment methods employed by these studies are organized below by study design.

(a) Cohort studies

Anttila et al. (1995) compiled measurements of trichloroethylene in urine, and of perchloroethylene [tetrachloroethylene] and 1,1,1-trichloroethane in blood collected in 1975–1983 by the Finnish Institute of Occupational Health. The authors reported that sampling methods may have changed over time. The timing of sample collection was not specified. A single measurement was available for 61% of the cohort exposed to 1,1,1-trichloroethane, and the only exposure metric developed was "exposed".

The study by Radican et al. (2008) presented a cohort of 14 455 aircraft-maintenance workers in the USA who were exposed to a variety of solvents (including 1,1,1-trichloroethane) and other chemicals. Work histories and employer records, job descriptions, walk-through surveys, air monitoring results, and interviews of employees were compiled to create a job-exposure matrix (JEM) comprising job titles that linked to study participants in a "yes/no" exposure evaluation for 14 solvents, including 1,1,1-trichloroethane (Stewart et al., 1991). Relative exposure levels were estimated semiquantitatively for "mixed solvents" (including 1,1,1-trichloroethane).

(b) Case–control studies

Three primary groups provided most of the human cancer studies available for critical review by the Working Group: the Montreal studies, the United States National Cancer Institute (NCI), and groups using the Nordic Occupational Cancer Study (NOCCA) JEM/FINJEM (job-exposure matrix/Finnish job-exposure matrix). In these and the other case–control studies reviewed, work histories had generally been collected (by interview, and for all jobs or jobs held for $\geq$ 6 or $\geq$ 12 months) and included job title, type of employer, tasks, materials and chemicals used, and frequency (referred to below as "standard work histories"). Typically, experts (chemists or industrial hygienists) reviewed the published literature (but not participant-specific air measurements) to estimate categorical levels of exposure probability, duration, and intensity (referred to below as "standard exposure assessment methods"). Other solvent exposures (trichloroethylene, perchloroethylene [tetrachloroethylene], methylene chloride [dichloromethane], and less often, carbon tetrachloride and chloroform) were typically evaluated. Unless otherwise identified, the case–control studies reviewed here used these methods.

The Montreal studies (Infante-Rivard et al., 2005; Christensen et al., 2013; Vizcaya et al., 2013) collected standard work histories with specialized questionnaires for technical information (Gérin et al., 1985). All information provided by the study participant, accrued from other studies by these experts, and personal or consultants' knowledge was considered when assessing participant-specific categories of the experts' degree of confidence [the Working Group noted that confidence was the assessors' confidence that exposure had actually occurred (possible, probable, definite), which is similar to probability or prevalence in other studies described here] that exposure to 1,1,1-trichloroethane had occurred and the frequency of exposure. Concentration of the agent (low, medium, high) was referenced to benchmark occupations. The studies assessed exposures to multiple solvents.

Three case–control studies used data from the Surveillance, Epidemiology, and End Results

(SEER) programme of the NCI (NCI-SEER; Gold et al., 2011; Purdue et al., 2017; Callahan et al., 2018). The studies collected standard work histories but also administered 20–39 job-specific modules. Standard assessment methods were followed. Assessments were participant-specific, but all three studies developed task- and job-exposure matrices for imputing estimates when participant-specific information was not available. Categorical estimates of probability, frequency, and confidence were assessed for 1,1,1-trichloroethane. Experts also estimated determinants of exposure by combining 947 measurements of 1,1,1-trichloroethane from the literature (Hein et al., 2010) to develop intensity estimates for task- and job-exposure matrices comprising probability, intensity, frequency, and confidence to impute exposure metrics when participant-specific information was unavailable. Probability was defined in these three studies as the theoretical probability of exposure to the solvent. Dermal exposure was considered for all. Other chlorinated solvents were evaluated.

Five other case–control studies were available from the NCI, in addition to a study by NIOSH in which the same general methodologies (although less sophisticated) for the assessment of exposure to 1,1,1-trichloroethane were employed as in the NCI-SEER studies, i.e. standard work histories for Neta et al. (2012), Ruder et al. (2013), and Heineman et al. (1994). In Neta et al. (2012), additional information was collected from 64 job-specific interview modules. The study by Ruder et al. (2013), a case–control study carried out by NIOSH and the NCI, included exposure modules for "solvents, thinners, glues, inks, varnishes, stains or paint strippers", rather than job modules. The interview questionnaire used by Dosemeci et al. (1999) only collected information on tasks, task duration, and full-time/part-time status for the most recent and usual occupation and industry, although duration of employment was collected for 20 jobs of interest [the Working Group noted that jobs or exposures were not

identified]. Standard assessment procedures were used by Neta et al. (2012) and Ruder et al. (2013), except that intensity was estimated using the methodology from Hein et al. (2010). Dosemeci et al. (1999) and Heineman et al. (1994) used JEMs that relied on standard information sources and exposure studies to develop an NCI-JEM for 1,1,1-trichloroethane by assigning categorical values for probability and intensity separately for jobs and for industry codes, which were then combined into a single estimate (Gomez et al., 1994) for probability and intensity. In the studies by Neta et al. (2012) and Ruder et al. (2013), exposure categories were assigned for probability, frequency, and confidence, and for continuous estimates of intensity. Other exposures evaluated by these four NCI studies included at least four other chlorinated solvents. Kernan et al. (1999) investigated exposure to 1,1,1-trichloroethane by coding jobs identified on death certificates from 24 states of the USA into broad categories of the 1980 USA census job codes. A JEM, for which the methods were not described, used categorical estimates of probability and intensity for several 11 specific chlorinated hydrocarbons, all chlorinated hydrocarbons, and all organic solvents combined.

Of the seven studies based in Nordic populations, five (Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017; Le Cornet et al., 2017) used self-reports to each participating country's 10-year census to obtain job titles resulting in multiple jobs over the censuses. [The Working Group noted that Talibov et al. (2014, 2017, 2019), and Hadkhale at al. (2017) are nested case–control studies from a larger cohort.] Pedersen et al. (2020) used a Danish register for the source of occupational histories. The jobs were coded to each country's standard occupational coding system. In the nested case–control study by Videnros et al. (2020), questionnaires were administered to the participants for the three latest occupations, collecting dates and tasks. Exposures for all seven studies were assigned to study participants

via NOCCA-JEM, which is based on FINJEM ([Kauppinen et al., 2009](#), [2014](#)). FINJEM used prevalence of jobs and measurement data from various Finnish databases to develop continuous estimates of prevalence and, for the exposed, the mean intensity of exposure to 1,1,1-trichloroethane ([Kauppinen et al., 2014](#)). Prevalence in these studies was defined as the percentage of people exposed in the job among those employed in the job. FINJEM information was reviewed by NOCCA-JEM experts in each of the countries and modified if the difference between the JEM and the study participant was likely to result in a substantial difference, on the basis of local expertise and country-specific data sets ([Kauppinen et al., 2009](#)). [The Working Group noted that no information was provided as to how this was done.] Five other chlorinated solvents were evaluated in each of the NOCCA-FINJEM studies, apart from [Pedersen et al. (2020)](#), in which the only other chlorinated solvent was trichloroethylene. Several studies examined other solvents (e.g. benzene) and non-solvent exposures.

The studies by [Sciannameo et al. (2019)](#) and [Miligi et al. (2006)](#) took place in Italy. No description was provided as to the "detailed" work histories collected in the former, whereas the latter used job- or industry-specific questionnaires. [Sciannameo et al. (2019)](#) used FINJEM; for [Miligi et al. (2006)](#), experts developed a JEM that served as a baseline to reduce differences between raters, but participant-specific estimates were assigned that incorporated categorical levels of probability and intensity of exposure to five chlorinated hydrocarbons, including 1,1,1-trichloroethane. [Sciannameo et al. (2019)](#) evaluated exposure to 29 agents previously classified by the *IARC Monographs* programme as *carcinogenic to humans* (Group 1) or *probably carcinogenic to humans* (Group 2A).

The exposure assessment in the Occupational Exposure and Brain Cancer (INTEROCC) study by [McLean et al. (2014)](#) collected standard work histories in seven countries (Australia, Canada, France, Germany, Israel, New Zealand, and the UK). An expert from each country coded the jobs to international occupation and industry coding systems using a guideline to increase consistency across the study sites ([van Tongeren et al., 2013](#)). FINJEM was modified by the exposure estimates used in the Montreal case–control studies to create an INTEROCC-JEM. The INTEROCC-JEM includes continuous estimates of probability of exposure to 1,1,1-trichloroethane. In this study, [McLean et al. (2014)](#) did not assign intensity values for participants with probability estimates of < 25%. Trichloroethylene, perchloroethyene [tetrachloroethylene], and methylene chloride [dichloromethane] were also evaluated in these studies, as were a limited number of other solvents.

(c) Case studies

Three case studies reported on individuals exposed to 1,1,1-trichloroethane. [Zarchy (1996)](#) described two cases in the USA in people with exposure from cleaning metal for 2–4 years for a frequency of 5–15 days per month. [Kubo et al. (2014a](#), [b](#)) reported on 3 cases in Japan in people who worked in printing shops removing ink residues. [Kumagai (2014)](#) reported on a single case in Japan in a person who worked in a printing company from 1984 to 1995 and was exposed to 1,1,1-trichloroethane at an estimated concentration of 240 ppm [1330 mg/m^3].

(d) Mechanistic studies

Two studies were available on mechanistic evidence of end-points related to the key characteristics of carcinogens in humans.

The study by [Muttray et al. (1999)](#) used an exposure chamber and a crossover design. Controlled exposures were to 1,1,1-trichloroethane (purity, > 99%) at 200.4 ppm [1112 mg/m^3] and 22 ppm [122 mg/m^3] (as measured by a MIRAN infrared analyser) for 4 hours at two separate time-points, 1 week apart. No other exposures occurred at the time of the experiment.

The study by Lemasters et al. (1999b) on aircraft-maintenance workers in the USA comprised two substudies. The first substudy (an exposure assessment pilot) assessed 1,1,1-trichloroethane exposures in air, breath, blood, and urine samples, and investigated correlations between these exposure measurements. The second substudy used a prospective, repeated-measures design to investigate the genotoxic effects of exposure to selected chlorinated and aromatic solvents, including 1,1,1-trichloroethane. On the basis of the results of the pilot study, only breath samples and industrial hygiene samples were used in the genotoxicity study. Three air samples from 8-hour shifts were taken on 5 consecutive days for "total solvents", which included 1,1,1-trichloroethane, with participants' breath sampled at the end of the 3 days. The mean concentration of total solvents was < 6 ppm (ranging up to 106 ppm, n = 286) [the Working Group noted that no information was provided on 1,1,1-trichloroethane]. Other solvents present included under total solvents were methyl ethyl ketone, xylenes, toluene, and methylene chloride [dichloromethane].

1.6.2 Critical review of exposure assessment

(a) Studies of cancer in humans

(i) Cohort studies

Anttila et al. (1995) provided limited information on exposure with which to interpret the epidemiological results. Blood concentration of 1,1,1-trichloroethane reflects short-term exposure [the Working Group noted that 90–95% of 1,1,1-trichloroethane is eliminated from the blood within 50 hours (NCBI, 2021)]. It is not known how representative of actual exposures the blood levels were, either within or outside the 9 years of reported measurements, especially since major changes in exposure levels in industry were believed to have taken place during the measurement period (1970s to 1980s). The assessment only stated "exposed", with no indication of the exposure levels these workers had experienced, since only the annual means for the entire 1,1,1-trichloroethane-exposed cohort were reported. It was not known whether decreases in mean measurements reflected changes in air concentrations of 1,1,1-trichloroethane in the work environment in the same job, in different jobs, or in different people exposed at different times, or whether the variability observed was attributable to day-to-day variability. [The Working Group noted that making inferences about the relation between air concentrations and expected corresponding blood concentrations is challenging (see Section 1.3.4). Other carcinogens, particularly chlorinated solvents, may have been confounders, because at this time in Finland, the same primary industries used both 1,1,1-trichloroethane and trichloroethylene. A strength of this study was that those participants identified as "exposed" were truly exposed. The limitations were likely to result in attenuation of the disease risk estimate to the null, since only "exposed" participants, many of whom may have low exposures to 1,1,1-trichloroethane, were identified.]

In the cohort study by Radican et al. (2008), a variety of sources of detailed data (both qualitative and quantitative) were used to assess exposure to solvents and other hazards, but the linkage between study participant and exposure was weak. Exposure to 1,1,1-trichloroethane was limited to "exposed" and "unexposed", and to "all solvents" (including 1,1,1-trichloroethane), so the disease risk estimates may be attenuated to the null, since both the "exposed" and "all solvents" category may contain participants with very low exposures to 1,1,1-trichloroethane, or for the "all solvents", with no exposure. Finally, exposure was only assessed up to 1982.

(ii) Case–control studies

All the case–control studies on 1,1,1-trichloroethane generally had the same limitations. First, there may have been differential recall bias (cases reporting differently than controls),

although Vizcaya et al. (2013) found no difference in the number of jobs reported per participant or in the interviewers' subjective ratings of interview quality. Jobs and industries were typically coded according to standard coding systems, which may result in the grouping of heterogeneously exposed study participants. Estimates of intensity were affected by substantial measurement limitations: few measurements were available, particularly before the 1970s when they were often non-existent; it is likely that no measurements were made on the study participants; and most measurements available probably represent companies with higher and lower exposure, so it is not known how representative the measurement results are of the participants' actual exposures. Details were rarely provided on how exposures were assessed when measurements were not available, making it difficult to interpret results. Estimates of probability were affected by the limited availability of historical use patterns for 1,1,1-trichloroethane. There was often limited or a lack of information available on the frequency of exposed tasks, so that participants exposed at a lower frequency may have been included in a higher-than-appropriate exposure category. JEMs were often used. The major weakness of JEMs is that they assign the same value to all participants with a particular set of exposure determinants (such as job/industry), although there is often high variability within jobs. JEMs are generally weighted to male workers' exposures, which may over- or underestimate women's exposures, depending on the work setting. Also, most estimates relied heavily on the experts' experience and knowledge, with little factual data to support the assessment. Exposures were generally semiquantitative. Dermal exposure was often not considered. Exposures were often low, increasing the chance that a potential association could be missed. Also, chlorinated solvents have been used interchangeably over the years for many purposes (particularly degreasers and glues) in the workplace,

which could have resulted in confounding; however, most of the studies did not adjust for exposure to other solvents. Correlation between exposures could thus have occurred, particularly between exposures to chlorinated solvents, either because the exposure assessor had coded a job as having some probability of exposure to several of these solvents or because of actual exposures experienced by the study participants. Table S1.6 identifies the correlations observed by the studies under review (see Annex 1, Supplementary material for 1,1,1-trichloroethane, Section 1, Exposure Characterization, available from: https://publications.iarc.fr/611).

Several of the studies included prevalence or confidence in the calculation of cumulative exposure. In cases where prevalence is multiplied by intensity to calculate a cumulative metric, bias has been found to be negligible when the prevalence of exposure in the studied population is either very low or very high (Burstyn et al., 2012). Moreover, although some of the limitations described above may be differential, measurement error generally results in non-differential misclassification (Armstrong, 1998). In general, then, the exposure assessment is likely to result in non-differential misclassification, which probably results in a decrease in calculated disease risk, although the exposure unit per outcome unit may be affected. Unless otherwise specified, generally the exposure assessment conducted in the case–control studies identified below is likely to attenuate disease risks to the null, with studies of lower quality probably having greater attenuation than those of higher quality.

Of the case–control studies on 1,1,1-trichloroethane, the Montreal studies (Infante-Rivard et al., 2005; Christensen et al., 2013; Vizcaya et al., 2013) were considered to have the highest quality of exposure assessment. The strength of these studies lies in the greater breadth of detailed information available from the study participants and from other sources compared with that in most of the other case–control

studies. The assessments were participant-specific estimates reached by consensus. Confidence (i.e. probability) was assessed in addition to frequency and intensity. Dermal exposure (yes/no) was considered. Although approximately 300 substances were evaluated, adjustment for possible confounding exposures was not performed. The exposure assessment was evaluated for reliability (Goldberg et al., 1986; Fritschi et al., 2003). A specific weakness of the study by Infante-Rivard et al. (2005), which assessed exposures in mothers of patients with childhood cancer, was that exposures were not evaluated in fathers, which could have confounded results.

The three case–control studies that used data from either the full or partial NCI-SEER data (i.e. Gold et al., 2011; Purdue et al., 2017; and Callahan et al., 2018) were also high-quality studies that developed participant-specific estimates, supported by job-specific modules and an extensive literature review. Experts were blinded to case status. The job- and task-exposure matrices were developed to impute missing data, which probably increased consistency in the evaluations. Exposure metrics were probability, frequency, duration, and confidence, which allowed exploration of multiple toxicity mechanisms.

A limitation of the studies based on FINJEM and NOCCA (NOCCA for Hadkhale et al., 2017; Talibov et al., 2014, 2017, 2019; NORD-TEST for Le Cornet et al., 2017) is that a brief job title with little detail was collected via the census once every 10 years, and there was no information on the date or duration of each job. Additionally, it was not possible to account for job changes after 1990 since this was the last year of job-code data linkage for the NOCCA cohort. Pedersen et al. (2020) contained slightly more information, noting registry-based jobs, but also industries, and dates. In contrast, Sciannameo et al. (2019) and Videnros et al. (2020) used a questionnaire to collect work-history information but used FINJEM for the exposure assessment. Videnros et al. (2020) additionally updated each prevalence

value on the basis of questionnaire data. The emphasis in the development of FINJEM was on highly prevalent occupations with substantial exposure, resulting in lower confidence for jobs that are less prevalent or have a lower exposure (Kauppinen et al., 2014). Later studies (after 2009) and those using NOCCA-JEM (which is based on FINJEM) may have had different distributions of jobs, and these exposure estimates may have had greater misclassification than the earlier FINJEM studies. It is not clear whether exposure situations in Finland are comparable to those in the other Nordic countries of NOCCA-JEM. While FINJEM has been compared to other JEMs, it is difficult to properly interpret its agreement or disagreement with exposure estimates in other Nordic countries.

A strength of FINJEM is that a substantial body of information was used in its development. [The Working Group noted that FINJEM and NOCCA-JEM are well-developed and strong JEMs, but that the NOCCA and NORD-TEST jobs are a source of much uncertainty due to their being job titles with little detail that were collected only once per 10 years.] FINJEM requires a certain minimum level of exposure and excludes all exposures whose prevalence in an occupation is < 5%, increasing specificity. [The Working Group noted that although 5% appears to be low, only two other studies (McLean et al., 2014 and Pedersen et al., 2020) used higher values. Most studies did not indicate any exclusion in the exposure assessment, and it is difficult to imagine the exposure assessors doing so without actual prevalence figures.] The JEM considered the intermittency of exposure in an annual mean exposure [although the source of this information was not identified]. Arithmetic means of the measurement results were calculated as long-term (1-year average during working hours) concentrations. [The Working Group noted that this strength was diminished by the categorization of intensity.] For NOCCA-JEM, FINJEM was reviewed and modified by a team of Nordic

experts to be country-specific, but it typically relied on FINJEM unless available information supported a substantial change. FINJEM is likely to be one of the better JEMs because the exposure prevalence in an occupation was based on actual worker populations and workplace measurements. A particular strength of Pedersen et al. (2020) is the use of the minimum criteria for defining exposure of > 10% probability and at least 1 year of employment, thus increasing specificity.

Gold et al. (2011), Purdue et al. (2017), and Callahan et al. (2018) all made use of detailed and well-described expert assessment processes supported by full occupational histories, the use of job-specific modules, and JEMs to derive a series of participant-specific detailed exposure metrics of probability, intensity, frequency, confidence, and duration of exposure. The experts assessing the exposures were blinded to case status, which reduces the risk of differential bias across cases and controls. No direct exposure-monitoring data were available, but the exposure assessment process was carefully considered and semiquantitative in nature, which is a key strength in the absence of monitoring data.

The strengths and weaknesses of four other studies (Heineman et al., 1994; Dosemeci et al., 1999; Neta et al., 2012; Ruder et al., 2013) varied. The strengths and weaknesses of Neta et al. (2012) were similar to those of the SEER-based studies. Exposures may have been missed by Ruder et al. (2013) owing to the use of exposure modules, and certainly were missed by Dosemeci et al. (1999) owing to the incomplete nature of the occupational history and the inclusion of only the most recent and longest-held jobs. In addition, it was unclear whether the method used by Heineman et al. (1994) and Dosemeci et al. (1999) involving an algorithm based on separate semiquantitative estimates for job and for industry developed valid exposure estimates.

Kernan et al. (1999) was the weakest of the case–control studies in terms of quality of exposure assessment. Only one job was collected per participant, and no information was available on dates or duration of the job, making the validity of the assessments questionable since exposures levels changed over time and across industries even in the same job.

The study by Miligi et al. (2006) benefited from job-specific questionnaires. One weakness was that it was unclear whether jobs with a duration of ≥ 5 years were included in this assessment, as was the case for a previous analysis of the same data set by the same authors. The authors did not indicate a minimum job duration for inclusion in the exposure assessment, but if they repeated their earlier cut point of 5 years, this would have led to exposed people being erroneously included in the unexposed category if critical jobs with solvent exposure occurred for shorter durations. The experts categorized intensity of exposure on the basis of the presence of exposure controls presumed in place, which was probably highly variable across jobs, years, and industries, and which might limit the validity of the exposure assessment.

The INTEROCC case–control analysis across seven countries by McLean et al. (2014) used a specialized JEM based on FINJEM and data from the Montreal exposure-assessment team, which is expected to have improved the quality of the exposure assessment. It was unclear how differences across countries were considered and how workplace exposures compared between Finland (the baseline) and the other countries in the study. Exposure intensity was assigned to participants with ≥ 25% probability of exposure, increasing specificity.

(b)   Mechanistic studies in humans

The study by Muttray et al. (1999) was appropriately designed. Exposure occurred only 20 minutes before the biological measures were taken, which may have been insufficient

for some markers. The analytical methods used were appropriate. It would have been informative to have included a time-point at which the participants were not exposed (0 ppm) to aid in interpretation of the effect of differences between exposure at 20 ppm [111 mg/m³] and 200 ppm [1110 mg/m³].

In the study by Lemasters et al. (1999b), genotoxicity end-points were assessed before beginning work and then at intervals of 15 and 30 weeks. The comparison group (controls) was unlikely to have had any significant exposure. The results are presented as aggregate "solvent" values by breath and industrial hygiene measurements, which hinders interpretation, particularly for 1,1,1-trichloroethane. The number of measurements of 1,1,1-trichloroethane was not stated, and it was not clear which analytical method was used to measure "total solvents". [The Working Group noted that the air and breath measurements of 1,1,1-trichloroethane made in the pilot study are of unknown significance to the genotoxicity study, since the exposure assessments were conducted separately over different time periods for different purposes. Owing to typical within-worker and between-worker variability in occupational exposure levels and the small number of workers included in the pilot study, no further inferences were made on the relevance of the pilot study to the genotoxicity study.]

2. Cancer in Humans

In this section, a review of the evidence from studies of cancer in humans exposed to 1,1,1-trichloroethane is presented. 1,1,1-Trichloroethane was previously considered in *IARC Monographs* Volumes 20 and 71 (IARC, 1979, 1999). For *IARC Monographs* Volume 20, no case reports or epidemiological studies were available to the Working Group. For *IARC Monographs* Volume 71, there was one cohort study in biologically monitored workers (Anttila et al., 1995), one population-based case–control study on astrocytic brain cancer (Heineman et al., 1994), and one hospital- and population-based case–control study on multiple cancer types (Siemiatycki, 1991). Results from several new studies have subsequently been published, including an updated analysis of Siemiatycki (1991) with a more refined exposure assessment, additional control for covariates, and more complete reporting (Christensen et al., 2013; Vizcaya et al., 2013).

The epidemiological database for this evaluation consisted of two cohort studies on biologically monitored workers in Finland (Anttila et al., 1995) and aircraft-maintenance workers in the USA (Radican et al., 2008), four large-scale case–control studies nested in the NOCCA study (Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017), one nested case–control study in a population-based cohort of Swedish women (Videnros et al., 2020), and sixteen largely population-based case–control studies conducted mainly in North America and Europe (Heineman et al., 1994; Dosemeci et al., 1999; Kernan et al., 1999; Infante-Rivard et al., 2005; Miligi et al., 2006; Gold et al., 2011; Neta et al., 2012; Christensen et al., 2013; Ruder et al., 2013; Vizcaya et al., 2013; McLean et al., 2014; Le Cornet et al., 2017; Purdue et al., 2017; Callahan et al., 2018; Sciannameo et al., 2019; Pedersen et al., 2020). There were also two case series described in multiple reports of biliary–pancreatic cancers in workers exposed to 1,1,1-trichloroethane in Japan and the USA. One of these concerned a cluster of cholangiocarcinoma cases, and the other reported on two cases of cholangiocarcinoma and ampullary carcinoma; they were included in the present review owing to the rarity of the outcomes (Zarchy, 1996; Kumagai et al., 2013, 2016; Kubo et al., 2014a, 2014b).

For this evaluation, the Working Group considered only studies that presented findings specifically for measured or estimated exposure to

1,1,1-trichloroethane. The quality of the exposure assessment was a critical consideration for the evaluation of the included studies and detailed critiques of each study are provided in Section 1.6. Although there were also other studies, including in specific occupational groups exposed to 1,1,1-trichloroethane, such as aircraft or electronics workers (Sung et al., 2007; Lipworth et al., 2011; DeBono et al., 2019a, b), or studies examining associations for grouped solvent exposures, including 1,1,1-trichloroethane combined with other solvents (Lee et al., 2002; Chang et al., 2003a, b, 2005; Dryver et al., 2004; Ojajärvi et al., 2007; Miligi et al., 2013; Silver et al., 2014; Olsson et al., 2018), such studies were considered by the Working Group to be uninformative and were excluded here since the independent contribution of 1,1,1-trichloroethane to any observed association with cancer was unclear. Also excluded here was an ecological study on drinking-water contamination (Cohn et al., 1994).

Where there were multiple publications derived from the same study, only the most relevant (i.e. longest follow-up, most detailed exposure assessment) was considered here (as such, Siemiatycki, 1991; Spirtas et al., 1991; Blair et al., 1998; and Videnros et al., 2019 were excluded). In one study, cumulative occupational exposures to 1,1,1-trichloroethane were estimated among study participants; however, owing to the very small number of exposed participants, associations with risk of glioma were not examined, and the study was not further considered here (Benke et al., 2017).

Identification of studies assessing cancer risk in humans exposed to 1,1,1-trichloroethane was initially performed through a comprehensive search of biomedical databases, using standard keyword searches of titles and abstracts as well as of MeSH terms (described in Section 6 of the *IARC Monographs* Preamble; IARC, 2019). After this, an expanded database search was conducted to identify studies for which the agent was not explicitly mentioned in the title or abstract, since in some studies 1,1,1-trichloroethane was examined along with multiple other occupational agents and not specifically mentioned in these search fields. The expanded search was performed both by including a broader range of search terms related to the chemical class, i.e. including expanded search terms for solvents, chlorinated solvents, chlorinated hydrocarbons, or aliphatic solvents or hydrocarbons, as well as additional synonyms for the agent not included in the initial search (e.g. methyl chloroform). Additionally, keyword searches were also performed (uniquely for the expanded search) in the full text of the manuscript in available databases, by searching beyond the title and abstract to further identify potentially relevant studies in which the agent name was mentioned only in the body of the manuscript. This expanded search resulted in an approximate doubling of the number of studies included in the evidence evaluation, but for most of these studies, 1,1,1-trichloroethane was not the main focus of the study.

Studies included in the evaluation assessed a range of cancer types, with the largest number of studies being on cancers of the haematopoietic and lymphoid tissues, followed by cancers of the genitourinary system, brain and nervous system, breast, and digestive tract; there were fewer studies on other cancer sites. Owing to the largely population-based nature of the available studies, the participants reported a wide range of occupations, although the prevalence of 1,1,1-trichloroethane exposure in most studies was generally low, and the intensity of exposure was probably also low. No cohort or case–control studies were found on environmental exposure to 1,1,1-trichloroethane and cancer.

2.1 Cancers of the haematopoietic and lymphoid tissues

2.1.1 Cohort studies

See Table 2.1.

The Working Group identified two cohort studies and two case–control studies nested within population-based cohorts in which the relation between occupational exposure to 1,1,1-trichloroethane and risk of cancers of the haematopoietic and lymphoid tissues had been investigated (Anttila et al., 1995; Radican et al., 2008; Talibov et al., 2014, 2017).

Anttila et al. (1995) conducted a retrospective cohort study in Finland that was constructed from a database of workers undergoing biological monitoring for occupational exposures to three chlorinated solvents. The cohort included 2050 male and 1924 female workers monitored by the Finnish Institute of Occupational Health via blood measurements of 1,1,1-trichloroethane (recorded between 1975 and 1983) and tetrachloroethylene (1974–1983) or urinary measurements of trichloroacetic acid, a metabolite of trichloroethylene (1965–1982). Approximately 94% of the workers were monitored for one solvent only; only for a small subset of the cohort ($n = 271$) were measurements available for 1,1,1-trichloroethane exposure. Mean age at the time of first measurement of 1,1,1-trichloroethane was 38.2 years and 39.9 years for men and women, respectively. Among those participants monitored for 1,1,1-trichloroethane, only one measurement was available for 61% and fewer than three measurements were available (average, 2.0 measurements per individual) for 79%. The workers were followed up for cancer incidence between 1967 and 1992 through linkage to the Finnish cancer registry; the mean duration of follow-up was 18 years. The observed incidence rates for exposed workers were compared with rates in the Finnish population categorized by sex, 5-year age group, and three calendar periods,

using standardized incidence ratios (SIRs). The standardized incidence ratio for any lymphohaematopoietic malignancy among workers with a 1,1,1-trichloroethane measurement was 4.23 (95% CI, 0.87–12.3; 3 cases). An excess of multiple myeloma was also observed, although the confidence limits were wide (SIR, 15.98; 95% CI, 1.93–57.7; 2 cases). [The strengths of the study included documentation of workers' exposure to 1,1,1-trichloroethane through blood measurements and long-term follow-up for cancer incidence through linkage to a national registry. An important limitation was the small sample size of workers exposed to 1,1,1-trichloroethane, which limited power and precluded more detailed analyses across exposure levels. The quantitative exposure level for these cases in the biological samples was not considered in analyses.]

Radican et al. (2008) conducted the most recent update to a cohort study on cancer mortality in 10 730 male and 3725 female civilian aircraft-maintenance workers employed at a United States Air Force base for at least 1 year between 1952 and 1956. In this cohort update, mortality was followed-up between 1953 and 2000. By the end of follow-up, approximately 60% of cohort members had died, and the average age of survivors was 75 years (standard deviation, 7). A comprehensive assessment was undertaken to characterize various exposures and was informed by walk-through surveys of the base by an industrial hygienist, interviews with employees, review of historical facility records, position descriptions, and monitoring data providing exposure measurements. A JEM was developed primarily on job title and, where known, department, creating 43 000 job-department code combinations. The most detailed exposure assessment was conducted for trichloroethylene; only qualitative (ever/never) assessments were performed for exposure to 1,1,1-trichloroethane and 12 other solvents, including other chlorinated solvents (methylene chloride [dichloromethane], carbon tetrachloride, *O*-dichlorobenzene,

Table 2.1 Cohort studies on exposure to 1,1,1-trichloroethane and cancers of the haematopoietic and lymphoid tissues

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Anttila et al. (1995) Finland Enrolment, 1965–1983 (1,1,1-TCE: 1975–1983)/ follow-up, 1967–1992	3974 workers (2050 men and 1924 women), 271 of whom were monitored for exposure to 1,1,1-TCE; workers biologically monitored for occupational exposure to three halogenated hydrocarbon solvents in Finland Exposure assessment method: quantitative measurements; a database of measurements in urine from trichloroethylene-exposed participants, and blood from tetrachloroethylene- and 1,1,1-trichloroethane-exposed participants was used to identify ever exposed to the chemicals	Lymphatic and haematopoietic (ICD-7, codes 200–204), incidence NHL (ICD-7, codes 200 and 202), incidence Multiple myeloma (ICD-7, code 203), incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure Compared with the general population (SIR): Any 1,1,1-TCE exposure Compared with the general population (SIR): Any 1,1,1-TCE exposure	3 1 2	4.23 (0.87–12.3) 3.87 (0.10–21.5) 15.98 (1.93–57.7)	Age, sex, calendar period	*Exposure assessment critique*: Exposed were truly exposed. Blood levels only reflect short-term (days) exposures for 9 yr. No information was provided on the interpretation of the measurements or the participants' exposures, including possible exposures to 1,1,1-TCE outside the 1975–1983 window or to other agents. *Strengths*: documented exposure to 1,1,1-TCE via blood measurements; long-term follow-up for cancer incidence ascertained through linkage to national cancer registry. *Limitations*: small sample size; no assessment of exposure–response relations.

Table 2.1   (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Radican et al. (2008) Utah, USA Enrolment, 1952–1956/ follow-up, 1953–2000	14 455 (10 730 men and 3725 women); civilian workers employed at Hill Air Force Base, an aircraft-maintenance facility, for ≥ 1 yr between 1952 and 1956 who were followed up for cancer mortality through linkage to the national death index. Exposure assessment method: review of facility records, jobs, walk-through surveys, interviews, measurements used to assign yes/no exposed by job group	NHL, mortality	Exposure to 1,1,1-TCE, men (HR):			Age, race	*Exposure assessment critique*: Extensive data collection, including measurements. Linkage of jobs to exposures was limited due to the limited information in the available records. Given 1,1,1-TCE was often interchanged with other chlorinated solvents, the difficulty in making these links was a non-trivial limitation. Job information used to assign yes/no. *Strengths*: exposure assessment conducted by industrial hygienists with access to base facilities and records; long follow-up period; internal comparison group. *Limitations*: small number of deaths among exposed workers; qualitative exposure assessment; potential co-exposures to other organic solvents.
			No exposure to solvents or chemicals	NR	1		
			Ever	12	1.51 (0.61–3.73)		
		NHL, mortality	Exposure to 1,1,1-TCE, women (HR):				
			No exposure to solvents or chemicals	NR	1		
			Ever	0	–		
		Multiple myeloma, mortality	Exposure to 1,1,1-TCE, men (HR):				
			No exposure to solvents or chemicals	NR	1		
			Ever	4	0.64 (0.18–2.30)		
		Multiple myeloma, mortality	Exposure to 1,1,1-TCE, women (HR):				
			No exposure to solvents or chemicals	NR	1		
			Ever	3	14.46 (3.24–64.63)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Talibov et al. (2014) Sweden, Finland, Norway, Iceland 1961–2005	Cases: 14 982 incident cases of AML diagnosed between 1961–2005 and identified within NOCCA, a registry-based cohort study of Nordic country residents who participated in censuses in 1960, 1970, 1980/81, or 1990 and were followed up through linkage to national cancer registries Controls: 74 505; 5 controls per case randomly selected from NOCCA cohort members alive and free of AML on the case's date of diagnosis and further matched on year of birth, sex, and country. Exposure assessment method: records; used self-reported jobs to the census and NOCCA-JEM that includes semiquantitative estimates of prevalence exposed, mean level of exposure, and duration	AML, incidence	Cumulative exposure to 1,1,1-TCE (HR):			Age, year of birth, sex, country, aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride [dichloromethane], perchloroethylene [tetrachloroethylene], other organic solvents, formaldehyde, ionizing radiation	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Intensity and prevalence estimates based on actual data. Could be missing exposed jobs due to 10 yr census collection. Prevalence was included in cumulative exposure but is not a component of toxicity. Other comments: conducted sensitivity analyses with 3, 5, 7, 10, and 20 yr exposure lags. Note: some of the reported exposure categories overlap. *Strengths*: very large study size; a detailed, time-specific, and quantitative JEM was applied; cancer diagnoses were ascertained through linkage to national cancer registries. *Limitations*: exposure estimates were based on census data on jobs, giving limited information on jobs held during the lifetime; no data on smoking habits were available
			No solvent exposures	NR	1		
			≤ 5.6 ppm-years	566	0.89 (0.76–1.04)		
			5.6–12.7 ppm-years	244	0.86 (0.71–1.05)		
			> 12.7 ppm-years	86	0.81 (0.61–1.08)		
			Trend-test *P* value, 0.58				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Talibov et al. (2017) Sweden, Finland, Norway, Iceland 1961–2005	Cases: 20 615; incident cases of CLL diagnosed between 1961 and 2005 with no previous history of cancer, identified within NOCCA, a registry-based cohort study of Nordic country residents who participated in censuses in 1960, 1970, 1980/81 or 1990 and were followed up through linkage to national cancer registries Controls: 103 075; 5 controls per case, randomly selected from NOCCA cohort members alive and with no previous history of cancer as of the case's date of diagnosis and further matched on year of birth, sex, and country. Exposure assessment method: records; used self-reported jobs to the census and NOCCA-JEM that includes semiquantitative estimates of prevalence exposed, mean level of exposure, and duration	NHL (CLL), incidence NHL (CLL), incidence	Cumulative exposure to 1,1,1-TCE, men (OR): No solvent exposures ≤ 5.6 ppm-years 5.6–12.9 ppm-years > 12.9 ppm-years Trend-test *P* value, 0.39 Cumulative exposure to 1,1,1-TCE, women (OR): No solvent exposures ≤ 5.6 ppm-years 5.6–12.9 ppm-years > 12.9 ppm-years Trend-test *P* value, 0.19	 NR 884 352 180 NR 96 41 6	 1 0.99 (0.86–1.13) 0.95 (0.81–1.12) 1.18 (0.95–1.45) 1 1.11 (0.76–1.62) 1.19 (0.73–1.96) 0.70 (0.28–1.75)	Age, year of birth, country, benzene, methylene chloride [dichloromethane], perchloroethylene [tetrachloroethylene], trichloroethylene, other organic solvents, formaldehyde, ionizing radiation	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Intensity and prevalence estimates based on actual data. Could be missing exposed jobs due to 10 yr census collection. Prevalence was included in cumulative exposure but is not a component of toxicity. Metrics were all categorical. Other comments: Conducted sensitivity analyses with 5, 10, and 20 yr exposure lags. Some of the reported exposure categories overlap. *Strengths*: very large study size; a detailed, time-specific, and quantitative JEM was applied; cancer diagnoses were ascertained through linkage to national cancer registries. *Limitations*: exposure estimates were based on census data on jobs, giving limited information on jobs held during the lifetime.

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; HR, hazard ratio; ICD, International Classification of Diseases; JEM, job-exposure matrix; NHL, non-Hodgkin lymphoma; NOCCA, Nordic Occupational Cancer Study; NOCCA-JEM, Nordic Occupational Cancer Study job-exposure matrix; NR, not reported; OR, odds ratio; ppm, parts per million; SIR, standardized incidence ratio; 1,1,1-TCE, 1,1,1-trichloroethane; yr, year.

tetrachloroethylene, and chloroform). Correlations between solvent exposures were not reported. Using Cox regression models, hazard ratios were calculated to estimate cancer risks for exposed versus unexposed workers using attained age as the time scale and adjusting for race. The authors observed a statistically non-significant association between exposure to 1,1,1-trichloroethane and mortality from non-Hodgkin lymphoma (NHL) among male workers (hazard ratio, HR, 1.51; 95% CI, 0.61–3.73; 12 exposed cases). No deaths attributable to NHL among exposed women were observed. For multiple myeloma, an association with 1,1,1-trichloroethane with wide confidence limits was observed among women (HR, 14.46; 95% CI, 3.24–64.63; 3 exposed cases). No association was apparent for men (HR, 0.64; 95% CI, 0.18–2.30; 4 exposed cases). [The study had several strengths, including a long period of follow-up and the use of an internal comparison group of unexposed workers for the analysis, avoiding potential "healthy worker effect" bias from comparisons with the general population. The exposure assessment was performed by industrial hygienists with access to the workplace facilities and records. Limitations included the small number of mortality end-points among the exposed, the qualitative nature of the exposure assessment, the difficulty in linking participants to estimates often associated with no more detail than job title, the lack of continued exposure assessment after 1982, and the potential for confounding from co-exposure to other organic solvents.]

A case–control study nested within a registry-based study on cancer caused by occupational exposures in the Nordic countries, known as the Nordic Occupational Cancer Study (NOCCA), investigated the risk of acute myeloid leukaemia (AML) in relation to occupational exposure to 1,1,1-trichloroethane and other solvents (Talibov et al., 2014). NOCCA is a cohort study including 14.9 million persons from Denmark, Finland, Iceland, Norway, and Sweden who participated in one or more population censuses in 1960, 1970, 1980/1981, and/or 1990. For Sweden and Norway, data used were from censuses in 1960 and later, and for Finland from 1970 or later. For Iceland, data from the census in 1981 were used. Participants from Denmark were not included in the case–control study since individual-level records were not accessible. Cases of AML diagnosed between 1961 and 2005 in the cohort were identified from the cancer registries in the respective countries. Five controls per case were randomly sampled from cohort members who were alive and free of AML on the date of diagnosis of the case and were further matched on year of birth, sex, and country. A JEM (the NOCCA-JEM) assigned exposure estimates for six individual solvents and four solvent groups to more than 300 occupations across four time periods: 1945–1959, 1960–1974, 1975–1984, and 1985–1994. Exposure to 1,1,1-trichloroethane for the study participants was estimated by application of the JEM to the job titles in the available censuses, and lifetime cumulative exposure was calculated as the product of exposure prevalence, exposure intensity, and exposure duration, summed over job titles in the censuses from ages 20 to 65 years. Conditional logistic regression was applied, adjusting for exposure to solvents other than 1,1,1-trichloroethane, formaldehyde, and ionizing radiation.

There were 7751 cases of AML among men and 7231 among women. The risk of AML was not related to cumulative exposure to 1,1,1-trichloroethane, with hazard ratios below 1 observed for each category of cumulative exposure. [The Working Group noted that the study had a strength in the very large sample size but that the use of census data for occupational titles gave limited information on jobs held over the lifetime. For early periods of follow-up only one census may have been available, and there was a long period (from 1990 until end of follow-up in 2005) for which exposure was not known. The JEM was well developed, but JEMs have limited

ability to identify persons with low and high exposure within an occupation and this issue, with the limited information from the census jobs and lack of information on industry, contributed to misclassification of exposure.]

Talibov et al. (2017) reported a study on chronic lymphocytic leukaemia (CLL) and exposure to solvents conducted within the NOCCA cohort using a nested case–control design similar to that of Talibov et al. (2014). The same cohort was used and analysed with similar methods, here focusing on 20 615 cases of CLL diagnosed in 1961–2005, and 103 075 controls, selected as in Talibov et al. (2014). A small difference in the exposure assessment was that occupational titles from the census in 1990 were not used for Norway. Exposure to six specific solvents and two groups of solvents were assessed by the NOCCA-JEM. In addition to cumulative exposure, peak exposure and average exposure levels were also assessed. Conditional logistic regression was applied, adjusting for exposure to the other included solvents, formaldehyde, and ionizing radiation.

The odds ratio for CLL in relation to occupational exposure to 1,1,1-trichloroethane was close to unity in all three categories of cumulative exposure and there was no evidence of an exposure–response relation for men (P for trend, 0.39) or women (P for trend, 0.19). Sensitivity analyses incorporating lag time, peak exposure, or average exposure level in the model gave no further evidence of an association with exposure to 1,1,1-trichloroethane. [The Working Group noted that the study had a strength in its very large sample size, but that the use of census data for occupational titles gave limited information on jobs held over the lifetime. For early periods of follow-up, only one census may have been available, and there was a long period (from 1990 until the end of follow-up in 2005) for which exposure was not known. The JEM was well developed, but JEMs have limited ability to identify persons with low or high exposure within an occupation,

and this issue, with the limited information from the census jobs and lack of information on industry, contributed to misclassification of exposure.]

2.1.2 Case–control studies

See Table 2.2.

The Working Group identified five case–control studies on the association between exposure to 1,1,1-trichloroethane and cancers of the haematopoietic and lymphoid tissues. All studies were population-based.

A case–control study investigating the association between childhood leukaemia and maternal exposure to organic solvents before and during pregnancy was performed in the province of Quebec, Canada (Infante-Rivard et al., 2005). Cases of acute lymphoblastic leukaemia (n = 790) were identified from hospitals with regional coverage. Children aged 0–9 years at diagnosis were included for the period 1980–1993, and children aged up to 14 years at diagnosis were included for 1994–2000. Controls (n = 790) individually matched on age and sex were identified from registers representing the population of the area. The response rate was high for cases (93.1%) and for controls (86.2%). The parents were contacted by telephone and a structured questionnaire was used to obtain occupational histories of the mothers from age 18 years up to birth of the child. For the 2 years before pregnancy and up to birth, a semi-structured questionnaire was used to investigate details of each occupation held, including job titles, industry type with address and location, and information about materials handled and produced, and the specific work environment. Job-specific questionnaires were used for certain occupations. Exposures to 21 specific solvents and 6 mixtures were assigned by a team of chemists and industrial hygienists using expert assessment methods. There were also questions about exposures to solvents during a hobby. Conditional logistic

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Infante-Rivard et al. (2005) Province of Quebec, Canada 1980–2000	Cases: 790 cases of incident childhood ALL were identified from hospitals with regional coverage; mothers responded to the questionnaire Controls: 790 controls; mothers of children (matched on age and sex of the case and identified from registers representing the population of the area) responded to the questionnaire Exposure assessment method: expert judgement; full work histories, specialized questionnaires [presumed measurement data], and extensive review used to assign participant-specific semiquantitative estimates of confidence, frequency, and intensity for each job held	Childhood cancer (ALL), incidence Childhood cancer (ALL), incidence	Maternal exposure to 1,1,1-TCE from 2 yr before pregnancy up to birth (OR): Never Ever Maternal exposure to 1,1,1-TCE during pregnancy (OR): Never Ever	NR NR NR NR	1 7.55 (0.92–61.97) 1 4.07 (0.45–36.7)	Age and sex of the child, maternal age, and education	*Exposure assessment critique*: Substantial data available for assessment including [presumably] published measurement data. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. confidence, frequency, and intensity) is a key strength. Cumulative exposure did not include intensity. Metrics were all categorical. *Strengths*: large study size and a very detailed and thorough process for exposure classification; high participation rate among cases and controls; cancer cases were ascertained through clinical diagnoses at hospitals. *Limitations*: very wide confidence intervals gave imprecise risk estimates.

Table 2.2   (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Miligi et al. (2006) Italy, 8 areas 1991–1993	Cases: 1428 cases of NHL, 304 cases of HD; incident cases in people aged 20–74 yr identified from hospitals and pathology departments; cases of CLL were included among the NHL cases Controls: 1530 controls were selected randomly from population register, frequency-matched on age and sex Exposure assessment method: expert judgement; full work histories and job- or industry-specific questionnaires used to assign participant-specific semiquantitative estimates of probability and intensity of exposure for each job; cited Costantini et al. (2001), which indicated that only jobs held for ≥ 5 yr more than 5 yr before diagnosis were considered	NHL	1,1,1-TCE exposure intensity, 5 yr lag (OR):			Age, sex, study area, education	*Exposure assessment critique*: Slightly more information was available for assessment because of the job- and industry-specific modules. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. probability and intensity) is a key strength. [Assumed from Costantini et al., 2001)] that only jobs with ≥ 5 yr of employment more than 5 yr before diagnosis were considered which could have resulted in exposed participants being assigned to the unexposed group. Cumulative exposure was not evaluated. Metrics were all categorical. *Strengths*: high participation rate; detailed exposure assessment method harmonized between centres; cancer diagnoses ascertained through hospital and pathology departments with additional review of doubtful cases. *Limitations*: low numbers precluded analysis according to exposure duration and subtypes of NHL.
			No exposure to any solvent	820	1		
			Very low or low	15	0.7 (0.3–1.3)		
			Medium or high	5	0.7 (0.2–2.2)		
			Trend-test *P* value, 0.24				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gold et al. (2011) USA, Seattle-Puget Sound region and Metropolitan Detroit 1 January 2000 to 31 March 2002	Cases: 180 incident cases of multiple myeloma identified from regional cancer registries Controls: 481 controls obtained from a parallel study on NHL from the population in same regions, obtained by random-digit dialling and from medical service files. Exposure assessment method: expert judgement; full work histories, job-specific modules, literature review, measurement data (for deterministic modelling of intensity) and [presumed] study-specific task- and job-exposure matrices (for imputation when participant-specific information was missing) used to assign participant-specific semiquantitative estimates of probability, frequency, and intensity for each job held for ≥ 1 yr	Multiple myeloma	Exposure to 1,1,1-TCE (OR): Unexposed 144 Ever 36		1 1.8 (1.1–2.9)	Age, sex, race, education, study area	*Exposure assessment critique*: Substantial data available for assessment including published measurement data. Evaluation was participant-specific. Job- and task-specific matrices (when participant-specific information was missing) probably increased consistency. Careful consideration of each job held by each participant (i.e. probability, frequency, intensity, and confidence of exposure) is a key strength. Metrics were all categorical. *Strengths*: study size and detailed exposure assessments; cancer diagnoses ascertained through regional cancer registries and medical record review. *Limitations*: low participation rate among controls; potential for survival bias as 18% of eligible cases died before they could be contacted.
		Multiple myeloma	Duration of exposure to 1,1,1-TCE (OR): Unexposed 144 1–3 yr 7 4–8 yr 11 9–21 yr 11 22–45 yr 7 Trend-test *P* value, 0.17		1 1.6 (0.6–4.3) 2.3 (1.0–5.3) 1.9 (0.8–4.5) 1.3 (0.5–3.3)		
		Multiple myeloma	Cumulative 1,1,1-TCE exposure index (OR): Unexposed 144 1–53 7 54–605 10 606–3750 8 3751– 57 000 11 Trend-test *P* value, 0.19		1 1.7 (0.7–4.4) 2.2 (0.9–5.3) 1.4 (0.5–3.4) 1.9 (0.8–4.4)		
		Multiple myeloma	Cumulative 1,1,1-TCE exposure index, 10 yr lag (OR): Unexposed 147 1–49 7 50–342 7 343–2781 8 2782– 49 500 11 Trend-test *P* value, 0.21		1 1.8 (0.7–4.6) 1.5 (0.6–3.3) 1.3 (0.5–3.3) 1.8 (0.8–4.1)		
		Multiple myeloma	Reanalysis with jobs assessed with low confidence considered unexposed: any exposure to 1,1,1-TCE (OR): Unexposed 163 Ever 17		1 2.2 (1.1–4.4)		

Table 2.2   (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gold et al. (2011) USA, Seattle-Puget Sound region and Metropolitan Detroit 1 January 2000 to 31 March 2002 (cont.)		Multiple myeloma	Reanalysis with jobs assessed with low confidence considered unexposed: duration of exposure to 1,1,1-TCE (OR):			Age, sex, race, education, study area	
			Unexposed	163	1		
			1–5 yr	5	1.8 (0.6–5.7)		
			6–16 yr	6	6.7 (1.5–29)		
			17–25 yr	4	1.6 (0.4–6.0)		
			26–45 yr	2	1.3 (0.2–7.4)		
			Trend-test P value, 0.27				
		Multiple myeloma	Reanalysis with jobs assessed with low confidence considered unexposed: cumulative 1,1,1-TCE exposure index (OR):				
			Unexposed	163	1		
			1–378	5	3.7 (1.0–13)		
			379–1938	2	1.1 (0.2–5.8)		
			1939–10 012	6	3.0 (0.9–10)		
			10 013–57 000	4	1.5 (0.4–5.8)		
			Trend-test P value, 0.33				
		Multiple myeloma	Reanalysis with jobs assessed with low confidence considered unexposed: cumulative 1,1,1-TCE exposure index, 10 yr lag (OR):				
			Unexposed	164	1		
			1–303	5	3.1 (0.9–11)		
			304–1690	0	–		
			1691–4500	5	2.3 (0.6–8.0)		
			4501–49 500	6	2.8 (0.8–9.9)		
			Trend-test P value, 0.07				

Table 2.2   (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985	Cases: 3730 cancer cases at 11 organ sites, including 215 NHL cases; male incident cases of histologically confirmed NHL from 18 large hospitals in Montreal metropolitan area, Canadian citizens aged 35–70 yr (median, 57 yr) Controls: 533 population controls, 2341 other cancer controls; population controls obtained randomly from population-based electoral lists, stratified by sex and age; other cancer controls from other participating cases Exposure assessment method: expert judgement; full work histories and specialized questionnaires, [presumed measurement data], and extensive review to assign participant-specific semiquantitative estimates of confidence, frequency and intensity for each job held	NHL (ICD-9, codes 200 and 202)	Any exposure to 1,1,1-TCE, 5 yr lag, men (OR):			Age, census tract median income, education, ethnicity, self/proxy, smoking (cigarette-years)	*Exposure assessment critique*: Substantial data available for assessment including [presumably] published measurement data. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. confidence, frequency, and intensity) is a key strength. Cumulative exposure included confidence, which is not a component of toxicity. Metrics were all categorical. *Strengths*: very detailed process for exposure classification; ascertained histologically confirmed cancer diagnoses through hospitals. *Limitations*: very low number of exposed cases ($n = 5$).
			No chlorinated solvent exposure	155	1		
			Any	5	1.2 (0.4–4.0)		
		NHL (ICD-9, codes 200 and 202)	Substantial exposure to 1,1,1-TCE, 5 yr lag, men (OR)				
			No chlorinated solvent exposure	155	1		
			Substantial	2	0.8 (0.1–4.0)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Callahan et al. (2018) USA (Iowa, Los Angeles, Seattle, Detroit) July 1998 to June 2000	Cases: 1189 incident cases of NHL identified from the NCI-SEER registry; response rate, 76%; cases of CLL were included among the NHL cases Controls: 982 controls, frequency-matched on age, sex, race, and area, were recruited via random-digit dialling for ages < 65 yr and from Medicare files for ages 65–74 yr; response rate, 52% Exposure assessment method: expert judgement; full work histories, job-specific modules, literature review, measurement data (for deterministic modelling of intensity), [presumed] study-specific task- and job- and task-specific matrices (for imputation when participant-specific information was missing) used to assign participant-specific semiquantitative estimates of probability, frequency, and intensity for each job held	NHL (ICD-O-3, codes 967–972)	1,1,1-TCE exposure probability (OR): Unexposed < 50% ≥ 50%	619 551 14	1 1.1 (0.9–1.3) 1.0 (0.4–2.1)	Age, sex, study area, race, education	*Exposure assessment critique*: Substantial data available for assessment including published measurement data. Evaluation was participant-specific. Deterministic modelling of intensity and job- and task-specific matrices (when participant-specific information was missing) probably increased consistency. Careful consideration of each job held by each participant (i.e. probability, frequency, intensity, and confidence of exposure) is a key strength. Published measurement data modelled to estimate intensity but was not used. Intensity not used in analyses. Metrics were all categorical. Other comments: conducted sensitivity analyses with 5 and 15 yr exposure lags *Strengths*: large study size; very detailed assessment of individual exposure; cancer diagnoses ascertained through regional cancer registries and medical record review. *Limitations*: a somewhat low response rate among controls.
		NHL (ICD-O-3, codes 967–972)	Duration of 1,1,1-TCE exposure at probability ≥ 50% (OR): Unexposed ≤ 312 h > 312 h Trend-test *P* value, 0.47	619 2 11	1 0.3 (0.1–1.6) 1.5 (0.6–4.3)		

ALL, acute lymphoblastic leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; HD, Hodgkin disease; ICD-9, International Classification of Diseases, 9th Revision; ICD-O-3, International Classification of Diseases for Oncology, 3rd Revision; NCI-SEER, United States National Cancer Institute-Surveillance, Epidemiology, and End Results Program; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; 1,1,1-TCE, 1,1,1-trichloroethane; yr, year.

regression was applied, adjusting for maternal age and education.

The exposure prevalence for specific solvents was not reported, with only the number of discordant exposure pairs provided. There were only eight discordant pairs for exposure to 1,1,1-trichloroethane from 2 years before pregnancy up to birth, and five discordant pairs for exposure during pregnancy. For the 2-year period before pregnancy and up to birth, the odds ratio associated with exposure to 1,1,1-trichloroethane was 7.55 (95% CI, 0.92–61.97). For exposures during pregnancy, the odds ratio was 4.07 (95% CI, 0.45–36.7). [The Working Group noted that there was a detailed exposure assessment process but very imprecise risk estimates, and it was not possible to examine exposure–response associations, which limited the informativeness of this study.]

The association between occupational exposure to organic solvents and risk of NHL and Hodgkin disease was investigated in a population-based case–control study in Italy (Miligi et al., 2006). Incident cases in people aged 20–74 years were identified between 1991 and 1993 from hospitals and pathology departments in eight study areas where manufacturing industries using solvents were prevalent. Controls were selected randomly from population registers in the same areas, frequency-matched on age and sex. Cases of CLL were included among the NHL cases since NHL and CLL were considered to represent the same disease entity. Occupational histories were obtained by interviews primarily carried out at the home of the study participants. A small proportion of interviews were performed via proxies. The response rate was 83% among NHL cases, 88% among cases of Hodgkin disease, and 73% among controls. Job-specific questionnaires were used, and exposure to specific solvents and groups of solvents were coded blindly by expert judgement. A JEM was developed to aid in harmonizing assessments between centres. Probability (low/medium/high) and intensity (very low/low/medium/high) of exposure were coded for eight specific solvents and five groups of solvents. Logistic regression models were applied adjusting for sex, age, area, and education, and using participants not exposed to any solvent as referents. For each agent, analyses were based on participants with a medium or high probability of exposure, while those assigned a low probability were excluded.

There were 1428 cases of NHL (including CLL), 304 cases of Hodgkin disease, and 1530 controls included in the final data set. There was a relatively low prevalence of exposure to 1,1,1-trichloroethane (20 cases of NHL and 32 controls were exposed), and odds ratios for NHL were below 1 regardless of exposure intensity. Analyses across categories of exposure duration and for individual NHL subtypes gave very low numbers and odds ratios were not estimated. The risk of Hodgkin disease in relation to exposure to 1,1,1-trichloroethane was not reported because numbers of cases were small. [The Working Group noted that there was a high participation rate and a detailed exposure assessment procedure. The classification of exposure as having had at least 5 years of employment more than 5 years before diagnosis may have reduced study informativeness, as those with a shorter exposure duration were included in the unexposed group.]

Gold et al. (2011) conducted a case–control study on the association between six chlorinated solvents and the risk of multiple myeloma. The study was based on cases and controls from two urban areas in the USA: the Seattle-Puget Sound region of Washington State and the Detroit metropolitan area of Michigan. The study included 180 incident cases (55% men), aged 35–74 years, diagnosed between 1 January 2000 and 31 March 2002, identified from regional cancer registries. Controls from a parallel study on NHL in the same areas (Chatterjee et al., 2004) were used as controls in the present study. Controls under age 65 years were recruited by random-digit dialling, and controls aged 65–74 years were identified

from medical service files. In total, 481 controls were included. The response rate among cases that were alive, could be located, and confirmed to be eligible was 71%. The response rate among controls used for this study was 52%. An occupational history (from 1941 for cases and 1946 for controls) was obtained by personal interviews, including description and main duties for each job held for at least 1 year. Job-specific questionnaires were used for 20 occupations involving potential exposure to solvents. Exposures were assessed by an occupational epidemiologist and reviewed by an industrial hygienist. Exposure probability, frequency, intensity, and confidence were assessed for each of six chlorinated solvents. Cumulative exposure was calculated as the product of intensity, frequency, and duration summed over jobs with a probability category of 2 or higher (i.e. participants with an exposure probability of 10% or more in the occupation) in the work history. Individuals with a probability of exposure of ≥ 10% to 1,1,1-trichloroethane included 36 cases (20%) and 65 controls (14%). Unconditional logistic regression was applied, adjusting for age, sex, race, education, and study area, and using those unexposed to the respective solvents as referents.

Ever versus never exposure to 1,1,1-trichloroethane was associated with an increased risk of multiple myeloma (OR, 1.8; 95% CI, 1.1–2.9), and this association remained in a sensitivity analysis reassigning jobs with low confidence in the assessment to the unexposed category. In analyses across categories of exposure duration, cumulative exposure, and 10-year lagged cumulative exposure, odds ratios were above unity but with no indication of an exposure–response trend. The risk was systematically higher in all categories of exposure versus the unexposed, but with an absence of trend with increasing exposure to any of the exposure metrics. Trend tests results gave $P = 0.17$ for duration, $P = 0.19$ for cumulative exposure, and $P = 0.21$ for cumulative exposure lagged 10 years. Similar findings

were obtained in a sensitivity analysis reassigning jobs with low confidence to the unexposed category. [The Working Group noted that there was a detailed exposure assessment procedure and that ever exposure to 1,1,1-trichloroethane was associated with a significantly increased risk of multiple myeloma. However, there was no exposure–response trend in terms of exposure duration, cumulative exposure, or 10-year lagged cumulative exposure. A lower participation rate among controls than among cases may have introduced bias. It was noted but not considered to be an important limitation that work histories for controls did not cover the period 1941–1946 (as it did for cases), since exposure to 1,1,1-trichloroethane was not common at that time.]

A case–control study on a large set of cancers was carried out in Montreal, Canada. Detailed data on methods and basic results were published earlier by Siemiatycki (1991). Findings regarding 11 selected cancers in relation to exposure to chlorinated solvents were investigated by Christensen et al. (2013). The study was based on incident cases of cancer among male Canadian citizens aged 35–70 years identified from the 18 largest hospitals in the Montreal area from 1979 to 1985. Population controls were selected randomly among men from electoral lists, frequency matched on age. The present report concerned 11 specific cancers sites, among them 215 cases of NHL (ICD-9, codes 200 and 202). The response rate among all cancer cases was 82%, but the response rate among NHL cases was not reported. There were 533 population controls (response rate, 72%). For certain analyses, cases of cancer at other organ sites than the one under study were used as controls (cancer controls) and were combined (weighted equally) with the population controls. Study participants were interviewed regarding demographic and lifestyle factors according to a structured questionnaire. For occupational history, a semi-structured questionnaire was used that included detailed

questions on job tasks, company, and workplace characteristics. Job-specific questionnaires were used for certain jobs. Exposures were assessed from the questionnaires by a team of chemists and industrial hygienists. For each job, the team coded confidence, frequency, and relative level of concentration of the exposure. Exposure was coded for two groups of chlorinated solvents and six specific chlorinated solvents, including 1,1,1-trichloroethane. Exposures occurring in the past 5 years were excluded owing to latency considerations. Unconditional logistic regression was applied, and adjusted for age, median income in neighbourhood of residence, education, ethnicity, self versus proxy respondent, and tobacco smoking (cigarette-years). Persons never exposed to chlorinated solvents were used as the referent category.

Exposure to 1,1,1-trichloroethane was relatively rare, with 1.9% of the population controls having been exposed. There were 5 cases of NHL in people who had been exposed to 1,1,1-trichloroethane. Using general population controls, no statistically significant elevated odds ratios were observed, either in those with any exposure to 1,1,1-trichloroethane (OR, 1.2; 95% CI, 0.4–4.0; 5 cases) or in those with substantial exposure to 1,1,1-trichloroethane (OR, 0.8; 95% CI, 0.1–4.0; 2 cases). Findings were similar using the general population and cancer controls combined. [The Working Group noted that there was a detailed process for exposure assessment but that the very low number of exposed cases of NHL limited the precision in risk estimates. In addition, intensity and/or cumulative exposure metrics were not specifically evaluated.]

The relation between cancer and occupational exposure to chlorinated organic solvents was investigated in the NCI-SEER study, a population-based case–control study performed in the USA (Callahan et al., 2018). This study investigated the risk of NHL in relation to exposure to 1,1,1-trichloroethane and four other specific chlorinated organic solvents. The study was based on data from four regions: the state of Iowa, Los Angeles county, and the metropolitan areas of Seattle and Detroit. Incident cases of NHL (ICD-O-3, codes 967–972) in people aged 20–74 years were identified between July 1998 and June 2000. Controls, frequency matched on age, sex, race, and area, were recruited via random-digit dialling for ages under 65 years and from Medicare files for ages 65–74 years. Among participants who could be traced, the response rate was 76% for cases and 52% for controls. Participants were interviewed in their homes using computer-aided questionnaires. Background data, occupational history, and various details about the work environment were recorded for every occupation held for 6 months or longer. Thirty-two job- or industry-specific modules were used to identify details regarding exposure to organic solvents, including type of solvent used, frequency and time spent on solvent-related tasks, work practices, and use of personal protective equipment. An industrial hygienist classified exposure to five specific chlorinated organic solvents by first developing JEMs specific for jobs and tasks for each of the five substances. The hygienist then used these matrices in addition to participant-specific work task information to assess the probability, frequency, and intensity of exposure. Levels of confidence were assessed for all estimates. Assessments were combined into metrics of duration, cumulative hours, and weekly average of exposure levels for each of the substances. Unconditional logistic regression was applied adjusting for age, sex, study area, race, and education.

The study showed no evidence of an association between exposure to 1,1,1-trichloroethane and NHL when investigating risk in relation to exposure probability (< 50% or ≥ 50%) or cumulative hours of exposure (≤ 312 hours and > 312 hours). There was evidence for an association between NHL and exposure to carbon tetrachloride. [The Working Group noted that there was a detailed exposure classification process but a low response rate, especially among controls.

The number of cases with a high probability of exposure to 1,1,1-trichloroethane was low.]

2.2 Cancers of the brain and nervous system

See Table 2.3.

The Working Group identified four case–control studies and one cohort study investigating the risk of cancer of the brain and nervous system associated with exposure to 1,1,1-trichloroethane. Two of the case–control studies were population-based, one was hospital-based, and one was a multicentre study.

A population-based case–control study on mortality from astrocytic brain cancer in White men was performed in three areas of the USA where exposure to organic solvents was prevalent in petroleum-refining and chemical-manufacturing industries (Heineman et al., 1994). The study included deaths from astrocytic brain cancer in southern Louisiana from 1 January 1978 to 30 June 1980, and in northern New Jersey and Philadelphia from 1 January 1979 to 31 December 1981. Controls were selected randomly among White male residents deceased from causes other than brain cancer, cerebrovascular disease, epilepsy, suicide, and homicide, and frequency-matched on age, year of death, and study area. The next of kin of cases and controls were interviewed regarding occupational history, including data on job titles, tasks, company, industry type, and products. Of the 741 cases and 741 controls, next of kin could be traced for 88% of the cases and 83% of the controls. Of these next of kin, 74% provided complete interviews for cases and 63% for controls. After exclusion of non-astrocytic tumours, the final data set comprised 300 cases. Of the 386 controls with completed interviews, 320 remained after exclusion of deaths from lung cancer, liver cancer, leukaemia, Hodgkin disease, NHL, and cirrhosis of the liver. Exposure to six specific chlorinated organic solvents, including methyl chloroform [1,1,1-trichloroethane], was assessed by a set of JEMs, specific to a level of intensity and probability of exposure for time periods where exposure had been deemed to occur for each job title and industry (Gomez et al., 1994). The matrices were applied to the job histories by an algorithm that considered whether the job or the industry was the primary generator of exposure to incorporate the estimates into a single cumulative exposure estimate. Three semiquantitative exposure metrics were derived: exposure duration, cumulative exposure score, and average intensity of exposure. Adjusted logistic regression was applied in a stratified analysis using maximum likelihood estimates, with those unexposed to the specific substance as referents. Trends in the odds ratio over strata of exposure were evaluated by the Mantel method.

The risk of death from astrocytoma was evaluated through analysis of risk in relation to a large number of combinations of exposure probability (low/medium/high), intensity (low–medium or high), duration (2–20 or $\geq$ 21 years) and cumulative exposure score (low/medium/high). Probability of exposure to 1,1,1-trichloroethane was assessed as low for most of the cases and controls. Little indication of an association with exposure to 1,1,1-trichloroethane was found. There was no consistent evidence of increasing risk with exposure probability or cumulative exposure; however, risk increased with exposure duration (all probabilities combined) when compared with the unexposed (OR for 2–20 years, 1.1; 95% CI, 0.7–1.7; OR for $\geq$ 21 years, 1.8; 95% CI, 1.0–3.3; P for trend, < 0.05). There were some indications of a trend with exposure intensity in those exposed for $\geq$ 21 years: OR for low and medium intensity, 1.6 (95% CI, 0.9–3.1); OR for high intensity, 3.7 (95% CI, 0.7–27.9); P for trend, < 0.05. The risk associated with the individual chlorinated solvents with simultaneous adjustment for the other solvents in the study was investigated, but 1,1,1-trichloroethane was not

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Heineman et al. (1994) USA, 3 areas 1978–1980 (area I) or 1979–1981 (area II+III) Case–control	Cases: 300 men; deaths from astrocytic brain cancer initially identified from death certificates and confirmed by hospital diagnoses Controls: 320 men; deaths other than brain cancer and excluding deaths from cerebrovascular disease, epilepsy, suicide, homicide, selected cancers (lung, liver, leukaemia, HD, NHL) and cirrhosis of the liver and frequency-matched to cases on age, year of death, and study area. Exposure assessment method: questionnaire; full work histories taken by proxy and expert JEM used; estimated (semiquantitative estimates) intensity and probability by assigning probability and intensity separately to each job and to each industry and then combining them using an algorithm	Brain (astrocytoma), mortality	Duration of exposure to methyl chloroform [1,1,1-TCE], all probabilities (OR):			Age, year of death, study area	*Exposure assessment critique*: Evaluated several metrics. Unclear whether exposure assessment method produced valid results. Jobs limited by proxy reporting of full job history, which may miss key exposures. Metrics were all categorical. Other comments: conducted sensitivity analyses with 10 and 20 yr exposure lags. *Strengths*: detailed work histories and detailed assessments of individual exposure using a set of JEMs developed for this study. *Limitations*: job histories from next of kin; exposure metrics were semiquantitative.
			Unexposed	188	1		
			2–20 yr	63	1.1 (0.7–1.7)		
			≥ 21 yr	38	1.8 (1.0–3.3)		
			Trend-test *P* value, < 0.05				
		Brain (astrocytoma), mortality	Cumulative methyl chloroform [1,1,1-TCE] exposure score, all probabilities (OR):				
			Unexposed	188	1		
			Low score	34	1.0 (0.6–1.8)		
			Medium score	47	1.6 (1.0–2.7)		
			High score	20	1.3 (0.6–2.6)		
			Trend-test *P* value, > 0.05				
		Brain (astrocytoma), mortality	Average intensity of methyl chloroform [1,1,1-TCE] exposure, exposure duration 2–20 yr (OR):				
			Unexposed	188	1		
			Low and medium intensity	54	1.1 (0.7–1.8)		
			High intensity	9	0.9 (0.3–2.6)		
			Trend-test *P* value, > 0.05				
		Brain (astrocytoma), mortality	Average intensity of methyl chloroform [1,1,1-TCE] exposure, exposure duration ≥ 21 yr (OR):				
			Unexposed	188	1		
			Low and medium intensity	32	1.6 (0.9–3.1)		
			High intensity	6	3.7 (0.7–27.9)		
			Trend-test *P* value, < 0.05				

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Heineman et al. (1994) USA, 3 areas 1978–1980 (area I) or 1979–1981 (area II+III) Case–control (cont.)		Brain (astrocytoma), mortality	Methyl chloroform [1,1,1-TCE] exposure probability (OR):			Age, year of death, study area	
			Unexposed	188	1		
			Low probability	97	1.2 (0.8–1.7)		
			Medium probability	11	2.2 (0.7–7.6)		
			High probability	4	1.2 (0.2–7.3)		
			Trend-test P value, > 0.05				

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Anttila et al. (1995) Finland Enrolment, 1965–1983 (1,1,1-TCE: 1975–1983)/ follow-up, 1967–1992 Cohort	3974 workers (2050 men and 1924 women), 271 of whom were monitored for exposure to 1,1,1-TCE; workers biologically monitored for occupational exposure to three halogenated hydrocarbon solvents in Finland Exposure assessment method: quantitative measurements; a database of measurements in urine from trichloroethylene-, and blood from tetrachloroethylene- and 1,1,1-TCE-exposed participants was used to identify ever-exposed to the chemicals	[Brain and] nervous system (ICD-7, code 193), incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure	3	6.05 (1.25–17.7)	Age, sex, calendar period	*Exposure assessment critique*: Exposed were truly exposed. Blood levels only reflect short-term (days) exposures for 9 yr. No information was provided on the interpretation of the measurements or the participants' exposures, including possible exposure to 1,1,1-TCE outside the 1975–1983 window or to other agents. *Strengths*: exposure assessment was based on biological monitoring of exposure; long-term follow-up for cancer incidence ascertained through linkage to national cancer registry. *Limitations*: findings for brain cancer were based on only 3 cases; the quantitative exposure for these cases was not reported.

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Neta et al. (2012) USA, three hospitals 1994–1998 Case–control	Cases: 484 gliomas, 197 meningiomas; identified from referrals, diagnoses verified by microscopy Controls: 797; controls were selected among patients referred for non-malignant conditions: injuries, cardiovascular diseases, musculoskeletal conditions, digestive disorders, and other diagnoses, and frequency-matched to cases on sex, age class, race, hospital, and proximity to the hospital Exposure assessment method: questionnaire; full work histories, job-specific modules, literature review, measurement data, and [presumed] study-specific task- and JEM (for imputation when participant-specific information was missing) used to assign participant-specific semiquantitative estimates of probability, frequency, intensity and confidence for each job	Brain (glioma; ICD-O-2, codes 9380–9473), incidence	Probability of exposure to 1,1,1-TCE (OR):			Sex, age, race, hospital, proximity to hospital	*Exposure assessment critique*: Substantial data available for assessment, including published measurement data. Evaluation was participant-specific. Deterministic modelling of intensity and job- and task-specific matrices (when participant-specific information was missing) probably increased consistency. Careful consideration of each job held by each participant (i.e. probability, frequency, intensity, and confidence of exposure) is a key strength. Metrics were all categorical. Other comments: conducted sensitivity analyses with 10 yr exposure lag. *Strengths*: detailed exposure assessment procedure; cancer diagnoses ascertained through hospitals. *Limitations*: use of hospital-based controls may attenuate observed risks.
			Unexposed	334	1		
			Possible	140	0.8 (0.6–1.0)		
			Probable	10	1.0 (0.4–2.4)		
		Brain (glioma), incidence	Years of probable exposure to 1,1,1-TCE (OR):				
			Unexposed	334	1		
			Low	5	1.0 (0.3–3.4)		
			High	5	0.8 (0.2–2.7)		
			Trend-test *P* value, 0.76				
		Brain (glioma), incidence	Cumulative probable exposure to 1,1,1-TCE (OR):				
			Unexposed	334	1		
			Low	6	1.1 (0.3–3.5)		
			High	4	0.7 (0.2–2.6)		
			Trend-test *P* value, 0.70				
		Brain (glioma), incidence	Average weekly probable 1,1,1-TCE exposure (OR):				
			Unexposed	334	1		
			Low	6	1.0 (0.3–3.3)		
			High	4	0.8 (0.2–2.8)		
			Trend-test *P* value, 0.76				
		Brain (glioma), incidence	Highest probable 1,1,1-TCE exposure (OR):				
			Unexposed	334	1		
			Low	5	0.9 (0.3–3.1)		
			High	5	0.9 (0.3–3.0)		
			Trend-test *P* value, 0.8				
		Brain (meningioma, ICD-O-2, codes 9530–9538), incidence	Probability of exposure to 1,1,1-TCE (OR):				
			Unexposed	146	1		
			Possible	46	0.8 (0.5–1.2)		
			Probable	5	2.3 (0.7–7.2)		

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ruder et al. (2013) Non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin, USA 1995–1997 Case–control	Cases: 457 men and 341 women; cases of histologically verified glioma were identified from participating medical facilities and neurosurgeon offices Controls: 648 men and 527 women; 2 controls per case, frequency-matched on sex and age, were selected from driving license registers (for ages < 65 yr) and from Medicare data tapes (ages 65–80 yr) Exposure assessment method: questionnaire; full work histories, exposure modules, literature review and measurement data for modelling of intensity used to assign participant-specific semiquantitative estimates of probability, frequency, and confidence for each job held	Brain (glioma), incidence	Any exposure to 1,1,1-TCE (OR):			Age, sex, education	*Exposure assessment critique*: Substantial data available for assessment available, including published measurement data. Evaluation was participant-specific. Deterministic modelling of intensity and job- and task-specific matrices (when participant-specific information was missing) probably increased consistency. Careful consideration of each job held by each participant (i.e. probability, frequency, intensity, and confidence of exposure) is a key strength. Metrics were all categorical. *Strengths*: detailed exposure assessment; histologically confirmed cancer diagnoses were ascertained through medical facilities. *Limitations*: uniformly, and largely statistically significantly, low risks in association with all six studied solvents raises the question of bias.
			Never	494	1		
			Ever	304	0.75 (0.61–0.90)		
		Brain (glioma), incidence	Any exposure to 1,1,1-TCE, men (OR):				
			Never	243	1		
			Ever	214	0.83 (0.64–1.06)		
		Brain (glioma), incidence	Any exposure to 1,1,1-TCE, women (OR):				
			Never	251	1		
			Ever	90	0.64 (0.47–0.88)		
		Brain (glioma), incidence	Natural logarithm of cumulative 1,1,1-TCE exposure (ppm):				
			Per 1-unit increase	304	0.97 (0.96–0.99)		

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
McLean et al. (2014) Australia, Canada, France, Germany, Israel, New Zealand, UK 2000–2004 Case–control	Cases: 1906 incident cases of meningioma in ages 30–59 yr (age range varied between centres) Controls: 5565 controls were randomly selected from the population in each centre, individually or frequency-matched to the cases on year of birth, sex, and study region Exposure assessment method: questionnaire; full work histories were used and coded using ISCO and ISIC and a coding guideline to help with consistency across study site along with a study-specific JEM (INTEROCC-JEM) that was based on FINJEM plus modification from Montreal data to assign prevalence and intensity for all jobs held for ≥ 6 months	Brain (meningioma), incidence	Ever exposed (probability ≥ 25%) to 1,1,1-TCE, 5 yr lag (OR): Never Ever	1811 1	1 1.35 (0.10–17.55)	Age, sex, region, education	*Exposure assessment critique*: Stronger study than many of the other FINJEM/NOCCA-JEM studies because work histories were self-reports from interviews that gathered more information than job only. FINJEM is a robust and well-developed JEM. FINJEM was normalized to the country. Intensity and prevalence estimates based on actual data. Definition of cumulative was unclear but may include prevalence, which is not a component of toxicity. The JEM was modified with Montreal data but unclear how. Differences across countries were taken into account during the exposure assessment, but details on this were not provided. Metrics were all categorical. Other comments: conducted sensitivity analyses with 1 and 10 yr exposure lags.

Table 2.3   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
McLean et al. (2014) Australia, Canada, France, Germany, Israel, New Zealand, UK 2000–2004 Case–control (cont.)							*Strengths*: large multicentre study; ascertained histologically confirmed or diagnostically unequivocal cancer diagnoses. *Limitations*: the method for exposure classification was not sensitive enough to identify persons with exposure to 1,1,1-TCE

CI, confidence interval; FINJEM, Finnish Job Exposure Matrix; HD, Hodgkin disease; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; INTEROCC, Occupational Exposures and Brain Cancer study; ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; JEM, job-exposure matrix; NHL, non-Hodgkin lymphoma; NOCCA, Nordic Occupational Cancer Study; NOCCA-JEM, Nordic Occupational Cancer Study job-exposure matrix; OR, odds ratio; SIR, standardized incidence ratio; 1,1,1-TCE, 1,1,1-trichloroethane; UK, United Kingdom; yr, year.

included in this analysis since the evidence for a primary effect of this substance was assessed as weak. [The Working Group noted that there were some weak indications of an increased risk of mortality from brain astrocytoma associated with exposure to 1,1,1-trichloroethane, but the study did not evaluate whether this could be caused by concurrent exposure to other chlorinated organic solvents. Work histories from next of kin and the use of an imprecise exposure assessment algorithm reflected limited consideration of temporal trends in use when estimating probability and intensity of exposure. Additionally, the use of semiquantitative exposure metrics and low specificity in the exposure assessment may have contributed to misclassification of exposure, leading to attenuated risks.]

The incidence of cancer was investigated in a cohort of Finnish workers undergoing mandatory biological monitoring for occupational exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane (Anttila et al., 1995). Details of the study have been reviewed in Section 2.1.1. The cohort comprised 3974 male and female workers. Of these, 140 men and 131 women had been exposed to 1,1,1-trichloroethane, monitored from 1975 to 1983, with on average two blood measurements of 1,1,1-trichloroethane per person. Cancer incidence was ascertained from date of first exposure to 1,1,1-trichloroethane up to 1992. Expected numbers of cancer cases specific to sex, age, and calendar period were derived from the Finnish general population, and SIRs were calculated by the person-year method.

The risk of cancer of the [brain and] nervous system (ICD-7, code 193) was significantly elevated among those exposed to 1,1,1-trichloroethane (SIR, 6.05; 95% CI, 1.25–17.7), although the estimate was based on only 3 exposed cases. There was no significantly elevated risk of brain cancer in those exposed to trichloroethylene or tetrachloroethylene. [The Working Group noted as a strength that exposure was defined from

biological monitoring, but that the positive finding for brain cancer was based on few exposed cases.]

The association between glioma and meningioma and exposure to six specific chlorinated organic solvents was investigated in a hospital-based case–control study in the USA (Neta et al., 2012). Study participants were recruited from three hospitals (all of which were regional referral centres for brain tumours) in Boston, Pittsburgh, and Phoenix. Cases of glioma and meningioma were identified from 1994 to 1998. Controls were selected among patients referred for non-malignant conditions: injuries, cardiovascular diseases, musculoskeletal conditions, digestive disorders, and other diagnoses, and frequency-matched on the cases by sex, age, race, hospital, and proximity to the hospital. The participation rate among cases was 92% for glioma, 94% for meningioma, and 86% for controls. There were 484 gliomas, 197 meningiomas, and 797 controls in the final data set. Study participants or, in some cases, next of kin, were interviewed regarding demographic factors and lifetime history of occupations held for at least six months, including information on job title, employer, full-time/part-time job, type of business or service, tasks, and materials. In all, 64 job-specific modules were developed to assess exposure to a variety of agents, including chlorinated organic solvents. Additional interviews were performed for clarification after initial assessment by an industrial hygienist. An industrial hygienist assessed the exposure to six solvents (1,1,1-trichloroethane, dichloromethane, trichloromethane, carbon tetrachloride, trichloroethylene, and tetrachloroethylene) during each job. Task-exposure matrices were developed for this assessment. For each participant's job, the hygienist estimated the exposure probability and frequency. In addition, eight known or inferred exposure determinants (mechanism of release, process condition, temperature, usage rate, type of ventilation, location, confined space,

proximity to the source), along with confidence in the estimations were assigned to each job. Each participant's job exposure intensity (continuous, in ppm) was modelled on the basis of a database of measurements extracted from the literature and the same exposure determinants. For participants with an exposure probability of ≥ 50%, the duration of exposure, cumulative exposure (ppm hours), average exposure, and highest exposure were assessed. Unconditional logistic regression was applied, adjusting for the variables used for frequency matching of the controls.

There was no consistent evidence of increased risk of glioma or meningioma associated with exposure to any of the six chlorinated organic solvents investigated. For glioma and exposure to 1,1,1-trichloroethane, there was no association with exposure probability, or indicators (low/high) for years exposed, cumulative exposure, average weekly exposure, or highest exposure. The risk of meningioma for those with probable exposure to 1,1,1-trichloroethane was non-significantly elevated (OR, 2.3; 95% CI, 0.7–7.2; 5 cases). In sensitivity analyses, participants categorized as probably exposed but with low confidence and participants with information from proxy respondents were not included, certain diagnoses in the control series were excluded, and a 10-year latency was applied. None of these analyses changed the risk estimates appreciably. [The Working Group noted that a strength of the study was the detailed exposure assessment; however, there were very few cases with probable exposure to 1,1,1-trichloroethane, and the use of hospital controls may have tended to attenuate the observed risks.]

A population-based case–control study on brain glioma was performed in non-metropolitan areas of Iowa, Michigan, Minnesota, and Wisconsin in the USA. The study was initiated by NIOSH with the primary purpose of investigating health risks related to farming and is known as the Upper Midwest Health Study. This study was used to investigate the risk of glioma

associated with exposure to six chlorinated organic solvents in non-farming jobs, since exposure to chlorinated solvents was considered to be low in farming jobs (Ruder et al., 2013). Cases of histologically verified glioma were identified from participating medical facilities and neurosurgeon offices from 1995 to 1997. Two controls per case (872 cases), frequency-matched on sex and age, were selected from driving licence registers (for ages < 65 years) and from Medicare data tapes (for ages 65–80 years). The participation rate was 91.5%, among cases (or their next of kin) and 70.4% among controls. Of the cases, 438 were interviewed in person and 360 via proxy respondents. All respondents were interviewed about their lifetime history of occupations held for at least 1 year, including data on employer name, industry, job titles, tasks, materials used, and employment frequency. Specific questions were asked regarding exposure to organic solvents. An industrial hygienist coded occupational exposure to 1,1,1-trichloroethane, carbon tetrachloride, chloroform, methylene chloride [dichloromethane], tetrachloroethylene, and trichloroethylene, based on job histories and databases of exposure levels. For each job, the industrial hygienist assessed the exposure probability, frequency of exposure, and confidence of probability and of frequency. In addition, the industrial hygienist used exposure determinants for jobs assigned a non-zero probability of exposure to estimate exposure intensity (ppm) using methods described above for the hospital-based case–control study (Neta et al., 2012). Duration, frequency, and intensity associated with each job, across all jobs, were used to calculate cumulative exposures in ppm-years. Unconditional logistic regression was applied to estimate associations for the six solvents, adjusting for the variables used for frequency matching, in addition to age (as a continuous variable) and education.

The study showed low risks of glioma associated with exposure to the studied solvents. The risk associated with any exposure to

1,1,1-trichloroethane was low (OR, 0.75; 95% CI, 0.61–0.90) for men and women combined. Exclusion of next-of-kin respondents did not change the results. A significantly negative exposure–response relation was found, with the odds ratio for a one-unit increase in natural-log transformed cumulative exposure to 1,1,1-trichloroethane (ppm-years) being 0.97 (95% CI, 0.96–0.99). Findings for the other five solvents were similar. Exclusion of unexposed cases and controls from the analysis still gave a significantly negative exposure–response relation. Exclusion of proxy respondents gave similar results. The potential reasons for the uniformly low risks for all studied solvents were discussed in terms of a possible selection of healthy individuals into exposed occupations or selection of less healthy individuals out of exposed occupations. Controls also were slightly older than cases, giving more opportunities to have worked in exposed occupations during earlier periods. [The Working Group noted that a strength of this study was the detailed exposure assessment; however, the uniformly negative, and partly statistically significantly negative association with exposure to any of the studied substances may have been attributable to bias caused by unidentified methodological problems.]

The relation between incidence of meningioma and exposure to seven specific and four groups of organic solvents was investigated in the INTEROCC study, a multicentre case–control study (McLean et al., 2014). The INTEROCC study was initially set up as and used data from the INTERPHONE study, the aim of which was to investigate the risk of brain cancer associated with mobile phone use. The study included ten centres in seven countries: Australia, Canada, France, Germany, Israel, New Zealand, and the UK. Cases and controls were identified from 2000 to 2004. Details in recruitment of cases and controls varied between countries. In most centres the study included residents aged 30–59 years in each region associated with the study centre.

Cases were either verified histologically or by unequivocal diagnostic imaging. Controls were randomly selected from the population in each centre, individually or frequency-matched on the cases by year of birth, sex, and study region. The final data set comprised 1906 cases and 5565 controls. Individuals were interviewed face-to-face, with a small number of proxy interviews. The interview covered background factors and a full occupational history, including job title, tasks, company name, and company activities. Occupational hygienists from each country coded job title and industry branch for all jobs held for at least 6 months. A JEM, the INTEROCC-JEM, was developed specifically for this study, and was based on adaptions of the FINJEM (Kauppinen et al., 1998) to reflect local conditions. The matrix linked quantitative estimates of exposure probability and intensity for seven specific organic solvents (including 1,1,1-trichloroethane) and four groups of organic solvents to each job in the job histories of the study participants. For each substance, participants with an exposure probability of ≥ 25% were classified as exposed, and participants with an exposure probability of ≥ 5% but < 25% were excluded from the analysis. [The Working Group noted that participants with an exposure probability of < 5% had already been classified as unexposed by the JEM.] Conditional logistic regression was applied, adjusting for the variables in matching of controls, and education.

No associations with any of the studied organic solvents were found. One case and three controls were classified as exposed to 1,1,1-trichloroethane, giving an odds ratio of 1.35 with a very wide confidence interval (95% CI, 0.10–17.55). [The Working Group noted that the JEM was well developed and based on more information than most of the other studies reviewed, although it was limited in identifying individuals with low and high exposure in a job title. The prevalence of exposure to 1,1,1-trichloroethane was very low, < 0.1% among cases and

controls, and the risk estimates were imprecise owing to low numbers.]

2.3 Cancer of the breast

See Table 2.4.

The Working Group identified one cohort study, two nested case–control studies, and one population-based case–control study in Nordic countries and the USA that investigated associations between risk of breast cancer and exposure to 1,1,1-trichloroethane.

As detailed in Section 2.1.1, Radican et al. (2008) extended the follow-up of a cohort of 14 455 civilian aircraft-maintenance workers employed for at least 1 year between 1952 and 1956 at a United States Air Force base to evaluate cancer mortality risks in relation to potential exposure to trichloroethylene and other chemicals according to job titles from personnel records. The follow-up was extended to 2000 using exclusively the national death index and included non-White workers. The cohort was mostly male (74%) and non-White workers accounted for only 2.7% of the cohort. The most detailed exposure assessment was for trichloroethylene, which was replaced by 1,1,1-trichloroethane in the degreasers after 1978. Exposure to 1,1,1-trichloroethane was only evaluated qualitatively as ever versus never in the analysis. Cox proportional hazard regression models were applied to estimate the risk for exposed versus unexposed workers. In this follow-up, there was an elevated risk of mortality attributable to breast cancer (HR, 2.35; 95% CI, 0.83–6.64) among women exposed to 1,1,1-trichloroethane, although this was based on only 4 exposed deaths. [The Working Group noted that this was a relatively large cohort with a long follow-up period. Limitations of the exposure assessment included its qualitative nature, the difficulty in linking participants to estimates often associated with no more detail than job title, and the lack of continued exposure assessment after 1982. There were very few breast cancer deaths among the exposed.]

Talibov et al. (2019) conducted a nested case–control study within the NOCCA cohort to evaluate occupational exposures in relation to breast cancer in men in Sweden, Finland, and Iceland. Occupational titles were available only for census years. The study included 1469 incident cases of breast cancer in men identified from national registries, and five controls per case matched on country, sex, and year of birth who were randomly selected from the NOCCA cohort. Information on occupation during the follow-up was obtained from computerized census records from 1960 in Sweden, 1970 in Finland and 1981 in Iceland. Occupational exposures were estimated by linking job titles of study participants to the NOCCA-JEM. A cumulative exposure index was derived as a product of exposure prevalence and annual average exposure each year over the employment period of the study participants, as assessed from the census data. Conditional logistic regression was applied, with adjustment for socioeconomic status using single (each exposure agent one at a time) and multiple (all 24 exposure agents, except those that were highly correlated, were added simultaneously) exposure models. Analyses were conducted with dichotomous (ever/never) or polytomous exposure (categorized by using 50th and 90th percentiles of exposure distribution among exposed controls with the unexposed group as the reference category). None of the odds ratios for exposure to 1,1,1-trichloroethane were statistically significant in these models. [The Working Group noted that a strength was the large sample size for cases and controls in the study and fairly accurate and complete cancer incidence data. A limitation was that the information on work histories was based on census data only. The JEM was well developed, but it was limited in its ability to identify persons with low and high exposure in a population-based study.]

Table 2.4 Cohort and case–control studies on exposure to 1,1,1-trichloroethane and cancer of the breast

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Radican et al. (2008) Utah, USA Enrolment, 1952–1956/ follow-up, 1953–2000 Cohort	14 455 (10 730 men and 3725 women); civilian workers employed at Hill Air Force Base, an aircraft-maintenance facility, for ≥ 1 yr between 1952 and 1956, who were followed up for cancer mortality through linkage to the national death index Exposure assessment method: expert judgement; review of facility records, jobs, walk-through surveys, interviews, measurements used to assign yes/no exposed by job group	Breast, mortality	Exposed to 1,1,1-TCE, women (HR): No chemical exposures Ever	NR 4	1 2.35 (0.83–6.64)	Age, race	*Exposure assessment critique*: Extensive data collection, including measurements. Linkage of jobs to exposures was limited owing to the limited information in the available records. Given 1,1,1-TCE was often interchanged with other chlorinated solvents, the difficulty in making these links is a non-trivial limitation. Job information used to assign yes/no. *Strengths*: relatively large cohort with a long follow-up period; exposure assessment was based on information regarding exposure and work processes provided by the United States Air Force. *Limitations*: very few cases for breast cancer deaths from exposure to 1,1,1-TCE; exposure not mutually exclusive; cancer incidence was not updated; data on lifestyle and other non-occupational risk factors, which might be confounders or effect modifiers, were not available for the cohort.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Talibov et al. (2019)](#) Sweden, Finland, Iceland Sweden (77%, 1960–2005), Finland (21%, 1970–2005), Iceland (2%, 1981–2004) Nested case–control	Cases: 1469 cases in men with breast cancer diagnosed 1961–2005 in Sweden, Finland, and Iceland within the NOCCA cohort; participants from the NOCCA cohort had to be aged ≥ 20 yr at the date of diagnosis of the case (index date) and had to have at least one census record before index date Controls: 7345; 5 controls for each case, randomly selected from the NOCCA cohort, matched on country, sex, and year of birth Exposure assessment method: records; used self-reported jobs to the census and NOCCA-JEM that includes semiquantitative estimates of prevalence exposed, mean level of exposure, and duration	Breast (men), incidence	Exposed to 1,1,1-TCE (OR): Never Ever	1288 181	1 1.01 (0.84–1.20)	Country, year of birth, socioeconomic status	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Intensity and prevalence estimates based on actual data. Could be missing exposed jobs owing to 10 yr census collection. Prevalence is included in cumulative exposure but is not a component of toxicity. Other comments: conducted sensitivity analyses with 5 and 10 yr exposure lags. *Strengths*: accuracy and completeness of cancer incidence data from this well-established large cohort in Nordic countries; ran models with one agent at a time as well as all agents simultaneously. *Limitations*: information was not available on potential confounders such smoking, alcohol, leisure time, physical activity, and obesity.
		Breast (men), incidence	Exposed to 1,1,1-TCE (OR): Never Ever	1288 181	1 1.02 (0.67–1.57)	Country, year of birth, socioeconomic status, up to 23 additional exposures (solvents, metals, gases, and others)	
		Breast (men), incidence	Cumulative 1,1,1-TCE exposure index (OR): Not exposed ≤ 5.6 ppm-years 5.7–13 ppm-years > 13 ppm-years Trend-test *P* value, 0.83	1288 122 41 18	1 0.98 (0.80–1.20) 1.10 (0.77–1.55) 1.01 (0.60–1.69)	Country, year of birth, socioeconomic status	
		Breast (men), incidence	Cumulative 1,1,1-TCE exposure index (OR): Not exposed ≤ 5.6 ppm-years 5.7–13 ppm-years > 13 ppm-years Trend-test *P* value, 0.73	1288 122 41 18	1 1.18 (0.70–1.98) 1.36 (0.74–2.50) 1.10 (0.50–2.41)	Country, year of birth, socioeconomic status, up to 23 additional exposures (solvents, metals, gases, and others)	

Table 2.4   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Videnros et al. (2020) Malmö city, Sweden 1991–1996 with follow-up to 31 December 2013 Nested case–control	Cases: 731 women with first-time diagnosis of invasive breast cancer in 1991–2013, identified through the Swedish cancer registry, excluding premenopausal cases, those with no self-reported work history, and breast cancer diagnosis before baseline; women were born in 1923–1950, living in Malmö city, Sweden, 1991–1996, and enrolled for a population-based prospective cohort study (MDCS) Controls: 1669; 2 controls per case, matched on age using density-based selection from the cohort	Breast (postmenopausal), incidence	Exposed to 1,1,1-TCE (OR): Never	721	1	Age	*Exposure assessment critique*: Stronger study than many of the other FINJEM/NOCCA-JEM studies because work histories were self-reports from interviews that gathered more information than job only. Although only 3 jobs collected, they generally covered most of work history. FINJEM is a robust and well-developed JEM. Normalized FINJEM to countries. Modified FINJEM/NOCCA-JEM to reflect study participants. Intensity and prevalence estimates based on actual data. Prevalence included in the mean intensity metric, although prevalence is not a component of toxicity. Metrics were all categorical. Leisure time physical activity covariate was confirmed with the authors.
			Ever	10	1.06 (0.50–2.24)		
		Breast (postmenopausal), incidence	Exposed to 1,1,1-TCE (OR): Never	721	1	Age, parity, age at first [full-] term pregnancy, months of breastfeeding per child, hormone replacement therapy, alcohol consumption, height, BMI, leisure time physical activity	
			Ever	10	1.17 (0.53–2.56)		
		Breast (postmenopausal), incidence	Duration of 1,1,1-TCE exposure (OR): Unexposed	721	1		
			1–10 yr	2	0.60 (0.13–2.89)		
			> 10 yr	8	1.55 (0.61–3.94)		
			Trend-test *P* value, 0.51				
		Breast (postmenopausal), incidence	Mean 1,1,1-TCE exposure intensity (OR): Unexposed	721	1		
			> 0–0.41 ppm (mean, 0.32 ppm)	5	1.20 (0.42–3.49)		
			0.47–1.34 ppm (mean, 0.83 ppm)	5	0.94 (0.33–2.69)		

Table 2.4   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Videnros et al. (2020) Malmö city, Sweden 1991–1996 with follow-up to 31 December 2013 Nested case– control (cont.)	Exposure assessment method: expert judgement; used questionnaires administered to participants for three jobs; reviewed FINJEM, NOCCA-JEM and participant-specific data to assign participant-specific semiquantitative estimates of prevalence, intensity, and duration for each job held	Breast (postmenopausal), incidence	Mean 1,1,1-TCE exposure intensity (OR): Unexposed > 0–0.41 ppm (mean, 0.32 ppm) 0.47–1.34 ppm (mean, 0.83 ppm) Trend-test P value, 0.76	721 5 5	1 1.23 (0.42–3.63) 1.10 (0.36–3.39)	Age, parity, age at first [full-] term pregnancy, months of breastfeeding per child, hormone replacement therapy, alcohol consumption, height, BMI, leisure time, physical activity	*Strengths*: this nested case–control study updated the authors' previous cohort study with improved exposure estimates on individual levels from an occupational hygienist; cancer diagnoses ascertained through linkage with national registry. *Limitations*: only 2 controls per case; low study power as exposures to 1,1,1-TCE and other chemicals were quite rare.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pedersen et al. (2020) Denmark Women born in Denmark in or after 1946; breast cancer cases identified by 2016 Case–control	Cases: 38 375 first primary breast cancer cases identified via the Danish cancer registry (established 1942) through 2016 and born in Denmark in or after 1946 with registration in the Danish Supplementary Pension Fund Register (ATP) for employment history (since 1964) Controls: 191 875; 5 random controls per case from the Danish Civil Registration System (established in 1968), matched on year of birth. Born in Denmark ≥ 1946 with employment history; alive and free of breast cancer at the date of diagnosis of the corresponding case (index date)	Breast, incidence	Any exposure to 1,1,1-TCE, women aged < 50 yr (OR):			Parity, age at first live birth, heavy physical activity at work	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Prevalence and intensity were based on actual data. Prevalence, which is not a component of toxicity, was included in cumulative exposure. Metrics were all categorical. Other comments: covariate adjustment for parity may have been unnecessary in parity stratified estimates. Considered exposure windows of 1–9, 10–20, and > 20 yr to evaluate latency *Strengths*: population-based case–control study with established exposure assessment methods; potential confounders related to breast cancer were included in analysis; analysis by breast cancer subtypes (ER + and ER−) reported; cancer diagnoses ascertained through linkage with national registry.
			Never	17 234	1		
			Ever	98	1.06 (0.85–1.32)		
		Breast, incidence	Any exposure to 1,1,1-TCE, women aged ≥ 50 yr (OR):				
			Never	20 885	1		
			Ever	158	0.95 (0.80–1.13)		
		Breast, incidence	Duration of 1,1,1-TCE exposure, women aged < 50 yr (OR):				
			Unexposed	17 234	1		
			1–9 yr	90	1.06 (0.85–1.34)		
			≥ 10 yr	8	1.05 (0.49–2.26)		
			Trend-test *P* value, 0.69				
		Breast, incidence	Duration of 1,1,1-TCE exposure, women aged ≥ 50 yr (OR):				
			Unexposed	20 885	1		
			1–9 yr	138	0.97 (0.81–1.17)		
			≥ 10 yr	20	0.85 (0.53–1.39)		
			Trend-test *P* value, 0.48				
		Breast, incidence	Cumulative 1,1,1-TCE exposure quartile, women aged < 50 yr (OR):				
			Unexposed	17 234	1		
			> 0–25%	32	1.43 (0.96–2.11)		
			> 25–50%	25	1.06 (0.69–1.64)		
			> 50–75%	23	1.03 (0.66–1.62)		
			> 75%	18	0.75 (0.45–1.23)		
			Trend-test *P* value, 0.66				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Pedersen et al. (2020)](#) Denmark Women born in Denmark in or after 1946; breast cancer cases identified by 2016 Case–control (cont.)	Exposure assessment method: records; using job information from a Danish register and NOCCA-JEM that includes semiquantitative estimates of prevalence exposed, mean level of exposure, and duration	Breast, incidence	Cumulative 1,1,1-TCE exposure quartile, women aged ≥ 50 yr (OR):			Parity, age at first live birth, heavy physical activity at work	*Limitations*: low prevalence of exposure to 1,1,1-trichloroethane among women (0.7%) may reduce power and result in limited positive findings; crosswalk between Nordic Classification of Occupations (NYK) based NOCCA-JEM and Danish industry code (DSE) may lead to exposure misclassification; JEM did not entail measurements of exposure > 1995 so metrics in the latest era (1985–95) were assumed.
			Unexposed	20 885	1		
			> 0–25%	6	0.37 (0.16–0.85)		
			> 25–50%	68	1.04 (0.80–1.35)		
			> 50–75%	47	1.13 (0.82–1.55)		
			> 75%	37	0.88 (0.62–1.25)		
			Trend-test *P* value, 0.65				
		Breast, incidence	Latency of 1,1,1-TCE exposure, women aged < 50 yr (OR):				
			Unexposed	17 234	1		
			1–9 yr	9	0.82 (0.40–1.67)		
			10–20 yr	38	1.36 (0.95–1.96)		
			> 20 yr	51	0.96 (0.71–1.29)		
		Breast, incidence	Latency of 1,1,1-TCE exposure, women aged ≥ 50 yr (OR):				
			Unexposed	20 885	1		
			1–9 yr	5	1.06 (0.40–2.78)		
			10–20 yr	13	1.59 (0.85–2.97)		
			> 20 yr	140	0.92 (0.76–1.10)		
		Breast, incidence	Timing of first job exposed to 1,1,1-TCE, parous women aged < 50 yr (OR):				
			Unexposed	17 234	1		
			Before first live birth	62	1.14 (0.86–1.51)		
			After first live birth	24	0.81 (0.52–1.26)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pedersen et al. (2020) Denmark Women born in Denmark in or after 1946; breast cancer cases identified by 2016 Case–control (cont.)		Breast, incidence	Timing of first job exposed to 1,1,1-TCE, parous women aged ≥ 50 yr (OR):			Parity, age at first live birth, heavy physical activity at work	
			Unexposed	20 885	1		
			Before first live birth	87	0.96 (0.74–1.21)		
			After first live birth	53	0.85 (0.63–1.15)		
		Breast (ER+), incidence	Any exposure to 1,1,1-TCE, women aged < 50 yr (OR):				
			Never	NR	1		
			Ever	51	0.99 (0.73–1.34)		
		Breast (ER+), incidence	Any exposure to 1,1,1-TCE, women aged ≥ 50 yr (OR):				
			Never	NR	1		
			Ever	127	1.08 (0.89–1.31)		
		Breast (ER−), incidence	Any exposure to 1,1,1-TCE, women aged < 50 yr (OR):				
			Never	NR	1		
			Ever	49	1.32 (0.88–1.97)		
		Breast (ER−), incidence	Any exposure to 1,1,1-TCE, women aged ≥ 50 yr (OR):				
			Never	NR	1		
			Ever	19	0.65 (0.40–1.06)		
		Breast (ER+), incidence	Duration of 1,1,1-TCE exposure, women aged ≥ 50 yr (OR):				
			Unexposed	NR	1		
			1–9 yr	111	1.12 (0.91–1.37)		
			≥ 10 yr	16	0.89 (0.52–1.51)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pedersen et al. (2020) Denmark Women born in Denmark in or after 1946; breast cancer cases identified by 2016 Case–control (cont.)		Breast (ER+), incidence	Cumulative 1,1,1-TCE exposure quartile, women aged ≥ 50 yr (OR):			Parity, age at first live birth, heavy physical activity at work	
			Unexposed	NR	1		
			> 0–25%	24	0.83 (0.54–1.28)		
			> 25–50%	37	1.29 (0.90–1.85)		
			> 50–75%	34	1.15 (0.79–1.67)		
			> 75%	32	1.06 (0.72–1.55)		
		Breast (ER+), incidence	Latency of 1,1,1-TCE exposure, women aged ≥ 50 yr (OR):				
			Unexposed	NR	1		
			1–9 yr	5	1.48 (0.54–4.01)		
			10–20 yr	11	1.81 (0.91–3.63)		
			> 20 yr	111	1.03 (0.84–1.26)		
		Breast, incidence	Any exposure to 1,1,1-TCE, parous women aged < 50 yr (OR):				
			Never	NR	1		
			Ever	86	1.03 (0.81–1.30)		
		Breast, incidence	Any exposure to 1,1,1-TCE, parous women aged ≥ 50 yr (OR):				
			Never	NR	1		
			Ever	140	0.92 (0.76–1.10)		
		Breast, incidence	Any exposure to 1,1,1-TCE, nulliparous women aged < 50 yr (OR):				
			Never	NR	1		
			Ever	12	0.41 (0.13–1.28)		
		Breast, incidence	Any exposure to 1,1,1-TCE, nulliparous women aged ≥ 50 yr (OR):				
			Never	NR	1		
			Ever	18	2.33 (0.66–8.14)		

BMI, body mass index; CI, confidence interval; ER, estrogen receptor; FINJEM, Finnish job-exposure matrix; JEM, job-exposure matrix; MDCS, Malmö Diet and Cancer Study; NOCCA, Nordic Occupational Cancer Study; NOCCA-JEM, Nordic Occupational Cancer Study job-exposure matrix; NR, not reported; OR, odds ratio; ppm, parts per million; 1,1,1-TCE, 1,1,1-trichloroethane; yr, year.

Videnros et al. (2020) conducted a follow-up nested case–control study, using exposure estimates that had been improved compared with those in the original study, to examine the association between workplace chemical exposures and postmenopausal breast cancer. The original study (Videnros et al., 2019) included 16 084 women born in 1923–1950, living in Malmö city, Sweden, in 1991–1996, and participating in the Malmö Diet and Cancer Study, a population-based prospective cohort study. Each participant at baseline filled out an extensive questionnaire on lifestyle, reproductive factors, and working history with specific tasks. Exposure to 1,1,1-trichloroethane and other chemicals was assessed through the NOCCA-JEM and FINJEM, adapted for Swedish working conditions. In this follow-up, two controls per case matched on age were included in analyses after excluding 239 cases with a missing questionnaire, for a total of 731 cases and 1669 controls. Also excluded were women with no self-reported work history ($n = 42$), a diagnosis of breast cancer before baseline ($n = 50$), and premenopausal status until the end of follow-up ($n = 55$). An occupational hygienist reviewed and reclassified the prevalence estimates in the NOCCA-JEM and FINJEM to reflect participant-specific data on work tasks. Both conditional and unconditional logistic regression was applied with adjustment for potential confounders (not including any other chemicals of interest in the study), however only results from unconditional logistic regression were reported. Women exposed to 1,1,1-trichloroethane had a slightly increased risk of breast cancer compared with unexposed women (OR, 1.17; 95% CI, 0.53–2.56). Exposure duration of > 10 years was associated with an odds ratio of 1.55 (95% CI, 0.61–3.94). This was not statistically significant and there was no significant trend. When investigating the risk according to mean intensity (ppm), there was no clear evidence of a trend in increasing risk of breast cancer with increasing mean intensity, with odds ratios changing from 1.23 (95% CI, 0.42–3.63) in the lower class (range, > 0–0.41 ppm; mean, 0.32 ppm) to 1.10 (95% CI, 0.36–3.39) in the higher class (range, 0.47–1.34 ppm; mean, 0.83 ppm) compared with women with no exposure to 1,1,1-trichloroethane. [The Working Group noted that a major strength was the exposure assessment by an occupational hygienist to estimate each woman's probability of exposure according to the specific work task specified in the baseline questionnaire. There was also extensive individual information on hormonal and reproductive factors as a control for confounding. The questionnaires for about 22% of the cases were lost before detailed work information could be extracted so they had to be excluded from this study. Only two controls per case were selected owing to feasibility concerns to allow exposure assessment by an occupational hygienist. Few participants in this population-based cohort had been exposed to 1,1,1-trichloroethane and, for those who had been exposed, exposure intensity was low. The highest average exposure intensity for an individual was 1.34 ppm (the current Swedish occupational exposure limit is 50 ppm).]

A population-based case–control study by Pedersen et al. (2020) was conducted to investigate the risk of breast cancer, including hormonal subtypes, among Danish women. It included 38 375 first primary breast cancer cases identified via the nationwide Danish Cancer Registry (established in 1942) through 2016, under age 70 years at the time of diagnosis, born in Denmark in or after 1946, and registered in the Danish Supplementary Pension Fund Register (ATP) (to ensure access to complete employment history). Five controls per case matched on year of birth were randomly selected using the Danish Civil Registration System (established in 1968) for a total of 191 875 controls with employment history who were alive and free of breast cancer at the date of diagnosis of the corresponding case (index date). Data retrieved from the ATP, which has obtained employment history

on all wage earners since 1964, included start and end of employment dates, company name, and a Danish five-digit branch/industry code (Danmarks Statistisk Erhvervsgrupperingskode, DSE) based on an extended version of the International Standard Industrial Classification of all Economic Activities (ISIC). Four of the historically most commonly used organic solvents in Denmark, including 1,1,1-trichloroethane, were selected for the study. Exposure to each of the four solvents was classified, based on each woman's employment history, using the Danish version of the NOCCA-JEM. A crosswalk between the Nordic Classification of Occupations (used in the NOCCA-JEM) and DSE codes was developed for exposed jobs in the Danish version. Conditional logistic regression was applied among women ever versus never exposed to each organic solvent and by different metrics for exposure, with adjustment for potential confounders (including reproductive variables and heavy physical activity at work), stratified by age at the index date (ages < 50 years and ≥ 50 years, approximating menopausal status) and further by estrogen hormone receptor status. The results showed no positive associations between exposure to 1,1,1-trichloroethane and breast cancer. Evaluations of the risk of breast cancer with exposure to 1,1,1-trichloroethane by various metrics including duration of exposure, quartiles of cumulative exposure, latency, and timing of first job with exposure (before or after first live birth) did not show any positive patterns of association. [The Working Group noted that this study included a large number of cases and controls. Participants who had a probability of exposure of < 10% and a job duration of < 1 year were classified as unexposed, probably increasing specificity. The ability of a JEM to identify participants with high or low exposure in a population-based study is limited. Further misclassification could be present since the JEM was not sex-specific.]

2.4 Cancers of the kidney and urinary bladder

See Table 2.5.

A total of six studies evaluated the association between exposure to 1,1,1-trichloroethane and cancers of the kidney or urinary bladder, including one retrospective cohort study on multiple cancer types (Anttila et al., 1995), one nested case–control study (Hadkhale et al., 2017), and four case–control studies (Dosemeci et al., 1999; Christensen et al., 2013; Purdue et al., 2017; Sciannameo et al., 2019).

In Finland, a cohort of 2050 men and 1924 women who were monitored biologically for regular occupational exposure to halogenated hydrocarbons at the Finnish Institute of Occupational Health were followed for cancer incidence through 1992; the cohort included 140 men and 131 women exposed to 1,1,1-trichloroethane between 1975 and 1983 (Anttila et al., 1995). There were no cases of kidney cancer observed among workers exposed to 1,1,1-trichloroethane, similar to the number of 0.40 expected. [The Working Group noted that despite the documented exposure of workers and complete follow-up, the small number of workers exposed to 1,1,1-trichloroethane (and lack of observed kidney cancer cases) limited the informativeness of the study.]

A population-based case–control study in Minnesota, USA, recruited 438 White newly diagnosed histologically confirmed cases of renal cell carcinoma (273 men and 165 women) from a state-wide cancer registry, and 687 White age- and sex-matched population controls (462 men and 225 women) in 1988–1990 (Dosemeci et al., 1999). Response rates were 87% for cases and 86% for controls for the overall interview. Trained interviewers captured information on a range of personal factors, including the most recent and usual occupation and industry, job activities, year of start and end, part-time or full-time status, and duration of employment in specific

Table 2.5 Cohort and case–control studies on exposure to 1,1,1-trichloroethane and cancers of the kidney and urinary bladder

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Anttila et al. (1995) Finland Enrolment, 1965–1983 (1,1,1-TCE: 1975–1983)/follow-up, 1967–1992 Cohort	3974 workers (2050 men and 1924 women), 271 of whom were monitored for exposure to 1,1,1-TCE; workers biologically monitored for occupational exposure to three halogenated hydrocarbon solvents in Finland Exposure assessment method: quantitative measurements; a database of measurements in urine from trichloroethylene-exposed participants, and blood from tetrachloroethylene- and 1,1,1-TCE-exposed participants was used to identify ever-exposed to the chemicals	Kidney, incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure Expected cases	0 0.4	0 (0–9.16) –	Age, sex, calendar period	*Exposure assessment critique*: Exposed were truly exposed. Blood levels only reflect short-term (days) exposures for 9 yr. No information was provided on the interpretation of the measurements or the participants' exposures, including possible exposures to 1,1,1-TCE outside the 1975–1983 window or to other agents. *Strengths*: documented exposure; complete follow-up for cancer incidence through linkage with national registry. *Limitations*: small number of workers exposed to 1,1,1-TCE; limited exposure information (timing of measurements, exposure duration,

Table 2.5   (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Anttila et al. (1995) Finland Enrolment, 1965–1983 (1,1,1-TCE: 1975–1983)/follow-up, 1967–1992 Cohort (cont.)							multiple solvent exposures (94.4% of worke rmonitored for one solvent, multiple exposures probably underestimated), limited information on potential confounders, worker selection unclear (estimated 4000 workers in Finland occupationally exposed at end of follow-up period).

Table 2.5   (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Dosemeci et al. (1999) Minnesota, USA 1988–1990 Case–control	Cases: 438 newly diagnosed cases of histologically confirmed RCC (273 White men and 165 White women) from Minnesota Cancer Surveillance System aged 20–85 yr with in-person interviews Controls: 687 (462 White men and 225 White women); random-digit dialling (20–64 yr) and Health Care Financing Administration (65–85 yr), age and sex-stratified controls with in-person interview Exposure assessment method: partial work histories and expert-developed JEM used; estimated (semiquantitative estimates) intensity and probability by assigning probability and intensity separately to each job and each industry and then combining using an algorithm	Kidney (RCC), incidence Kidney (RCC), incidence Kidney (RCC), incidence	Exposure to methyl chloroform [1,1,1-TCE] (OR): Never Ever Exposure to methyl chloroform [1,1,1-TCE], men (OR): Never Ever Exposure to methyl chloroform [1,1,1-TCE], women (OR): Never Ever	 NR 66 NR 53 NR 13	 1 0.94 (0.7–1.3) 1 0.88 (0.6–1.3) 1 1.26 (0.6–2.8)	Age, sex, smoking, hypertension and/or use of diuretics and/or hypertension drugs, BMI	*Exposure assessment critique*: Proxy respondents (next of kin) were required for 35% of cases, so these were excluded from the analysis. Unclear whether exposure assessment method produced valid results. Work histories limited to longest and most recent jobs, which may miss key exposures. Metrics were all categorical. *Strengths*: objective exposure assessment; histologically confirmed cancer diagnoses ascertained through state-wide registry

Table 2.5   (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Dosemeci et al. (1999) Minnesota, USA 1988–1990 Case–control (cont.)							*Limitations*: small number of exposed participants; lack of. lifetime occupational history information; lack of exposure specificity; limited consideration of multiple CAHC exposures; potential survival bias (35% of cases who had died excluded).

Table 2.5 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control	Cases: 3730 cancer cases at 11 sites, including 177 kidney and 484 bladder cancer cases; male incident histologically confirmed kidney and bladder cancer cases from 18 large hospitals in Montreal metropolitan area, Canadian citizens aged 35–70 yr (median, 59 and 60 yr, respectively) Controls: 533 population controls, 1999 and 2299 other cancer controls respectively; population controls obtained randomly from population-based electoral lists, stratified by sex and age, other cancer controls from other participating cases	Kidney (ICD-9, code 189), incidence	Any exposure to 1,1,1-TCE, 5 yr lag, men (OR): No chlorinated solvent exposure Ever-analysis limited to population controls Ever-analysis including both population and other cancer controls	134 4 4	1 1.1 (0.3–3.7) 1.3 (0.4–4.0)	Age, census tract median income, education, ethnicity, self/proxy, smoking, coffee, beer, wine, and spirit intake	*Exposure assessment critique*: Substantial data available for assessment including [presumably] published measurement data. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. confidence, frequency, and intensity) is a key strength. Cumulative exposure included confidence, which is not a component of toxicity. Metrics were all categorical.

Table 2.5 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control (cont.)	Exposure assessment method: expert judgement; full work histories and specialized questionnaires, [presumed measurement data], and extensive review to assign participant-specific semiquantitative estimates of confidence, frequency and intensity for each job held	Kidney (ICD-9, code 189), incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag, men (OR):			Age, census tract median income, education, ethnicity, self/proxy, smoking, coffee, beer, wine, and spirit intake	Strengths: detailed lifetime occupational histories and expert exposure assessment, some semiquantitative exposure estimates, multiple control groups; histologically confirmed cancer diagnoses ascertained through hospitals. Limitations: small numbers of workers exposed to 1,1,1-TCE; retrospective exposure assessment.
			No chlorinated solvent exposure	134	1		
			Ever-analysis limited to population controls	3	1.2 (0.3–5.0)		
			Ever-analysis including both population and other cancer controls	3	1.5 (0.4–5.3)		
		Urinary bladder (ICD-9, code 188), incidence	Any exposure to 1,1,1-TCE, 5 yr lag, men (OR):			Age, census tract median income, education, ethnicity, self/proxy, smoking, coffee intake, aromatic amines exposure	
			No chlorinated solvent exposure	372	1		
			Ever-analysis limited to population controls	5	0.6 (0.2–1.8)		
			Ever-analysis including both population and other cancer controls	5	0.7 (0.2–1.9)		
		Urinary bladder (ICD-9, code 188), incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag, men (OR):			Age, census tract median income, education, ethnicity, self/proxy, smoking, coffee intake, aromatic amines exposure	
			No chlorinated solvent exposure	372	1		
			Ever-analysis limited to population controls	3	0.5 (0.1–2.2)		
			Ever-analysis including both population and other cancer controls	3	0.6 (0.2–2.4)		

Table 2.5 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Purdue et al. (2017) USA; Detroit and Chicago, USKC study 2002–2007 Case–control	Cases: 1217 histologically confirmed incident cases of kidney cancer identified in Metropolitan Cancer Surveillance System (Detroit), and review of pathology reports from 56 hospitals (Chicago), patients aged 20–79 yr Controls: 1235; Department of Motor Vehicle records (ages 20–64 yr) and Medicare files (ages 65–79 yr) frequency-matched on sex, age, and race Exposure assessment method: expert judgement; full work histories, job-specific modules, literature review, measurement data, and [presumed] study-specific job- and task-specific matrices (for imputation when participant-specific information was missing) used to assign participant-specific semiquantitative estimates of probability, frequency, intensity and confidence for each job held	Kidney, incidence	Probability of exposure to 1,1,1-TCE (OR):			Age, sex, race, study centre, education level, smoking status, BMI, history of hypertension	*Exposure assessment critique*: Substantial data available for assessment including published measurement data modelled to estimate intensity but was not used. Evaluation was participant-specific. Use of job- and task-specific matrices (when participant-specific information was missing) probably increased consistency. Careful consideration of each job held by each participant (i.e. probability, frequency, and confidence of exposure) is a key strength. Cumulative exposure did not include intensity. Metrics were all categorical. Other comments: conducted sensitivity analyses with 5 and 15 yr exposure lags.
			Unexposed	579	1		
			< 50%	562	1.2 (1.0–1.4)		
			50–89%	41	1.0 (0.6–1.6)		
			≥ 90%	7	1.2 (0.4–4.1)		
		Kidney, incidence	Cumulative hours exposed to 1,1,1-TCE at a high intensity (OR):				
			Unexposed	579	1		
			Low: ≤ 520 h	9	0.6 (0.2–1.6)		
			Medium: 521–1456 h	14	0.8 (0.3–2.0)		
			High: > 1456 h	21	1.6 (0.8–3.2)		
			Trend-test *P* value, 0.3				

Table 2.5   (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Purdue et al. (2017)](#) USA; Detroit and Chicago, USKC study 2002–2007 Case–control (cont.)							*Strengths*: detailed lifetime occupational histories and expert exposure assessment, some quantitative exposure estimates; histologically confirmed cancer diagnoses ascertained through regional cancer registries. *Limitations*: small numbers of workers exposed to 1,1,1-TCE; retrospective exposure assessment; low rate of participation in controls.

Table 2.5   (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hadkhale et al. (2017) Finland, Iceland, Norway, Sweden, NOCCA database 1961–2005 Nested case–control	Cases: 113 343 incident bladder cancer cases from NOCCA cohort (14.9 million persons), aged ≥ 20 yr, occupational information from at least one census from 1960–1990 before index date, cases identified through linkage with cancer registries Controls: 566 715 controls from NOCCA cohort matched on country, sex, birth year at index date Exposure assessment method: used self-reported jobs to the census and NOCCA-JEM that includes semiquantitative estimates of prevalence mean level of exposure, and duration	Urinary bladder, incidence	Cumulative exposure to 1,1,1-TCE, 10 yr lag (HR): Unexposed < 5.60 ppm-years 5.60–10.15 ppm-years > 10.15 ppm-years Trend-test *P* value, 0.67	105 469 6011 1160 703	1 0.98 (0.93–1.02) 1.00 (0.92–1.07) 1.00 (0.89–1.07)	Age, year of birth, sex, country, trichloroethylene, perchloroethylene [tetrachloroethylene], aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, other organic solvents, ionizing radiation, asbestos, benzo[*a*]-pyrene, diesel engine exhaust, sulfur dioxide	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Prevalence and intensity were based on actual data. Could be missing exposed jobs due to 10 yr census collection. Prevalence was included in cumulative exposure, but it is not a component of toxicity. Metrics were all categorical. Other comments: Conducted sensitivity analyses with 0, 10 and 20 yr exposure lags. *Strengths*: large-scale population-based study, quantitative cumulative exposure estimates, consideration of other occupational exposures; cancer diagnoses ascertained through linkage to national cancer registries.
		Urinary bladder, incidence	Cumulative exposure to 1,1,1-TCE, 10 yr lag, age < 50 yr (HR): Unexposed < 5.60 ppm-years 5.60–10.15 ppm-years > 10.15 ppm-years Trend-test *P* value, 0.12	54 167 2897 283 101	1 1.00 (0.91–1.05) 0.85 (0.73–1.00) 0.90 (0.70–1.11)		
		Urinary bladder, incidence	Cumulative exposure to 1,1,1-TCE, 10 yr lag, age ≥ 50 yr (HR): Unexposed < 5.60 ppm-years 5.60–10.15 ppm-years > 10.15 ppm-years Trend-test *P* value, 0.06	51 302 3114 877 602	1 1.00 (0.90–1.03) 1.08 (1.00–1.20) 1.03 (0.92–1.14)		

Table 2.5 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hadkhale et al. (2017) Finland, Iceland, Norway, Sweden, NOCCA database 1961–2005 Nested case–control (cont.)		Urinary bladder, incidence	Cumulative exposure to 1,1,1-TCE, 10 yr lag, men (HR):			Age, year of birth, country, trichloroethylene, perchloroethylene [tetrachloroethylene], aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, other organic solvents, ionizing radiation, asbestos, benzo[a]-pyrene, diesel engine exhaust, sulfur dioxide	*Limitations*: no information on other potential personal confounding variables such as cigarette smoking; limited occupational information; occupational titles updated infrequently (every 10 yr).
			Unexposed	77 107	1		
			< 5.60 ppm-years	5711	1.00 (0.92–1.01)		
			5.60–10.15 ppm-years	1120	1.00 (0.91–1.07)		
			> 10.15 ppm-years	691	1.00 (0.90–1.07)		
			Trend-test *P* value, 0.6				
		Urinary bladder, incidence	Cumulative exposure to 1,1,1-TCE, 10 yr lag, women (HR):				
			Unexposed	28 362	1		
			< 5.60 ppm-years	300	1.04 (0.85–1.30)		
			5.60–10.15 ppm-years	40	1.15 (0.80–1.70)		
			> 10.15 ppm-years	12	1.11 (0.58–2.20)		
			Trend-test *P* value, 0.98				
Sciannameo et al. (2019) Turin and Brescia, Italy 1992–2012 Case–control	Cases: 893 incident cases of histologically confirmed bladder cancer diagnosed at a local hospital in Turin in men aged 40–74 yr; or at the urology department of two local hospitals in Brescia in men aged 20–80 yr	Urinary bladder (ICD-9, code 188), incidence	Exposed to [1,1,1-]TCE, 10 yr lag, men (OR):			Age, smoking status, intensity of smoking, study	*Exposure assessment critique*: Stronger study than many of the other FINJEM/NOCCA-JEM studies because work histories were self-reports from interviews that gathered more information than job only. NOCCA-JEM is a robust and well-developed JEM. FINJEM was normalized to the country.
			Never	531	1		
			Ever (≥ 2 yr)	362	1.18 (0.96–1.46)		
		Urinary bladder (ICD-9, code 188), incidence	Cumulative exposure to [1,1,1-]TCE, 10 yr lag, men (OR):				
			Never	531	1		
			Low	181	1.33 (1.02–1.73)		
			High	181	1.08 (0.83–1.41)		

Table 2.5 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sciannameo et al. (2019) Turin and Brescia, Italy 1992–2012 Case–control (cont.)	Controls: 978; controls in Turin were males aged 40–74 yr, hospitalized in same hospital as cases in general medicine, otolaryngology, orthopaedic, and cardiology departments without neoplastic, metabolic, urological, or smoking-related disease; controls in Brescia were hospitalized males at the same hospital as cases for urological non-neoplastic diseases, frequency-matched on age, period, and hospital. Exposure assessment method: used self-reported work histories and assessed by FINJEM that included semiquantitative estimates of prevalence exposed, mean level of exposure, and duration	Urinary bladder (ICD-9, code 188), low grade, incidence	Exposed to [1,1,1-]TCE, 10 yr lag, men (OR): Never Ever (≥ 2 yr)	327 229	1 1.23 (0.97–1.55)	Age, smoking status, intensity of smoking, study	Intensity and prevalence estimates were based on actual data. Definition of cumulative is unclear but may include prevalence, which, is not a component of toxicity. *Strengths:* examination of tumour grade, semiquantitative exposure estimates; histologically confirmed cancer diagnoses ascertained through medical facilities. *Limitations:* hospital-based design; representativeness of study participants unclear; large proportion of exposed workers; limited consideration of multiple occupational exposures.
		Urinary bladder (ICD-9, code 188), low grade, incidence	Cumulative exposure to [1,1,1-]TCE, 10 yr lag, men (OR): Never Low High	327 111 118	1 1.31 (0.97–1.76) 1.15 (0.86–1.55)		
		Urinary bladder (ICD-9, code 188), high grade, incidence	Exposed to [1,1,1-]TCE, 10 yr lag, men (OR): Never Ever (≥ 2 yr)	209 136	1 1.16 (0.87–1.54)		
		Urinary bladder (ICD-9, code 188), high grade, incidence	Cumulative exposure to [1,1,1-]TCE, 10 yr lag, men (OR): Never Low High	209 72 64	1 1.35 (0.95–1.93) 0.98 (0.68–1.42)		

BMI, body mass index; CAHC, chlorinated aliphatic hydrocarbons; CI, confidence interval; FINJEM, Finnish job-exposure matrix; HR, hazard ratio; ICD, International Classification of Diseases; JEM, job-exposure matrix; NOCCA, Nordic Occupational Cancer Study; NR, not reported; OR, odds ratio; ppm, parts per million; RCC, renal cell carcinoma; SIR, standardized incidence ratio; USKC, United States Kidney Cancer study; 1,1,1-TCE, 1,1,1-trichloroethane; yr, year.

occupations/industries of interest. Participants with complete and personal (excluding next of kin) interviews comprised 63% of cases and 97% of controls. Exposure to six specific chlorinated organic solvents, including methyl chloroform [1,1,1-trichloroethane], was assessed by a set of JEMs specific to a level of intensity and to the probability of exposure for time periods where exposure had been deemed to occur for each job title and each industry (Gomez et al., 1994). The matrices were applied to the job histories by an algorithm that considered whether the job or the industry was the primary generator of exposure and incorporated the estimates into a single cumulative exposure estimate. A total of 15% of cases and 17% of controls were exposed to methyl chloroform [1,1,1-trichloroethane] (19% and 21%, respectively, of men, and 8% and 7%, respectively, of women). [The Working Group noted the relatively high exposure prevalence in this population-based study and the low specificity in the exposure assessment.] Logistic regression was applied adjusting for age, sex, smoking, hypertension and/or use of diuretics and/or anti-hypertension drugs, and body mass index in overall analyses. For methyl chloroform [1,1,1-trichloroethane], there was no clear association with ever exposure observed overall (OR, 0.94; 95% CI, 0.7–1.3). In findings by sex, there was a weak positive although imprecise and non-significant association observed in women (OR, 1.26; 95% CI, 0.6–2.8), but not men (OR, 0.88; 95% CI, 0.6–1.3). [The Working Group noted the limited occupational history and lack of lifetime work information, the small size of the study and inability to examine level of exposure, and the lack of consideration of multiple exposures to chlorinated aliphatic hydrocarbons in the analysis. These factors limited the informativeness of the study. The use of an exposure assessment algorithm with limited consideration of temporal trends in use when estimating probability and intensity of exposure, as well as the use of semiquantitative exposure metrics and low

specificity in the exposure assessment (Gomez et al., 1994), may have resulted in misclassification. The analysis also included only surviving cases, excluding the 35% who had died.]

A population-based case–control study in Montreal, Quebec, Canada, recruited 3730 incident cases of histologically confirmed cancer at 11 different cancer sites in men in 1979–1985, and included 177 cases of kidney cancer and 484 cases of bladder cancer, and 533 population controls (Christensen et al., 2013). For certain analyses, cases of cancer at sites other than the one under study were used as controls (cancer controls) and were combined with equal weight with the population controls. Detailed interviews captured a range of information on each job held during working life. Expert chemists and industrial hygienists assigned categories of confidence of exposure, frequency of exposure, and relative exposure level for a total of 294 agents, including six chlorinated solvents (two chlorinated alkenes, and four chlorinated alkanes, including 1,1,1-trichloroethane). Exposures occurring in the past 5 years were excluded due to latency considerations. A total of 2.3% of kidney cancer cases, 1.9% of population controls, and 1.3% of other cancer controls had any exposure to 1,1,1-trichloroethane. For kidney cancer, unconditional logistic regression was applied adjusting for age, census tract median income, education, ethnicity, self/proxy, smoking, coffee, beer, wine, and spirit intake. There was no clear association between any or substantial exposure to 1,1,1-trichloroethane and kidney cancer risk (odds ratios were elevated, ranging from 1.1 to 1.5, but were imprecise). For bladder cancer, 1.0% of cases had any exposure to 1,1,1-trichloroethane. There was also no clear association between any or substantial exposure to 1,1,1-trichloroethane (odds ratios ranged from 0.5 to 0.7 and were imprecise) and bladder cancer risk in analysis adjusting for age, census tract median income, education, ethnicity, self/proxy, smoking, coffee, and exposure to aromatic amines. Similar results

[not reported] in the analysis of self-respondents (excluding proxies) were also observed. [The Working Group noted that the detailed exposure assessment was a strength of the study, while the small number of workers exposed to 1,1,1-trichloroethane limited its informativeness. Also, intensity and/or cumulative exposure metrics were not specifically evaluated.]

A population-based case–control study in Detroit and Chicago, USA, recruited 1217 incident cases of histologically confirmed kidney cancer and 1235 controls in 2002–2007 (Purdue et al., 2017). The sampling strategy was designed to oversample Black participants. Response rates were 77% among cases and 54% among controls. Participants completed a mailed work history calendar and responded to additional occupational and job-specific modules in interviews focusing on solvent exposures. An expert industrial hygienist assigned levels of exposure probability, frequency, and intensity for six chlorinated solvents, including 1,1,1-trichloroethane, to each job. A total of 4.0% of cases and 4.4% of controls had a 50% or greater probability of exposure to 1,1,1-trichloroethane. Unconditional logistic regression was applied adjusting for age, sex, race, study centre, education level, smoking status, body mass index, and history of hypertension. There was no clear association between categories of probability of exposure to 1,1,1-trichloroethane and kidney cancer risk. The odds ratio among those with a < 50% probability of exposure relative to those who were unexposed to 1,1,1-trichloroethane was 1.2 (95% CI, 1.0–1.4); the odds ratio for a ≥ 90% probability of exposure was 1.2 (95% CI, 0.4–4.1) based on 7 exposed cases. In the analysis of categories of cumulative hours of exposure among high-intensity jobs, there was a positive although imprecise estimate in the highest tertile (> 1456 hours) (OR, 1.6; 95% CI, 0.8–3.2; P for trend, 0.30; 21 exposed cases). [The Working Group noted that the detailed exposure assessment was a strength of the study, while the small number of highly exposed workers, correlations of varying strength with other occupational exposures to solvents, and low response rate among controls limited its informativeness.]

A population-based case–control study nested in the NOCCA database included 113 343 incident cases of bladder cancer (84 629 men and 28 714 women) and 566 715 matched controls from four countries (Finland, Iceland, Norway, and Sweden) from 1961 to 2005 (Hadkhale et al., 2017). The NOCCA-JEM was used to estimate the proportion and level of exposure to selected solvents, including 1,1,1-trichloroethane, based on occupational titles in census records. A total of 6.9% of cases and 6.4% of controls were occupationally exposed to 1,1,1-trichloroethane with a 10-year lag (8.9% of cases and 8.2% of controls among men, and 1.2% of cases and 1.0% of controls among women). Conditional logistic regression was applied in the overall analysis adjusting for age, sex, country, and exposure to trichloroethylene, perchloroethylene [tetrachloroethylene], aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, other organic solvent, ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust, and sulfur dioxide. Although positive associations were observed with occupational exposure to some solvents, no association was observed between categories of cumulative exposure to 1,1,1-trichloroethane and risk of bladder cancer risk, with the estimate in the highest category (> 10.15 ppm-years) being 1.00 (95% CI, 0.89–1.07; P for trend, 0.67) relative to those unexposed to 1,1,1-trichloroethane. There were also no clear associations observed in results stratified by age at diagnosis (< 50 years and ≥ 50 years). Although there were some weakly elevated hazard ratios in some categories of cumulative exposure among women, findings were imprecise and there was no evidence for a trend (P for trend, 0.98). [The Working Group noted that the large-scale population-based design was a strength of the study, as was the consideration of occupational exposures

to other solvents through adjustment of study findings for other such agents. The study also used a well-developed JEM. The lack of data on other personal potentially confounding factors (i.e. cigarette smoking), the limited information on occupational history (based on census records updated only every 10 years), and the inability of a JEM to identify workers with high and low exposure within a population, limited the informativeness of the study.]

Two hospital-based case–control studies in Brescia and Turin, Italy, were pooled to include a total of 893 incident cases of histologically confirmed bladder cancer in men diagnosed in local hospitals and clinics and 978 hospitalized controls (Sciannameo et al., 2019). Response rates were > 90% for both cases and controls at both study sites. Information on lifetime occupational history was obtained and linked to FINJEM, assigning probability and intensity of exposure for 29 selected agents, including trichloroethane for the years 1960–1984. [The Working Group noted that the published manuscript did not explicitly specify 1,1,1-trichloroethane, but rather "trichloroethane", as the agent examined here. The manuscript also apparently incorrectly noted the current IARC classification of [1,1,1-]trichloroethane as Group 2A or 2B, rather than Group 3.] After the application of a 10-year lag, a total of 40.5% of cases and 36.6% of controls were ever exposed (2 years or longer) to [1,1,1-]trichloroethane. [The Working Group noted the large proportion of exposed participants in this study in contrast to that in most other studies reviewed here.] Logistic regression was applied adjusting for age, smoking status, intensity of smoking, and study. A positive, non-significant estimate of 1.18 (95% CI, 0.96–1.46) for ever exposure to [1,1,1-]trichloroethane was observed relative to never exposure; among the highly exposed, the odds ratio was 1.08 (95% CI, 0.83–1.41). Results were generally similar when stratified by high- or low-grade disease. [The Working Group noted the hospital-based design and questions regarding the representativeness of study participants as limitations of the study, as well as a lack of consideration of multiple occupational exposures in analysis. The JEM was well developed, but the exposure assignment and large proportion of exposed participants was of concern, possibly reflecting low specificity in the JEM-based approach.]

2.5 Cancers of the digestive, respiratory, or genital tract, and other solid cancers

See Table 2.6.

Several studies (two cohort, four case–control, two case series) reported on occupational exposure to 1,1,1-trichloroethane in relation to cancers not covered in Sections 2.1–2.4 of the present monograph (Anttila et al., 1995; Zarchy, 1996; Kernan et al., 1999; Radican et al., 2008; Christensen et al., 2013; Kumagai et al., 2013; Vizcaya et al., 2013; Kubo et al., 2014a, b; Kumagai et al., 2016; Le Cornet et al., 2017). The malignancies included melanoma and cancers of the bone, lung, oesophagus, stomach, colon, rectum, liver, pancreas, bile duct, cervix, prostate and testis.

Anttila et al. (1995) conducted a 26-year cancer incidence follow-up of Finnish workers undergoing biological monitoring for exposure to 1,1,1-trichloroethane, trichloroethylene and tetrachloroethylene. In the analysis of 271 workers exposed to 1,1,1-trichloroethane, standardized incidence ratios were reported for all cancers (SIR, 1.58; 95% CI, 0.92–2.52; 17 exposed cases) and cancers of the lung (SIR, 1.31; 95% CI, 0.16–4.71; 2 exposed cases) and cervix (SIR, 8.28; 95% CI, 0.21–46.1; 1 exposed case). [Strengths of the study included its documentation of workers' exposure to 1,1,1-trichloroethane through blood measurements and long-term follow-up for cancer incidence through linkage to a national registry. An important limitation was the small sample size of workers exposed to 1,1,1-trichloroethane,

Table 2.6 Cohort and case–control studies on exposure to 1,1,1-trichloroethane and cancers of the digestive, respiratory, and genital tract, and other solid cancers

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Anttila et al. (1995) Finland Enrolment, 1965–1983 (1,1,1-TCE: 1975–1983)/follow-up, 1967–1992 Cohort	3974 workers (2050 men and 1924 women), 271 of whom were monitored for exposure to 1,1,1-TCE; workers biologically monitored for occupational exposure to three halogenated hydrocarbon solvents in Finland Exposure assessment method: quantitative measurements; a database of measurements in urine from trichloroethylene-exposed participants, and blood from tetrachloroethylene- and 1,1,1-TCE-exposed participants was used to identify ever exposed to the chemicals	All cancers combined, incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure	17	1.58 (0.92–2.52)	Age, sex, calendar period	*Exposure assessment critique*: Exposed were truly exposed. Blood levels only reflect short-term (days) exposures for 9 yr. No information was provided on the interpretation of the measurements or the participants' exposures, including possible exposures to 1,1,1-TCE outside the 1975–1983 window or to other agents. *Strengths*: documented exposure to 1,1,1-TCE via blood measurements; long-term follow-up for cancer incidence through linkage to national cancer registry. *Limitations*: small sample size; no assessment of exposure–response relationships.
		Lung, incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure	2	1.31 (0.16–4.71)		
		Uterine cervix, incidence	Compared with the general population (SIR): Any 1,1,1-TCE exposure	1	8.28 (0.21–46.1)	Age, calendar period	

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Radican et al. (2008) Utah, USA Enrolment, 1952–1956/ follow-up, 1953–2000 Cohort	14 455 (10 730 men and 3725 women); civilian workers employed at Hill Air Force Base, an aircraft-maintenance facility, for ≥ 1 yr between 1952 and 1956, who were followed up for cancer mortality through linkage to the national death index Exposure assessment method: review of facility records, jobs, walk-through surveys, interviews, measurements used to assign yes/no exposed by job group	Bone, mortality Bone, mortality	Exposure to 1,1,1-TCE, women (HR): No chemical exposures Ever Exposure to 1,1,1-TCE, men (HR): No chemical exposures Ever	 NR 1 NR 0	 – 17.87 (1.12–286) – –	Age, race	*Exposure assessment critique*: Extensive data collection, including measurements. Linkage of jobs to exposures was limited due to the limited information in the available records. Given 1,1,1-TCE was often interchanged with other chlorinated solvents, the difficulty in making these links is a non-trivial limitation. Job information used to assign yes/no. *Strengths*: large cohort size and long follow-up period; internal comparison group. *Limitations*: small number of deaths among exposed workers; qualitative exposure assessment; potential co-exposures with other organic solvents.

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level		Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kernan et al. (1999) USA 1984–1993 Case–control	Cases: 63 097; death certificates from 24 states, with pancreatic cancer listed as the underlying cause of death Controls: 252 386; death certificates from 24 states, with other underlying cause of death (excluding cancer, pancreatitis, and other pancreatic diseases), frequency-matched on state, race, sex, and 5 yr age group Exposure assessment method: source of job information was death certificates, and assessed for probability and intensity using a JEM	Pancreas, mortality	Intensity of methyl chloroform [1,1,1-TCE] exposure, Black women (OR):				Age, metropolitan status, region of residence, marital status	*Exposure assessment critique*: Weakest of the case–control studies reviewed. Death certificates provide only a single job, so other exposed jobs were likely to have been missed. No important other information available (industry, dates, tasks, etc.). No information was provided as to the development of the JEM. Estimates of cumulative exposure were not developed. Metrics were all categorical. *Strengths*: large sample size. *Limitations*: death certificate information may not accurately capture usual job; as only one job is listed, exposures from other jobs were probably missed; no information was available regarding duration of usual employment or potential confounders.
			Unexposed	NR	1			
			Low	312	1.0 (0.8–1.1)			
			Medium	22	1.1 (0.7–1.7)			
			High	42	0.8 (0.5–1.1)			
		Pancreas, mortality	Intensity of methyl chloroform [1,1,1-TCE] exposure, Black men (OR):					
			Unexposed	NR	1			
			Low	926	0.9 (0.9–1.0)			
			Medium	101	1.1 (0.9–1.5)			
			High	83	1.2 (0.9–1.5)			
		Pancreas, mortality	Intensity of methyl chloroform [1,1,1-TCE] exposure, White women (OR):					
			Unexposed	NR	1			
			Low	1003	1.1 (1.0–1.2)			
			Medium	236	1.0 (0.8–1.1)			
			High	382	1.1 (1.0–1.2)			
		Pancreas, mortality	Intensity of methyl chloroform [1,1,1-TCE] exposure, White men (OR):					
			Unexposed	NR	1			
			Low	5359	1.0 (0.9–1.0)			
			Medium	1027	1.0 (0.9–1.1)			
			High	507	0.9 (0.8–0.9)			
		Pancreas, mortality	Probability of methyl chloroform [1,1,1-TCE] exposure, Black women (OR):					
			Unexposed	NR	1			
			Low	274	0.9 (0.8–1.1)			
			Medium	25	0.7 (0.5–1.1)			
			High	4	1.2 (0.4–3.7)			

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kernan et al. (1999) USA 1984–1993 Case–control (cont.)		Pancreas, mortality	Probability of methyl chloroform [1,1,1-TCE] exposure, Black men (OR):			Age, metropolitan status, region of residence, marital status	
			Unexposed	NR	1		
			Low	673	0.9 (0.9–1.1)		
			Medium	5	0.5 (0.2–1.3)		
			High	8	2.9 (1.2–7.5)		
		Pancreas, mortality	Probability of methyl chloroform [1,1,1-TCE] exposure, White women (OR):				
			Unexposed	NR	1		
			Low	762	1.1 (1.1–1.2)		
			Medium	36	0.7 (0.4–0.9)		
			High	41	1.0 (0.7–1.4)		
		Pancreas, mortality	Probability of methyl chloroform [1,1,1-TCE] exposure, White men (OR):				
			Unexposed	NR	1		
			Low	3943	0.9 (0.9–1.0)		
			Medium	47	1.0 (0.7–1.3)		
			High	48	0.9 (0.7–1.3)		

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control	Cases: 3730 cancer cases at 11 organ sites, including 103 melanoma and 99 oesophagus, 251 stomach, 496 colon, 248 rectum, 48 liver, 116 pancreas, and 449 prostate cancer cases; male incident histologically confirmed cancers from 18 large hospitals in the Montreal metropolitan area, Canadian citizens, aged 35–70 yr Controls: 533 population controls, 1295–2525 other cancer controls; population controls obtained randomly from population-based electoral lists, stratified by sex and age, other cancer controls from other participating cases	Prostate, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, beer, wine, and spirit intake	*Exposure assessment critique*: Substantial data available for assessment including [presumably] published measurement data. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. confidence, frequency, and intensity) is a key strength. Metrics were all categorical. *Strengths*: detailed expert-based exposure assessment; histologically confirmed cancer diagnoses ascertained through hospitals. *Limitations*: small case sample sizes; no quantitative exposure metrics.
			No chlorinated solvent or hydrocarbon exposure	335	1		
			Ever-analysis limited to population controls	5	0.7 (0.2–2.1)		
			Ever-analysis including both population and other cancer controls	5	0.8 (0.3–2.4)		
		Prostate, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	335	1		
			Ever-analysis limited to population controls	5	1.3 (0.4–4.6)		
			Ever-analysis including both population and other cancer controls	5	1.6 (0.5–5.1)		

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Christensen et al. (2013)](#) Montreal, Canada 1979–1985 Case–control (cont.)	Exposure assessment method: expert judgement; full work histories and specialized questionnaires, [presumed measurement data], and extensive review to assign participant-specific semiquantitative estimates of confidence, frequency and intensity for each job held	Colon, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, beer, wine, and spirit intake	
			No chlorinated solvent or hydrocarbon exposure	365	1		
			Ever-analysis limited to population controls	5	0.6 (0.2–1.7)		
			Ever-analysis including both population and other cancer controls	5	0.6 (0.2–1.7)		
		Colon, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	365	1		
			Ever-analysis limited to population controls	4	0.7 (0.2–2.7)		
			Ever-analysis including both population and other cancer controls	4	0.8 (0.3–2.6)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control (cont.)		Stomach, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, beer, wine, and spirit intake	
			No chlorinated solvent or hydrocarbon exposure	195	1		
			Ever-analysis limited to population controls	4	1.1 (0.3–3.8)		
			Ever-analysis including both population and other cancer controls	4	1.2 (0.4–3.8)		
		Stomach, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	195	1		
			Ever-analysis limited to population controls	2	0.8 (0.2–4.3)		
			Ever-analysis including both population and other cancer controls	2	0.9 (0.2–4.4)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Christensen et al. (2013)](#) Montreal, Canada 1979–1985 Case–control (cont.)		Rectum, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, beer intake	
			No chlorinated solvent or hydrocarbon exposure	192	1		
			Ever-analysis limited to population controls	2	0.4 (0.1–2.0)		
			Ever-analysis including both population and other cancer controls	2	0.4 (0.1–1.8)		
		Rectum, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	192	1		
			Ever-analysis limited to population controls	2	0.6 (0.1–3.3)		
			Ever-analysis including both population and other cancer controls	2	0.6 (0.1–3.0)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control (cont.)		Melanoma, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking	
			No chlorinated solvent or hydrocarbon exposure	69	1		
			Ever-analysis limited to population controls	2	0.9 (0.2–4.5)		
			Ever-analysis including both population and other cancer controls	2	0.9 (0.2–4.3)		
		Melanoma, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	69	1		
			Ever-analysis limited to population controls	1	0.5 (0.1–4.8)		
			Ever-analysis including both population and other cancer controls	1	0.6 (0.1–5.3)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Christensen et al. (2013)](#) Montreal, Canada 1979–1985 Case–control (cont.)		Pancreas, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, coffee, beer, wine, and spirit intake	
			No chlorinated solvent or hydrocarbon exposure	95	1		
			Ever-analysis limited to population controls	1	0.6 (0.1–5.7)		
			Ever-analysis including both population and other cancer controls	1	0.8 (0.1–6.0)		
		Pancreas, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	95	1		
			Ever-analysis limited to population controls	1	0.8 (0.1–7.5)		
			Ever-analysis including both population and other cancer controls	1	1.1 (0.1–8.8)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Christensen et al. (2013) Montreal, Canada 1979–1985 Case–control (cont.)		Oesophagus, incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, coffee, tea, beer, wine, and spirit intake	
			No chlorinated solvent or hydrocarbon exposure	75	1		
			Ever-analysis limited to population controls	2	1.4 (0.3–7.5)		
			Ever-analysis including both population and other cancer controls	2	1.9 (0.4–8.7)		
		Oesophagus, incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	75	1		
			Ever-analysis limited to population controls	1	1.1 (0.1–10)		
			Ever-analysis including both population and other cancer controls	1	1.4 (0.2–12)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Christensen et al. (2013)](#) Montreal, Canada 1979–1985 Case–control (cont.)		Liver (hepatocellular carcinoma), incidence	Any exposure to 1,1,1-TCE, 5 yr lag (OR):			Age, census tract median income, educational attainment, ethnicity, questionnaire respondent (self vs proxy), smoking, beer, wine, and spirit intake	
			No chlorinated solvent or hydrocarbon exposure	33	1		
			Ever-analysis limited to population controls	1	1.8 (0.2–17)		
			Ever-analysis including both population and other cancer controls	1	2.3 (0.3–19)		
		Liver (hepatocellular carcinoma), incidence	Substantial exposure to 1,1,1-TCE, 5 yr lag (OR):				
			No chlorinated solvent or hydrocarbon exposure	33	1		
			Ever-analysis limited to population controls	1	2.2 (0.2–22)		
			Ever-analysis including both population and other cancer controls	1	3.2 (0.4–28)		

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vizcaya et al. (2013) Montreal, Canada 1980–1986 and 1995–2001 Case–control	Cases: 1586 (study I, n = 851; study II, n = 735); male Montreal residents (study I, aged 35–70 yr; study II, aged 35–75 yr) diagnosed with lung cancer at one of 18 local hospitals Controls: 1431 (study I, n = 533; study II, n = 898); male Montreal residents on electoral list, frequency-matched to sex and age distributions of cases Exposure assessment method: expert judgement; full work histories and specialized questionnaires, [presumed measurement data], and extensive review to assign participant-specific semiquantitative estimates of confidence, frequency and intensity for each job held	Lung, incidence	Any exposure to 1,1,1-TCE (OR):			Age, educational attainment, socioeconomic status, ethnicity, questionnaire respondent (self vs proxy), exposure to eight known carcinogens, smoking habit, study	*Exposure assessment critique*: Substantial data available for assessment including [presumably] published measurement data. Evaluation was participant-specific. Careful consideration of each job held by each participant (i.e. confidence, frequency, and intensity) is a key strength. Lifetime exposure included confidence, which is not a component of toxicity. Metrics were all categorical. *Strengths*: detailed expert-based exposure assessment; large sample size. *Limitations*: absence of quantitative exposure metrics.
			No chlorinated solvent or vinyl chloride exposure	1313	1		
			Ever	22	1.1 (0.5–2.3)		
		Lung, incidence	Substantial exposure to 1,1,1-TCE (OR):				
			No chlorinated solvent or vinyl chloride exposure	1313	1		
			Ever	13	1.1 (0.4–2.7)		

Table 2.6   (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level		Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
[Le Cornet et al. (2017)](#) Finland, Norway, Sweden Finland, 1988–2012; Norway, 1978–2010; Sweden, 1979–2011 Case–control	Cases: 8112; first-primary testicular germ cell tumour cases, aged 14–49 yr, captured in national cancer registries of Finland, Norway and Sweden Controls: 26 264; cancer-free men sampled from central population registries individually matched to cases (4:1 ratio) by year and country of birth Exposure assessment method: used self-reported jobs to the census and NOCCA-JEM that includes semiquantitative estimates of prevalence exposed and mean level of exposure	Testis, incidence	Maternal exposure to 1,1,1-TCE (OR):				Year, country of child's birth	*Exposure assessment critique*: NOCCA-JEM is a robust and well-developed JEM. NOCCA-JEM was normalized to the country. Prevalence and intensity were based on actual data. Could be missing exposed jobs due to 10 yr census collection. Exposure metric unclear. Authors indicate exposure is binary but then discuss none, low and high [could be based on prevalence × intensity]. *Strengths*: large sample size; opportunity to link to census records to estimate parental exposure before participants' birth; use of country-specific JEM; cancer diagnoses ascertained through linkage with national registries. *Limitations*: the use of census data for occupational titles and absence of data on industry of employment provided little information for use in exposure assessment.
			Unexposed		6937	1		
			Low		45	0.95 (0.68–1.33)		
			High		36	1.14 (0.77–1.67)		
		Testis, incidence	Paternal exposure to 1,1,1-TCE (OR):				Year, country of child's birth	
			Unexposed		7017	1		
			Low		380	1.10 (0.98–1.25)		
			High		458	1.07 (0.95–1.19)		

CI, confidence interval; HR, hazard ratio; JEM, job-exposure matrix; NOCCA, Nordic Occupational Cancer Study; NR, not reported; OR, odds ratio; ppm, parts per million; SIR, standardized incidence ratio; 1,1,1-TCE, 1,1,1-trichloroethane; yr, year; vs, versus.

which limited power and precluded more detailed analyses across exposure levels.]

In an updated mortality follow-up of 10 730 male and 3725 female civilian aircraft-maintenance workers at a United States Air Force base in a study conducted by Radican et al. (2008), a hazard ratio for bone cancer of 17.87 (95% CI, 1.12–286) among exposed versus unexposed women was observed based on a single death. However, as no bone cancer deaths were observed among male workers, it is possible that this finding is attributable to chance. [Study strengths included a long period of follow-up and the use of internal comparisons with unexposed workers to estimate relative risk. Also, the exposure assessment was performed by industrial hygienists with access to the base facilities and records. Limitations included the small number of exposed mortality end-points for 1,1,1-trichloroethane, the qualitative nature of the exposure assessment, the difficulty in linking participants to estimates often associated with no more detail than job title, and the lack of continued exposure assessment after 1982.]

Kernan et al. (1999) conducted a case–control study on occupational risk factors for pancreatic cancer using death certificate records from 24 states in the USA, with controls selected from death records unrelated to cancer or non-malignant pancreatic disease, frequency-matched on state, race, sex, and 5-year age group. Decedents' usual occupation and industry were coded from death certificates and a JEM was applied to the coded occupational data to assess potential exposure to formaldehyde and 11 chlorinated hydrocarbons, including 1,1,1-trichloroethane [referred to as methyl chloroform]. Odds ratios were estimated separately for Black women, Black men, White women, and White men using logistic regression models adjusted for age, marital status, and metropolitan and residential status. A statistically significant elevated odds ratio for pancreatic cancer mortality in relation to high probability of exposure to 1,1,1-trichloroethane

(versus those never exposed to the solvent) was observed among Black men (OR, 2.9, 95% CI, 1.2–7.5; 8 exposed deaths). However, as null findings were observed for all other sex and race strata, as well as in analyses of 1,1,1-trichloroethane exposure intensity, it is possible that this finding is attributable to chance. [A strength of this study was its large sample size, although the one statistically significant finding was based on a small number of exposed deaths. Death certificates provided only a single job; other exposed jobs were likely to have been missed. No information regarding industry, duration of usual employment, or potential confounders was available.]

Christensen et al. (2013) investigated occupational exposure to 1,1,1-trichloroethane and other chlorinated solvents in relation to several cancer sites in a case–control study in male residents of Montreal, Canada. Cancers of interest in this analysis included melanoma ($n = 103$) and cancers of the oesophagus ($n = 99$), stomach ($n = 251$), colon ($n = 496$), rectum ($n = 248$), liver ($n = 48$), pancreas ($n = 116$), and prostate ($n = 449$). Participants completed a detailed in-person interview that included a semi-structured occupational history questionnaire collecting information regarding employer details, tasks performed, use of protective equipment and other workplace characteristics for each job held for at least 6 months. Interviews were conducted with proxy respondents if a participant had died or could not otherwise be interviewed. A team of industrial chemists and hygienists reviewed participants' occupational histories and translated each job into potential exposures from a list of 293 substances. Odds ratios were estimated using unconditional logistic regression in relation to two different control groups: population controls only ($n = 533$) and population controls combined with cases of other cancers ($n = 1295$ to $n = 2525$). All models adjusted for age, ethnicity, and socioeconomic status. Additional covariates were adjusted for depending on the cancer

type (oesophagus: smoking, coffee, tea, and alcohol intake; stomach, colon and liver: smoking, coffee, tea, and alcohol intake; rectum: smoking and beer intake; pancreas: smoking, coffee, and alcohol intake; prostate: smoking and alcohol intake). Exposures occurring in the previous 5 years were excluded due to latency considerations. For 1,1,1-trichloroethane exposure, the odds ratios for these cancers were close to the null or based on very small numbers of exposed participants. [A strength of this analysis was the detailed expert-based retrospective exposure assessment methodology. Study limitations included the absence of quantitative exposure metrics and the small case sample sizes.]

Vizcaya et al. (2013) conducted an analysis of exposure to chlorinated solvents and lung cancer risk among men, using data from two studies: the Montreal case–control study on different cancer sites analysed by Christensen et al. (2013) and a subsequent case–control study on lung cancer conducted in Montreal using a nearly identical study design and exposure assessment approach. Unconditional logistic regression was applied with adjustment for age, census median income, ethnicity, educational attainment, respondent type (self versus proxy), smoking, and exposure to occupational lung carcinogens (asbestos, crystalline silica, chromium(VI), arsenic compounds, diesel exhaust emissions, soot, wood dust, and benzo[a]pyrene). In the pooled analysis, exposure to 1,1,1-trichloroethane was not associated with lung cancer risk, with odds ratios of 1.1 observed for any exposure and for "substantial" exposure. [Strengths of this analysis included the detailed expert-based retrospective exposure assessment methodology and the large pooled sample size. A limitation was the absence of quantitative exposure metrics.]

Le Cornet et al. (2017) performed a registry-based case–control study on testicular germ cell tumours within three Nordic countries to investigate associations with parental occupational exposures to several organic solvents,

including 1,1,1-trichloroethane, during the prenatal period. Unique personal identification codes assigned to residents of each country provided the opportunity to create linkages between cancer and other population registries, including parents' census records. Testicular cancer cases in men diagnosed between ages 14 and 49 years from 1988 to 2012 in Finland, 1978 to 2010 in Norway, and 1979 to 2011 in Sweden were selected for the study (n = 8112). Four controls randomly selected from the national population registers were individually matched on each case by year and country of birth. Job codes for the parents of each participants were retrieved from the last census conducted before the participant's birth and the first census conducted afterward. Parental occupational exposures to 1,1,1-trichloroethane and five other individual solvents were estimated using the NOCCA-JEM. Odds ratios for high exposure to 1,1,1-trichloroethane, estimated using conditional logistic regression, were close to unity for both maternal and paternal occupations (OR, 1.14; 95% CI, 0.77–1.67; and OR, 1.07; 95% CI, 0.95–1.19, respectively) versus no exposure to 1,1,1-trichloroethane). Findings were similar in sensitivity analyses restricting to solvent exposure within the year before childbirth and excluding participants exposed to other solvents. [A strength of this study was the unique opportunity within Nordic countries to create linkages across different administrative data records, which enabled the capture of census-defined parental occupations in the prenatal period of cases, and controls for exposure assessment. Other strengths included the large sample size and the availability of a well-developed country-specific JEM to enable semiquantitative assessments of exposure to 1,1,1-trichloroethane and other solvents. The use of census data for occupational titles and absence of data on industry of employment provided little information for use in exposure assessment, and the JEMs had limited ability to identify individuals with low and high exposure.]

In addition to the previously mentioned cohort and case–control studies, two case studies on biliary–pancreatic cancers diagnosed among workers exposed to 1,1,1-trichloroethane and other chemicals have also been reported. A cluster of 17 cases of cholangiocarcinoma diagnosed at a relatively young age among former and current employees of an offset proof-printing plant in Osaka, Japan, was described in a series of reports by Kumagai et al. (2013) and Kubo et al. (2014a, b). While some of the cases had been exposed to 1,1,1-trichloroethane, all shared a history of high-level, long-term exposure to 1,2-dichloropropane. A subsequent retrospective cohort study among workers employed at the same company demonstrated a strong exposure–response relation between exposure to 1,2-dichloropropane and cholangiocarcinoma (Kumagai et al., 2016). [These findings were influential in the classification of 1,2-dichloropropane as *carcinogenic to humans*, IARC Group 1, in *IARC Monographs* Volume 110 (IARC, 2016).] A small case study in the USA by Zarchy (1996), reporting on two cases of cholangiocarcinoma and ampullary carcinoma diagnosed in workers exposed to 1,1,1-trichloroethane, tetrachloroethylene, and other unspecified chemicals, provided no evidence of value towards clarifying the carcinogenicity of this agent.

2.6 Evidence synthesis for cancer in humans

The epidemiological database for this evaluation comprised two cohort studies, five nested case–control studies, and sixteen population-based case–control studies, with most of these having been published since the previous evaluations of 1,1,1-trichloroethane in *IARC Monographs* Volumes 20 and 71 (IARC, 1979, 1999). The largest number of studies examined cancers of the haematopoietic and lymphoid tissues, followed by cancers of the kidney and urinary bladder, the brain and nervous system, and the breast. There were a smaller number of studies on other cancers at other sites, including digestive tract, skin (melanoma), and cancers of the bone, lung, cervix, prostate, and testis. There were also two case studies on cholangiocarcinoma and ampullary carcinoma.

2.6.1 Studies evaluated

In the assessment of the carcinogenicity of 1,1,1-trichloroethane in humans, some studies were considered to be somewhat more informative on the basis of study quality, since they included aspects of study power, exposure assessment, potential co-exposure to other occupational agents, and confounding and selection bias (further discussed below). In some studies on 1,1,1-trichloroethane, there was a low prevalence of exposure and/or small study size, leading to very few exposed cases, and the resulting effect estimates were imprecise (Anttila et al., 1995; Infante-Rivard et al., 2005; Radican et al., 2008; Christensen et al., 2013; McLean et al., 2014). Low prevalence of exposure was a limitation observed in most studies, and lead to small numbers of exposed cases.

The Working Group determined that reports from two case studies on cholangiocarcinoma and ampullary carcinoma were uninformative for assessing the association between exposure to 1,1,1-trichloroethane and cancer and are not further discussed here (Zarchy, 1996; Kumagai et al., 2013, 2016; Kubo et al., 2014a, b).

2.6.2 Exposure assessment and misclassification of exposure

The Working Group considered that the quality of the exposure assessment was a major factor in the evaluation of epidemiological studies on the carcinogenicity of occupational exposure to 1,1,1-trichloroethane. A summary and detailed evaluation of the strengths and limitations of the

exposure assessment in previous epidemiological studies is provided in Sections 1.6.1 and 1.6.2, respectively.

Exposure assessment in cohort studies was performed using either data on biological monitoring of workers (Anttila et al., 1995) or a detailed exposure assessment approach, including review of facility records, jobs, walk-through surveys, interviews, and measurements to assign exposure status by job group (Radican et al., 2008). Although exposure was documented among monitored workers, there are concerns regarding the representativeness of measurements as well as their small number (Anttila et al., 1995). In Radican et al. (2008), there was limited information on participant job history with which to assign exposure estimates. In both studies, there were no quantitative exposure–response analyses and limitations in exposure assessment are likely to result in attenuation of disease risk towards the null.

In several large-scale nested case–control studies based in the NOCCA cohort, estimates of cumulative exposure to 1,1,1-trichloroethane were assigned on the basis of census job data using the well-developed NOCCA-JEM. However, census job data was limited to job titles captured every 10 years and ending in 1990; this may have led to non-differential misclassification of exposure history (Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017). In another nested case–control study in a population-based cohort, an expert hygienist review was conducted of exposure prevalence in the NOCCA-JEM/FINJEM based on more detailed questionnaire data captured on work tasks in recent jobs, although exposure prevalence and intensity were low in this study (Videnros et al., 2020).

Case–control studies were largely population-based, and exposure assessment ranged from studies assessing detailed participant-specific quantitative or semiquantitative estimates of exposure based on combinations of work histories, job- or task-specific modules, literature/

measurement data, and expert review (Infante-Rivard et al., 2005; Miligi et al., 2006; Gold et al., 2011; Neta et al., 2012; Christensen et al., 2013; Ruder et al., 2013; Vizcaya et al., 2013; Purdue et al., 2017; Callahan et al., 2018), to studies relying on study-specific JEMs or the NOCCA-JEM/FINJEM assigned to participant lifetime job history or to the longest or most recent job(s) (Heineman et al., 1994; Dosemeci et al., 1999; Kernan et al., 1999; McLean et al., 2014; Le Cornet et al., 2017; Sciannameo et al., 2019; Pedersen et al., 2020). A weakness of JEM-based studies is the fact that the JEM does not take into account variability between workers in the same occupation, leading to limited ability to identify participants with high exposure, as well as low specificity (Dosemeci et al., 1999; Sciannameo et al., 2019). In some JEM-based studies, higher probabilities of exposure (for example of > 10% or > 25%) were applied (instead of the 5% typically used) in an attempt to improve specificity (McLean et al., 2014; Pedersen et al., 2020). JEMs were also not sex-specific.

In general, non-differential misclassification is expected to result in attenuation of risk estimates towards the null in case–control studies, with attenuation probably greater in lower-quality studies than in higher-quality studies. There may also be some degree of Berkson-type error from JEM or other group-based exposure estimation, probably resulting in a reduction in precision of the effect estimate (but not bias). Recall bias may also be present in retrospective studies based on occupational information reported when disease status is known. In some studies, interviews relied fully or partially on proxy or next-of-kin respondents, possibly leading to misclassification in occupational histories, although findings in sensitivity analysis (where performed) excluding such respondents did not materially change study findings (Heineman et al., 1994; Miligi et al., 2006; Neta et al., 2012; Christensen et al., 2013; Ruder et al., 2013). One study comparing findings using either general-population

controls or other cancer cases combined (and weighted equally) with general-population controls reported similar findings by control group (Christensen et al., 2013). In one study, jobs held for at least 2 years were captured in an attempt to minimize recall bias, although there may be misclassification of exposures in jobs held for shorter periods of time (Sciannameo et al., 2019).

There is also co-exposure to other occupational agents that may pose a carcinogenic hazard (see below). With few exceptions (Anttila et al., 1995; Dosemeci et al., 1999; Radican et al., 2008), most studies examined several quantitative or semiquantitative exposure categories such as exposure duration, intensity, probability, or cumulative exposure. Some studies assigned exposure using a lag period, ranging from approximately 3 to 20 years, in either the overall or the sensitivity analysis (Heineman et al., 1994; Gold et al., 2011; Neta et al., 2012; Christensen et al., 2013; McLean et al., 2014; Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017; Purdue et al., 2017; Sciannameo et al., 2019; Pedersen et al., 2020). The appropriate lag period for 1,1,1-trichloroethane may differ substantially according to the cancer site evaluated (e.g. in adults, latency for acute leukaemia may be much shorter than for CLL or other types of NHL). In other studies, there was little information on the timing of jobs or exposure for individual study participants (Kernan et al., 1999; Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017).

Owing to the correlated nature of exposures to several chlorinated solvents, and their interchangeable use over time, there may also be some degree of misclassification and uncertainty in the assignment of exposure to a specific solvent over time (see also below). In one study, published information was used to assign a probability of exposure that the solvent was used in a particular time period, although uncertainties remain (Gold et al., 2011).

2.6.3 Co-exposures to other occupational agents of relevance for cancer hazard identification

Although all studies assessed exposure not only to 1,1,1-trichloroethane, but also to multiple other solvents or agents with occupational exposures, few explicitly provided information on the correlation structure with exposure to such agents (Dosemeci et al., 1999; Gold et al., 2011; McLean et al., 2014; Le Cornet et al., 2017; Purdue et al., 2017; Callahan et al., 2018; Talibov et al., 2019; Pedersen et al., 2020; Videnros et al., 2020). Other solvents assessed typically included trichloroethylene (IARC Group 1, with *sufficient* evidence for kidney cancer and *limited* evidence for cancers of the liver and bile duct and for NHL other than multiple myeloma and CLL), tetrachloroethylene (Group 2A, with *limited* evidence for bladder cancer), dichloromethane (Group 2A, with *limited* evidence for cancer of the biliary tract and for NHL other than multiple myeloma and CLL) and, less often, carbon tetrachloride (Group 2B) and chloroform (Group 2B). In some studies, moderate to strong correlations between 1,1,1-trichloroethane and other occupational exposures to solvents were observed (see Table S1.6; Annex 1, Supplementary material for 1,1,1-trichloroethane, Section 1, Exposure Characterization, available from: https://publications.iarc.fr/611). There were also moderate to strong correlations with exposure to other occupational agents (i.e. metals such as chromium, nickel, and lead; and welding fumes, a Group 1 carcinogen with *sufficient* evidence for lung cancer and *limited* evidence for kidney cancer). It may therefore be difficult to distinguish the agent responsible for any positive association observed, depending on the cancer site, and there may be confounding by other occupational exposures (see also below). In Anttila et al. (1995), workers were typically monitored for exposure to one solvent only. As noted above, due to interchanges in the occupational use of solvents over time, there

may also be some degree of misclassification and uncertainty in the assignment of exposures to specific solvents over the study period (Radican et al., 2008; Gold et al., 2011). Owing to the multiple solvents or agents assessed for occupational exposure in each study, multiple testing is also of concern. There was no information on chemicals added to 1,1,1-trichloroethane as stabilizers or solvents, or other impurities, in epidemiological studies described here.

2.6.4 Confounding, selection bias, and outcome measurement error

Studies generally adjusted in their design and/or analysis for personal data, such as age, sex, race, or education, which were usually captured from personal interviews; registry or death certificate-based studies adjusted for fewer personal data. Some studies adjusted for other known cancer site-specific risk factors, such as reproductive factors for breast cancer (Pedersen et al., 2020; Videnros et al., 2020) and hypertension for kidney cancer (Dosemeci et al., 1999; Purdue et al., 2017). For several other studies, there was no information available on other personal or lifestyle factors to control for their potentially confounding effects. For example, although Hadkhale et al. (2017) adjusted for a range of occupational agents in their analysis of 1,1,1-trichloroethane and cancer of the urinary bladder, no data were available on cigarette smoking or other personal factors within the linked population registers used in that study. For census-based studies in particular, limited data were available on other potential risk factors, including exposure to other occupational carcinogens. For studies on some other cancer sites for which there are fewer known risk factors, there is less concern regarding potential residual confounding (e.g. brain and nervous system tumours, bone cancer, multiple myeloma).

The potential for selection bias is expected to be minimal in the large-scale NOCCA-based

studies, given their composition of records from comprehensive national registries of all residents in the Nordic countries participating in decennial population censuses, and diagnoses from nation-wide registries of cancer incidence. Some case–control studies had low participation rates, particularly among proxy or next-of-kin controls, possibly leading to some degree of selection bias and underrepresentation of exposed controls (Heineman et al., 1994; Gold et al., 2011; Purdue et al., 2017; Callahan et al., 2018). There are also concerns regarding potential selection or other methodological sources of bias in some hospital-based studies (Neta et al., 2012; Sciannameo et al., 2019), as well as in studies in which consistently inverse associations were observed (Miligi et al., 2006; Neta et al., 2012; Ruder et al., 2013). The selection of workers for monitoring in the study by Anttila et al. (1995) was not clear. There may be some degree of survival bias in studies excluding large proportions of deceased cases (Dosemeci et al., 1999; Gold et al., 2011).

In most studies, case identification was comprehensive and of high quality. In several studies, cancer cases were identified from comprehensive, population-wide cancer registry or surveillance systems (Anttila et al., 1995; Dosemeci et al., 1999; Gold et al., 2011; Talibov et al., 2014, 2017, 2019; Hadkhale et al., 2017; Le Cornet et al., 2017; Purdue et al., 2017; Callahan et al., 2018; Pedersen et al., 2020; Videnros et al., 2020). Other studies used extensive hospital- or treatment centre-based recruitment (Infante-Rivard et al., 2005; Miligi et al., 2006; Neta et al., 2012; Christensen et al., 2013; Ruder et al., 2013; Vizcaya et al., 2013; McLean et al., 2014). In one study, the representativeness of included cases was unclear (Sciannameo et al., 2019). In other studies, case identification was based on death certificates or death registries (Heineman et al., 1994; Kernan et al., 1999; Radican et al., 2008). Heineman et al. (1994) confirmed cause of death with hospital diagnostic records.

2.6.5 Cancers of the haematopoietic and lymphoid tissues

Two cohort studies ([Anttila et al., 1995](#); [Radican et al., 2008](#)), two nested case–control studies ([Talibov et al., 2014](#), [2017](#)), and five case–control studies ([Infante-Rivard et al., 2005](#); [Miligi et al., 2006](#); [Gold et al., 2011](#); [Christensen et al., 2013](#); [Callahan et al., 2018](#)) investigated the association between haematopoietic and lymphatic malignancies and exposure to 1,1,1-trichloroethane.

Findings from studies on NHL showed no clear association with exposure to 1,1,1-trichloroethane. [Anttila et al. (1995)](#) reported a positive although imprecise standardized incidence ratio based on a single exposed case. [Radican et al. (2008)](#) reported a weak positive but non-statistically significant association between ever exposure to 1,1,1-trichloroethane and mortality attributable to NHL in men (HR, 1.51; 95% CI, 0.61–3.73; 12 exposed cases). There were no deaths from NHL among exposed women. Co-exposure with other organic solvents having suggested associations with NHL (i.e. trichloroethylene and dichloromethane) in this study remains of concern. [Talibov et al. (2017)](#) reported odds ratios close to unity for incident cases of NHL (CLL) in both men and women (1416 and 143 exposed cases, respectively) among categories of cumulative exposure based on the NOCCA-JEM in a large-scale nested case–control study, with no evidence for a trend. Among the case–control studies, [Miligi et al. (2006)](#) reported odds ratios of < 1.0 for incident cases of NHL in association with expert-derived categories of low-very low (15 exposed cases), or medium-high intensity of exposure (5 exposed cases). Only jobs held for at least 5 years and for more than 5 years before diagnosis were considered. [Christensen et al. (2013)](#) reported no association between NHL and any or substantial exposure to 1,1,1-trichloroethane; there were few exposed cases. [Callahan et al. (2018)](#) reported no association between NHL

and categories of exposure probability or cumulative hours of exposure to 1,1,1-trichloroethane in a case–control study with detailed individual exposure assessments (565 exposed cases).

Among studies on multiple myeloma, some positive although sometimes imprecise associations were observed in the available studies. [Anttila et al. (1995)](#) reported a significant positive standardized incidence ratio for multiple myeloma, in men and women combined, of 15.98 (95% CI, 1.93–57.7; 2 exposed cases). [Radican et al. (2008)](#) reported a significant positive association between ever exposure to 1,1,1-trichloroethane and mortality attributable to multiple myeloma in women (HR, 14.46; 95% CI, 3.24–64.63; 3 exposed cases), but not in men (HR, 0.64; 95% CI, 0.18–2.30; 4 exposed cases); an overall HR for the cohort was not estimated. [Gold et al. (2011)](#), in a case–control study including 180 incident cases and 481 controls, reported a significant positive association between ever exposure to 1,1,1-trichloroethane and multiple myeloma (OR, 1.8; 95% CI, 1.1–2.9; 36 exposed cases). The association remained in a sensitivity analysis that assigned jobs with low confidence in the assessment to the referent (unexposed) category (OR, 2.2; 95% CI, 1.1–4.4; 17 exposed cases). Odds ratios were elevated across most categories of exposure duration, unlagged cumulative exposure, and cumulative exposure with a 10-year lag, although no evidence of a positive trend with increasing exposure category was observed. The limitations of this study included the small numbers of exposed participants, misclassification and uncertainties in the assignment of correlated chlorinated solvent exposures, potential survival bias, and selection bias, possibly resulting in some bias in the findings observed.

There was no clear association between maternal prenatal exposure to 1,1,1-trichloroethane and incident cases of childhood ALL; odds ratios were elevated although imprecise ([Infante-Rivard et al., 2005](#)). There was also no association between exposure to 1,1,1-trichloroethane

and incident cases of adult AML in a large-scale study, with odds ratios of < 1.0 observed in all categories of cumulative exposure, based on 896 exposed cases (Talibov et al., 2014).

Overall, the Working Group considered that in the body of available evidence, a positive association between exposure to 1,1,1-trichloroethane and multiple myeloma was credible; however, associations were imprecise in two cohort studies and, to a lesser extent, in one case–control study. The small numbers of exposed participants, potential misclassification in exposure assessment, and potential selection bias were further limitations of these studies. The available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence of a causal association between exposure to 1,1,1-trichloroethane and NHL, AML, or childhood ALL.

2.6.6 Cancers of the brain and nervous system

One retrospective cohort study (Anttila et al., 1995) and four case–control studies (Heineman et al., 1994; Neta et al., 2012; Ruder et al., 2013; McLean et al., 2014) evaluated the association between 1,1,1-trichloroethane exposure and cancers of the brain and nervous system.

Overall, there was no clear association between cancers of the brain and nervous system and exposure to 1,1,1-trichloroethane. Although Heineman et al. (1994) observed an elevated odds ratio for astrocytoma in the highest category of exposure duration (all probabilities combined) (OR, 1.8; 95% CI, 1.0–3.3; 38 exposed cases) and a significant trend compared with the unexposed ($P < 0.05$) in a death certificate-based study, there were no clear associations with categories of cumulative exposure or exposure probability. Limitations in exposure assessment, next-of-kin interviews, and small numbers of exposed cases reduced the informativeness of the study. Anttila et al. (1995) observed a significantly

elevated standardized incidence ratio for cancer of the nervous system (SIR, 6.05; 95% CI, 1.25–17.7) based on 3 exposed cases. Neta et al. (2012) reported no evidence of an increased risk of incident glioma with categories of exposure probability, duration, cumulative exposure, average weekly exposure, or highest exposure to 1,1,1-trichloroethane using a detailed individual exposure assessment approach. For meningioma, there was a non-significantly elevated odds ratio for probable exposure to 1,1,1-trichloroethane (OR, 2.3; 95% CI, 0.7–7.2) based on 5 exposed cases. McLean et al. (2014) observed no clear association between ever exposure to 1,1,1-trichloroethane and meningioma risk (based on 1 exposed case). There also was no evidence of an increased risk of incident glioma with exposure to 1,1,1-trichloroethane (overall or across categories of cumulative exposure) in Ruder et al. (2013), with odds ratios significantly lower than 1.0 observed, possibly due to selection or other methodological sources of bias.

Overall, the Working Group considered that the available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence of a causal association between exposure to 1,1,1-trichloroethane and cancers of the brain and nervous system.

2.6.7 Cancer of the breast

One cohort study (Radican et al., 2008), one nested case–control study (Videnros et al., 2020), and one population-based case–control study (Pedersen et al., 2020) evaluated the association between exposure to 1,1,1-trichloroethane and breast cancer in women. There was one nested case–control study on breast cancer in men (Talibov et al., 2019).

Findings from studies on breast cancer in women showed no association with exposure to 1,1,1-trichloroethane. A positive although imprecise association (HR, 2.35; 95% CI, 0.83–6.64) based on only 4 exposed cases was observed

in the cohort study by [Radican et al. (2008)](). [Videnros et al. (2020)]() observed no association between ever exposure to 1,1,1-trichloroethane and incidence of post-menopausal breast cancer on the basis of expert hygienist review of exposure prevalence in the NOCCA-JEM/FINJEM; there were 10 exposed cases. There was also no trend with categories of exposure duration or mean exposure intensity, although levels of exposure intensity were low. [Pedersen et al. (2020)]() observed no association between ever exposure to 1,1,1-trichloroethane based on the NOCCA-JEM and incident breast cancer risk by age group (< 50 and ≥ 50 years, including 98 and 158 exposed cases, respectively) overall or by categories of duration of exposure, cumulative exposure, or latency among women, or timing of first exposed job among parous women. There were also no clear associations according to tumour estrogen receptor or parity status.

There was also no evidence of an association between breast cancer in men and exposure to 1,1,1-trichloroethane. [Talibov et al. (2019)]() reported no association with NOCCA-JEM-based categories of ever exposure or cumulative exposure in a large-scale nested case–control study, based on 181 exposed cases. Data on occupational history were limited, and there were few highly exposed participants.

Overall, the Working Group considered that the available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence of a causal association between exposure to 1,1,1-trichloroethane and risk of breast cancer in either women or men.

2.6.8 Cancers of the kidney and urinary bladder

One retrospective cohort study ([Anttila et al., 1995]()) and three case–control studies ([Dosemeci et al., 1999](); [Christensen et al., 2013](); [Purdue et al., 2017]()) evaluated the association between exposure to 1,1,1-trichloroethane and kidney cancer.

Findings from studies on kidney cancer showed no association with 1,1,1-trichloroethane. [Anttila et al. (1995)]() observed no cases of kidney cancer (compared with 0.4 expected). [Dosemeci et al. (1999)]() observed no association between ever exposure to 1,1,1-trichloroethane and incidence of renal cell carcinoma, either overall (66 exposed cases) or by sex. There was the potential for survival bias, given the exclusion of 35% of deceased cases from the analysis. There were no clear associations with kidney cancer incidence in [Christensen et al. (2013)](); odds ratios were weakly elevated although imprecise, based on 4 exposed cases. [Purdue et al. (2017)](), using a detailed expert-based exposure assessment approach, observed no association between incidence of kidney cancer and categories of probability or cumulative hours of exposure (610 exposed cases). Although there was a positive non-significant odds ratio (1.6; 95% CI, 0.8–3.2) in the highest tertile of cumulative hours of exposure among high-intensity jobs, there were few exposed cases ($n = 21$) and no evidence for a trend. Potential selection bias from low participation rates among controls, and occupational co-exposure to other solvents that cause kidney cancer are also of concern.

One nested case–control study ([Hadkhale et al., 2017]()) and two case–control studies ([Christensen et al., 2013](); [Sciannameo et al., 2019]()) evaluated the association between exposure to 1,1,1-trichloroethane and cancer of the urinary bladder. Findings from studies on bladder cancer showed no clear association with 1,1,1-trichloroethane. In a large-scale study, [Hadkhale et al. (2017)]() reported no association with NOCCA-JEM-based categories of cumulative exposure, both overall and by sex or age group, after adjustment for a range of other occupational solvents and agents. The study was large (7874 exposed cases) but limited census-based data on occupational history were available. [Christensen et al. (2013)]() reported imprecise inverse associations, based on 5 exposed cases. Although [Sciannameo]()

et al. (2019) observed a weakly positive non-significant association between ever exposure to 1,1,1-trichloroethane based on FINJEM estimates and incidence of urinary bladder cancer (OR, 1.18; 95% CI, 0.96–1.46, 362 exposed cases), potential selection bias and limitations in exposure assessment remain of concern.

Overall, the Working Group considered that the available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence of a causal association between exposure to 1,1,1-trichloroethane and cancers of the kidney or urinary bladder.

2.6.9 Cancers of the digestive, respiratory, or genital tract, and other solid cancers

Two cohort studies (Anttila et al., 1995; Radican et al., 2008) and four case–control studies (Kernan et al., 1999; Christensen et al., 2013; Vizcaya et al., 2013; Le Cornet et al., 2017) evaluated the association between exposure to 1,1,1-trichloroethane and cancers of the digestive, respiratory, and genital tract, or other solid cancers.

Anttila et al. (1995) reported a positive but imprecise association between biologically monitored 1,1,1-trichloroethane and total cancer incidence (SIR, 1.58; 95% CI, 0.92–2.52; 17 exposed cases). There were few exposed cases for cancer at other sites (Anttila et al., 1995; Radican et al., 2008). Study weaknesses including the small number of exposed cases, limited monitoring data, and potential co-exposure to other occupational solvents are of concern. Kernan et al. (1999) in a death certificate-based study reported a significantly elevated odds ratio (2.9; 95% CI, 1.2–7.5; 8 exposed cases) for mortality attributable to pancreatic cancer among Black males with a high probability of exposure; however, there were no positive associations in other sex/race strata or according to intensity of exposure. There are also limitations in exposure assessment in the death certificate-based study. Christensen

et al. (2013) and Vizcaya et al. (2013) reported no clear association between ever exposure (any or substantial) to 1,1,1-trichloroethane exposure and several cancer types, including melanoma and cancers of the prostate, colon, stomach, rectum, pancreas, oesophagus, liver, and lung; there were few exposed cases. Le Cornet et al. (2017) reported odds ratios close to unity in a large-scale registry-based study; they included semi-quantitative categories of prenatal maternal and paternal occupational exposure to 1,1,1-trichloroethane in the year of or before birth, and testicular germ cell tumours in the child.

Overall, the Working Group considered that the few available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence of a causal association between exposure to 1,1,1-trichloroethane and cancers of the digestive, respiratory, or genital tract, or other solid cancers.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

3.1.1 Inhalation

In a well-conducted chronic toxicity and carcinogenicity study that complied with Good Laboratory Practice (GLP), groups of 50 male and 50 female Crj:BDF$_1$ mice (age, 6 weeks) were exposed by inhalation (whole-body exposure) to 1,1,1-trichloroethane (purity, > 95%; one of the impurities was identified as para-dioxane [1,4-dioxane], present at 3.34–3.50%) at a concentration of 0, 200, 800, or 3200 ppm for the control group, and the groups at the lowest, intermediate, and highest doses, respectively, for 6 hours per day, 5 days per week, for 104 weeks (Ohnishi et al., 2013). In the group of male mice at the highest dose, the survival rate was slightly

Table 3.1 Studies of carcinogenicity in experimental animals exposed to 1,1,1-trichloroethane

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF₁ (M) 6 wk 104 wk Ohnishi et al. (2013)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, > 95% (impurity, 1,4-dioxane ranging from 3.34% to 3.50%) Air 0, 200, 800, 3200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 40, 34, 34, 31	*Lung* Bronchioloalveolar adenoma 4/50, 8/50, 4/50, 1/50 Bronchioloalveolar carcinoma 3/50, 5/50, 6/50, 10/50 Bronchioloalveolar adenoma or carcinoma (combined) 7/50, 13/50, 10/50, 11/50 *Liver* Hepatocellular adenoma 10/50, 8/50, 12/50, 15/50 Hepatocellular carcinoma 14/50, 12/50, 10/50, 15/50 Hepatocellular adenoma or carcinoma (combined) 23/50, 19/50, 21/50, 26/50 *Spleen*: malignant lymphoma 3/50 (6%), 4/50 (8%), 3/50 (6%), 9/50 (18%) *Harderian gland*: adenoma 1/50 (2%), 4/50 (8%), 4/50 (8%), 8/50 (16%)*	 NS $P < 0.01$, Peto trend test $P < 0.05$, Peto trend test $P < 0.05$, Peto trend test NS NS $P < 0.01$, Peto trend test $P < 0.01$, Peto trend test; *$P < 0.05$, Fisher exact test	Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; well-conducted GLP study; adequate number of mice per group Historical controls: spleen lymphoma, 24/597 (4%); range, 2–8%; Harderian gland adenoma, 30/598 (5%); range, 2–10%

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF₁ (F) 6 wk 104 wk Ohnishi et al. (2013)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, > 95% (impurity, 1,4-dioxane ranging from 3.34% to 3.50%) Air 0, 200, 800, 3200 ppm 6 h/day, 5 days/wk 50, 48, 50, 49 29, 28, 29, 29	*Lung* Bronchioloalveolar adenoma 0/50, 0/48, 0/50, 5/49 (10.2%) Bronchioloalveolar carcinoma 1/50, 3/48, 1/50, 2/49 Bronchioloalveolar adenoma or carcinoma (combined) 1/50 (2%), 3/48 (6%), 1/50 (2%), 7/49 (14%)* *Liver* Hepatocellular adenoma 2/50 (4%), 9/48 (19%)*, 14/50 (28%)**, 19/49 (39%)** Hepatocellular carcinoma 2/50 (4%), 1/48 (2%), 2/50 (4%), 1/49 (2%) Hepatocellular adenoma or carcinoma (combined) 4/50 (8%), 10/48 (20%), 16/50 (32%)*, 20/49 (40%)**	$P < 0.01$, Peto trend test NS $P < 0.01$, Peto trend test; *$P < 0.05$, Fisher exact test $P < 0.01$, Peto trend test; *$P < 0.05$ and **$P < 0.01$, Fisher exact test NS $P < 0.01$, Peto trend test; *$P < 0.05$ and **$P < 0.01$, Fisher exact test.	Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; well-conducted GLP study; adequate number of mice per group Historical controls: bronchioloalveolar adenoma, 23/599 (3.8%); range, 0.0–10.0%; bronchioloalveolar adenoma or carcinoma (combined), 40/599 (6.7%); range, 2.0–12.0%; hepatocellular adenoma, 29/599 (4.8%); range, 2.0–10.0%; hepatocellular adenoma or carcinoma (combined), 40/599 (6.7%); range, 2.0–12.0%; hepatocellular carcinoma, 12/599 (0.2%); range, 0.0–4.0%
Full carcinogenicity Mouse, B6C3F₁ (M) 5–6 wk 24 mo Quast et al. (1988)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, ~94% (5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol, nitroethane, and nitromethane), and < 1% minor impurities) Air 0, 150, 500, 1500 ppm (equivalent to 0, 0.82, 2.73, or 8.19 mg/L in air); 6 h/day, 5 days/wk (except holidays) 50, 50, 50, 50 NR	*Lacrimal/Harderian gland*: adenoma or cystadenoma (combined) 8/50, 8/49, 5/50, 4/50	NS	Principal strengths: males and females used; adequate duration of exposure and observation; multiple doses used; well-conducted study; adequate number of mice per group Principal limitations: number of mice at study termination was not reported Other comments: no effect of treatment on survival [range, 40–70% across groups; read from Figure]

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (F) 5–6 wk 24 mo Quast et al. (1988)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, ~94% (5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol, nitroethane, and nitromethane), and < 1% minor impurities) Air 0, 150, 500, 1500 ppm (equivalent to 0, 0.82, 2.73, or 8.19 mg/L in air); 6 h/day, 5 days/wk (except holidays) 50, 50, 50, 50 NR	*Lacrimal/Harderian gland* Adenoma 0/50, 0/50, 0/50, 1/50 Cystadenoma 3/50, 1/50, 2/50, 6/50 Adenoma or cystadenoma (combined) 3/50, 1/50, 2/50, 7/50	NS NS $P < 0.05$, Cochran–Armitage trend test (one-sided)	Principal strengths: males and females used; adequate duration of exposure and observation; multiple doses used; well-conducted study; adequate number of mice per group Principal limitations: number of mice at study termination was not reported No effect of treatment on survival [range, 55–70% across groups; read from Figure]
Full carcinogenicity Mouse, B6C3F$_1$ (M) 5 wk 90 wk NTP (1977)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ~95% (3% *para*-dioxane [1,4-dioxane] and 2% minor impurities, probably 1,1-dichloroethane and 1,1 dichloroethylene) Corn oil 0, 2807, 5615 mg/kg bw (TWA) 5 days/wk for 78 wk 20, 50, 50 2, 15, 11	*Liver* Hepatocellular adenoma 0/15, 0/47, 3/49 Hepatocellular carcinoma 0/15, 0/47, 1/49 Hepatocellular adenoma, hepatocellular carcinoma, or neoplastic nodule (combined) 0/15, 0/47, 4/49	NS NS $P < 0.05$, Cochran–Armitage trend test	Principal limitations: limited size of control group; decreased survival rate at the higher dose

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (F) 5 wk 90–91 wk NTP (1977)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ~95% (3% *para*-dioxane [1,4-dioxane] and 2% minor impurities, probably 1,1-dichloroethane and 1,1 dichloroethylene) Corn oil 0, 2807, 5615 mg/kg bw (TWA) 5 days/wk for 78 wk 20, 50, 50 11, 23, 13	No significant increase in tumour incidence in treated animals		Principal limitations: limited size of control group; decreased survival rate at the higher dose Other comments: histopathological evaluation of 18 controls, 48 mice at the lower dose, and 50 at the higher dose
Full carcinogenicity Rat, F344/DuCrj (M) 6 wk 104 wk Ohnishi et al. (2013)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, > 95% (impurity, 1,4-dioxane ranging from 3.34% to 3.50%) Air 0, 200, 800, 3200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 34, 36, 36, 28	*Peritoneum*: mesothelioma 1/50 (2%), 2/50 (4%), 1/50 (2%), 16/50 (32%)* *Lung*: bronchioloalveolar adenoma 0/50, 1/50 (2%), 7/50 (14%)*, 4/50 (8%)	$P < 0.01$, Peto trend test; *$P < 0.01$, Fisher exact test $P < 0.05$, Peto trend test; *$P < 0.05$, Fisher exact test.	Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; well-conducted GLP study; adequate number of rats per group Historical controls: peritoneum mesothelioma, 17/649 (2.6%); range, 0–8%; bronchioloalveolar adenoma, 16/649 (2.5%); range, 0–6%
Full carcinogenicity Rat, F344/DuCrj (F) 6 wk 104 wk Ohnishi et al. (2013)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, > 95% (impurity, 1,4-dioxane ranging from 3.34% to 3.50%) Air 0, 200, 800, 3200 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 38, 42, 38	No significant increase in tumour incidence in treated animals		Principal strengths: males and females used; multiple doses used; adequate duration of exposure and observation; well-conducted GLP study; adequate number of rats per group

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344 (M) 4–6 wk 24 mo Quast et al. (1988)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, ~94% (5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol, nitroethane, and nitromethane), and < 1% minor impurities) Air 0, 150, 500, 1500 ppm (equivalent to 0, 0.82, 2.73, or 8.19 mg/L in air); 6 h/day, 5 days/wk (except holidays) 50, 50, 50, 50 NR	*Testis* Interstitial cell tumour, benign, unilateral 7/50, 11/50, 3/50, 4/50 Interstitial cell tumour, benign, bilateral 36/50, 30/50, 38/50, 45/50 Interstitial cell tumour, benign, unilateral or bilateral (combined) 43/50, 41/50, 41/50, 49/50	NS P = 0.02, Cochran–Armitage trend test (two-sided) NS	Principal strengths: males and females used; adequate duration of exposure and observation; multiple doses used; well-conducted study; adequate number of rats per group Principal limitations: number of rats at study termination was not reported Other comments: no effect of treatment on survival [range, 50–70% across groups, read from Figure]
Full carcinogenicity Rat, F344 (F) 4–6 wk 24 mo Quast et al. (1988)	Inhalation (whole-body exposure) 1,1,1-Trichloroethane, ~94% (5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol, nitroethane, and nitromethane), and < 1% minor impurities) Air 0, 150, 500, 1500 ppm (equivalent to 0, 0.82, 2.73, or 8.19 mg/L in air); 6 h/day, 5 days/wk (except holidays) 50, 50, 50, 50 NR	No significant increase in tumour incidence in treated animals		Principal strengths: males and females used; adequate duration for exposure and observation; multiple doses used; well-conducted study; adequate number of rats per group Principal limitations: number of rats at study termination was not reported No effect of treatment on survival [range, 35–55% across groups, read from Figure]; 50 rats per group were evaluated histopathologically; the body weight of females at the intermediate and highest dose decreased compared with controls

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Osborne-Mendel (M) 7 wk 110 wk NTP (1977)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ~95% (3% *para*-dioxane [1,4-dioxane] and 2% minor impurities, probably 1,1-dichloroethane and 1,1 dichloroethylene) Corn oil 0, 750, 1500 mg/kg bw 5 days/wk for 78 wk 20, 50, 50 0, 0, 0	No significant increase in tumour incidence in treated animals		Principal limitations: limited size of control group; survival rate of both treated groups decreased compared with controls Histopathological evaluation of 20 controls, 49 rats at the lower dose, and 50 at the higher dose
Full carcinogenicity Rat, Osborne-Mendel (F) 7 wk 110 wk NTP (1977)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ~95% (3% *para*-dioxane [1,4-dioxane] and 2% minor impurities, probably 1,1-dichloroethane and 1,1 dichloroethylene) Corn oil 0, 750, 1500 mg/kg bw 5 days/wk for 78 wk 20, 50, 50 3, 2, 1	No significant increase in tumour incidence in treated animals		Principal limitations: limited size of control group; survival rate of both treated groups decreased compared with controls Other comments: histopathological evaluation of 20 control, 50 low-dose, and 50 high-dose animals

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (M) 7 wk ≤ 141 wk Maltoni et al. (1986)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ≥ 95% (stabilizers and impurities: 3.8% 1,4-dioxane, 0.47% 1,2-epoxybutane, 0.27% nitromethane, and < 1% minor impurities) Olive oil 0, 500 mg/kg bw 4–5 days/wk for 104 wk 50, 40 0, 0	*All organs*: "leukaemias" 3/50, 9/40*	* [P < 0.05, Fisher exact test]	Principal strengths: None Principal limitations: only one dose group. Other comments: all rats were allowed to survive until spontaneous death (≤ 141 wk); "leukaemias" included lymphoblastic lymphosarcomas, lymphoid leukaemias, immunoblastic lymphosarcomas and reticulohistiocytosarcomas
Full carcinogenicity Rat, Sprague-Dawley (F) 7 wk ≤ 141 wk Maltoni et al. (1986)	Oral administration (gavage) 1,1,1-Trichloroethane, technical grade, ≥ 95% (stabilizers and impurities: 3.8% 1,4-dioxane, 0.47% 1,2-epoxybutane, 0.27% nitromethane, and < 1% minor impurities) Olive oil 0, 500 mg/kg bw 4–5 days/wk for 104 wk 50, 40 0, 0	*All organs*: "leukaemias" 1/50, 4/40	[NS]	Principal limitations: only one dose group. Other comments: all rats were allowed to survive until spontaneous death (≤ 141 wk); "leukaemias" included lymphoblastic lymphosarcomas, lymphoid leukaemias, immunoblastic lymphosarcomas and reticulohistiocytosarcomas

bw, body weight; F, female; GLP, Good Laboratory Practice; M, male; mo, month; NR, not reported; NS, not significant; ppm, parts per million; TWA, time-weighted average; wk, week.

lower than that in the control group. The survival rate in all other groups of males exposed to 1,1,1-trichloroethane and all groups of exposed females was similar to that for their respective controls. At study termination, survival was 40/50, 34/50, 34/50, and 31/50 in males, and 29/50, 28/48, 29/50, and 29/49 in females, for the control group and the groups at the lowest, intermediate, and highest dose, respectively. The body weights of male and female mice exposed to 1,1,1-trichloroethane were similar to those of their respective controls. All mice underwent complete necropsy (except for two females at the lowest dose and one female at the highest dose). All organs and tissues from all the animals were sampled for histopathological examination.

In male mice, there was a significant positive trend in the incidence of bronchioloalveolar carcinoma and of bronchioloalveolar adenoma or carcinoma (combined) ($P < 0.01$ and $P < 0.05$, respectively, Peto test). There was a significant positive trend in the incidence of hepatocellular adenoma in male mice ($P < 0.05$, Peto test). A significant positive trend in the incidence of malignant lymphoma in the spleen ($P < 0.01$, Peto test) was observed: control, 3/50 (6%); lowest dose, 4/50 (8%); intermediate dose, 3/50 (6%); and highest dose, 9/50 (18%). The incidence of malignant lymphoma in the spleen in male mice at the highest dose exceeded the upper bound of the range observed in historical controls in this laboratory: 24/597 (4%); range, 2–8%. A significant positive trend in the incidence of Harderian gland adenoma ($P < 0.01$, Peto test) was also observed in male mice, with incidence being significantly increased at the highest dose – control, 1/50 (2%); lowest dose, 4/50 (8%); intermediate dose, 4/50 (8%); and highest dose, 8/50 (16%); $P < 0.05$, Fisher exact test – and exceeding the upper bound of the range observed in historical controls in this laboratory: 30/598 (5%); range, 2–10%.

In female mice, inhalation of 1,1,1-trichloroethane caused a significant positive trend in the incidence of bronchioloalveolar adenoma and bronchioloalveolar adenoma or carcinoma (combined) (both $P < 0.01$, Peto test). The incidence of bronchioloalveolar adenoma at the highest dose exceeded the upper bound of the range observed in historical controls in this laboratory (23/599, 3.8%; range, 0–10%). The incidence of bronchioloalveolar adenoma or carcinoma (combined) was significantly increased at the highest dose – control, 1/50 (2%); lowest dose, 3/48 (6%); intermediate dose, 1/50 (2%); and highest dose, 7/49 (14%) ($P < 0.05$, Fisher exact test) – exceeding the upper bound of the range observed in historical controls in this laboratory (40/599, 6.7%; range, 2–12%). A significant positive trend in the incidence of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) (both $P < 0.01$, Peto test) was observed; with the incidence of hepatocellular adenoma being significantly increased at all doses (lowest dose, $P < 0.05$; and intermediate and highest dose, $P < 0.01$, Fisher exact test) and the incidence of hepatocellular adenoma or carcinoma (combined) being significantly increased at the intermediate and highest doses ($P < 0.05$ and $P < 0.01$, respectively; Fisher exact test). The incidence of hepatocellular adenoma – control, 2/50 (4%); lowest dose, 9/48 (18%); intermediate dose, 14/50 (28%); and highest dose, 19/49 (38%) – and of hepatocellular adenoma or carcinoma (combined) – control, 4/50 (8%); lowest dose, 10/48 (20%); and intermediate dose, 16/50 (32%); and highest dose, 20/49 (40%) – in all treated groups exceeded the upper bound of the range observed in historical controls in this laboratory: 29/599 (4.8%); range, 2–10%; and 40/599 (6.7%); range, 2–12%, respectively. No significant increase in the incidence of hepatocellular carcinoma was observed (control, 2/50; lowest dose, 1/48; intermediate dose, 2/50; highest dose, 1/49). [The Working Group noted the lack of a significant positive trend or a significant increase in the incidence of hepatocellular carcinoma in any of the treated groups compared with controls, making the contribution of the

hepatocellular carcinomas to the increased incidence of hepatocellular adenoma or carcinoma (combined) negligible.]

Regarding non-neoplastic lesions, none that were related to treatment with 1,1,1-trichloroethane were observed in males or females. [The Working Group noted that this was a well-conducted study that complied with GLP, males and females were used, the durations of exposure and observation were adequate, and an adequate number of animals per group and multiple doses were used.]

In another well-conducted study, groups of 50 male and 50 female B6C3F$_1$ mice (age, 5–6 weeks) were exposed by inhalation (whole-body exposure) to 1,1,1-trichloroethane (purity, ~94%; 5% stabilizers and < 1% minor impurities) at a concentration of 0, 150, 500, or 1500 ppm, for the control group and groups at the lowest, intermediate, and highest dose, respectively, for 6 hours per day, 5 days per week (except holidays), for 24 months (Quast et al., 1988). The survival rates of all groups of males and females exposed to 1,1,1-trichloroethane were similar to those of their respective control groups. [The Working Group noted that the number of animals at study termination was not reported.] The body weights of all groups of male and female mice exposed to 1,1,1-trichloroethane were similar to those of their respective controls. All mice underwent complete necropsy. Histopathological evaluation was performed on the main tissues and organs.

In female mice, a significant positive trend in the incidence of lacrimal/Harderian gland adenoma or cystadenoma (combined) was observed ($P < 0.05$, Cochran–Armitage trend test). In male mice, 1,1,1-trichloroethane had no significant effects on the incidence of tumours. Regarding non-neoplastic lesions, no effects related to exposure to 1,1,1-trichloroethane were observed in male or female mice. [The Working Group noted that this was a well-conducted study, males and females were used, the durations of exposure and observation were adequate, and an adequate

number of animals per group and multiple doses were used.]

3.1.2 Oral administration (gavage)

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 5 weeks) were treated by gavage with two dose levels of 1,1,1-trichloroethane (purity, ~95%; with 3% *para*-dioxane [1,4-dioxane] and 2% minor impurities probably including 1,1-dichloroethane and 1,1-dichloroethylene) in corn oil for 5 days per week, for 78 weeks (NTP, 1977; also reported in Weisburger, 1977). At the lower dose level, male and female mice received 1,1,1-trichloroethane at 2000 mg/kg body weight (bw) per day for weeks 1–10, 2500 mg/kg bw per day for weeks 11–20, and 3000 mg/kg bw per day for weeks 21–78. At the higher dose level, male and female mice received 1,1,1-trichloroethane at 4000 mg/kg bw per day for weeks 1–10, 5000 mg/kg bw per day for weeks 11–20, and 6000 mg/kg bw per day for weeks 21–78. Time-weighted average (TWA) doses for the mice at the lower and higher doses were, respectively, 2807 and 5615 mg/kg bw. Control groups of 20 male and 20 female mice received corn oil alone for 78 weeks. After 78 weeks of treatment, all groups of mice were maintained without treatment until study termination 12–13 weeks later. At study termination, survival was: 2/20, 15/50, and 11/50 in males, and 11/20, 23/50, and 13/50 in females, for the control group and groups at the lower and higher dose, respectively. The survival rates of females treated with 1,1,1-trichloroethane were lower than that of the respective control group. [The Working Group noted that survival at 78 weeks was low: 6/20 (control), 21/50 (lower dose), and 14/50 (higher dose) in males; 12/20 (control), 28/50 (lower dose), and 14/50 (higher dose) in females.] In treated male and female mice, body-weight gain was lower than that of their respective controls over the course of the study. All mice underwent complete necropsy.

Histopathological evaluation was performed on the main tissues and organs.

In male mice, there was a significant positive trend in the incidence of hepatocellular adenoma, hepatocellular carcinoma, or neoplastic nodule (combined) of the liver ($P < 0.05$, Cochran–Armitage test). In female mice, the incidence of neoplasms of all organs and types was not affected by treatment with 1,1,1-trichloroethane.

[The Working Group noted that this study was limited by the small number of animals evaluated in the control groups of males and females, the low survival of control males, and the decreased survival of females at the highest dose. For this reason, the Working Group considered this study inadequate for the evaluation of the carcinogenicity of 1,1,1-trichloroethane in experimental animals.]

3.2 Rat

3.2.1 Inhalation

In a well-conducted chronic toxicity and carcinogenicity study that complied with GLP (Ohnishi et al., 2013), groups of 50 male and 50 female F344/DuCrj rats (age, 6 weeks) were exposed by inhalation (whole-body exposure) to 1,1,1-trichloroethane (purity, > 95%; one of the impurities was identified as 1,4-dioxane, present at concentrations ranging from 3.34% to 3.50%) at a concentration of 0, 200, 800, or 3200 ppm for the control group and the groups at the lowest, intermediate, and highest dose, respectively, for 6 hours per day, 5 days per week, for 104 weeks. The survival rate of males at the highest dose was slightly lower than that of controls; this was attributable to neoplasm-related deaths. The survival rates of all groups of females treated with 1,1,1-trichloroethane were similar to that of controls. At study termination, survival was 34/50, 36/50, 36/50, and 28/50 in males, and 38/50, 38/50, 42/50, and 38/50 in females, for the control group and the groups at the lowest, intermediate,

and highest dose, respectively. The body weights of the groups of male and female rats exposed to 1,1,1-trichloroethane were similar to those of their respective controls. All rats underwent complete necropsy. All organs and tissues were sampled for histopathological examination in all the animals.

In male rats, there was a significant positive trend ($P < 0.01$, Peto test) in the incidence of peritoneal mesothelioma – control, 1/50 (2%); lowest dose, 2/50 (4%); intermediate dose, 1/50 (2%); and highest dose, 16/50 (32%) – with the incidence being significantly increased at the highest dose ($P < 0.01$, Fisher exact test), and exceeding the upper bound of the range observed in historical controls in this laboratory: 17/649 (2.6%); range, 0–8%. There was a significant positive trend ($P < 0.05$, Peto test) in the incidence of bronchioloalveolar adenoma – control, 0/50; lowest dose, 1/50 (2%); intermediate dose, 7/50 (14%); and highest dose, 4/50 (8%) – with the incidence being significantly increased at the intermediate dose ($P < 0.05$, Fisher exact test). The incidence of bronchioloalveolar adenoma in male rats at the intermediate and highest dose exceeded the upper bound of the range observed in historical controls in this laboratory: 16/649 (2.5%); range, 0–6%.

In female rats, there were no significant treatment-related effects on the incidence of any tumour.

Regarding non-neoplastic lesions, no effects related to treatment with 1,1,1-trichloroethane were observed in male or female rats. [The Working Group noted that this was a well-conducted study that complied with GLP, males and females were used, the durations of exposure and observation were adequate, and an adequate number of animals per group and multiple doses were used.]

In another well-conducted study, groups of 50 male and 50 female Fischer 344 rats (age, 4–6 weeks) were exposed by inhalation (whole-body exposure) to 1,1,1-trichloroethane (purity,

~94%; with 5% stabilizers and < 1% minor impurities) at a concentration of 0, 150, 500, or 1500 ppm for 6 hours per day, 5 days per week, for 24 months (Quast et al., 1988). The survival rates of all groups of 1,1,1-trichloroethane-exposed males and females were similar to those in the respective control groups. [The Working Group noted that the number of animals at study termination was not reported.] The body weights of female rats at 500 and 1500 ppm were lower than those of the controls. The body weights of all groups of male rats exposed to 1,1,1-trichloroethane were similar to those of the controls. All rats underwent complete necropsy. Histopathological evaluation was performed on main tissues and organs.

In male rats, a significant positive trend in the incidence of bilateral benign interstitial cell tumour of the testis (P = 0.02, Cochran–Armitage trend test) was observed. Exposure to 1,1,1-trichloroethane had no significant effect on the incidence of unilateral or bilateral (combined) benign interstitial cell tumours of the testis or on the incidence of unilateral benign interstitial cell tumours of the testis.

In female rats, exposure to 1,1,1-trichloroethane had no significant effect on the incidence of tumours. Regarding non-neoplastic lesions, no effects related to treatment with 1,1,1-trichloroethane were observed in male or female rats. [The Working Group noted that this was a well-conducted study, males and females were used, the durations of exposure and observation were adequate, and an adequate number of animals per group and multiple doses were used.]

3.2.2 Oral administration (gavage)

Groups of 50 male and 50 female Osborne-Mendel rats (age, 7 weeks) were treated by gavage with 1,1,1-trichloroethane (purity, ~95%; with approximately 3% *para*-dioxane [1,4-dioxane] and 2% minor impurities probably including 1,1-dichloroethane and 1,1-dichloroethylene) at 750 mg/kg bw (lower dose) or 1500 mg/kg bw (higher dose) in corn oil for 5 days per week, for 78 weeks, followed by study termination 32 weeks later (NTP, 1977; also reported in Weisburger, 1977). Control groups of 20 male and 20 female rats received corn oil alone. At study termination, survival was 0/20, 0/50, and 0/50 in males, and 3/20, 2/50, and 1/50 in females, for the control group and the groups at the lower and higher dose, respectively. The survival rates of all males and females exposed to 1,1,1-trichloroethane were lower than those of their respective control groups. [The Working Group noted that survival at 78 weeks was low: 7/20, 1/50, and 4/50 in males; 14/20, 9/50, and 12/50 in females, for the control group and the groups at the lower and higher dose, respectively.] The body weights of male and female rats exposed to 1,1,1-trichloroethane were lower than those of their respective controls. All rats underwent complete necropsy. Histopathological evaluation was performed on main tissues and organs.

The incidence of neoplasms of all organs and types in male and female rats treated with 1,1,1-trichloroethane was similar to that observed in their respective control groups. [The Working Group noted that this study was limited by the low number of animals evaluated in the male and female control groups and the decreased survival of rats treated with 1,1,1-trichloroethane. For this reason, the Working Group considered this study inadequate for the evaluation of the carcinogenicity of 1,1,1-trichloroethane in experimental animals.]

In another study, groups of 40 male and 40 female Sprague-Dawley rats (age, 7 weeks) were treated by gavage with 1,1,1-trichloroethane (purity, ≥ 95%; stabilizers: 1,4-dioxane, 3.8%; 1,2-epoxybutane, 0.47%; and nitromethane, 0.27%; and < 1% minor impurities) at a dose of 500 mg/kg bw in olive oil for 4–5 days per week, for 104 weeks (Maltoni et al., 1986). Control groups of 50 male and 50 female rats (same

strain and age) were treated with olive oil alone. All surviving animals at the end of the treatment period were maintained until spontaneous death (up to 141 weeks). The survival rates and body weights of male and female rats exposed to 1,1,1-trichloroethane were similar those of the controls. All rats underwent complete necropsy. Histopathological evaluation was performed on main tissues and organs.

In male rats, treatment with 1,1,1-trichloroethane significantly increased [$P < 0.05$, Fisher exact test] the incidence of all leukaemias (combination of various histological types) in a variety of organs and tissues; incidences being 3/50 (control), and 9/40 (500 mg/kg bw). No increase in the incidence of neoplasms of any organ or type was observed in female rats treated with 1,1,1-trichloroethane. [The Working Group noted that this study was limited by the use of only one dose level.]

3.3 Evidence synthesis for cancer in experimental animals

The carcinogenicity of 1,1,1-trichloroethane has been assessed in one well-conducted GLP study in male and female Crj:BDF$_1$ mice (Ohnishi et al., 2013), in one well-conducted GLP study in male and female F344/DuCrj rats (Ohnishi et al., 2013), in one well-conducted study in male and female B6C3F$_1$ mice (Quast et al., 1988), and in one well-conducted study in male and female Fischer 344 rats (Quast et al., 1988) treated by inhalation with whole-body exposure. The carcinogenicity of 1,1,1-trichloroethane in mice and rats was also evaluated in studies that did not comply with GLP. Specifically, there was one study in male and female B6C3F$_1$ mice (NTP, 1977), one study in male and female Osborne-Mendel rats (NTP, 1977), and one study in male and female Sprague-Dawley rats (Maltoni et al., 1986) treated by oral administration (gavage).

In the inhalation study that complied with GLP in male and female Crj:BDF$_1$ mice, there was a significant positive trend in the incidence of malignant lymphoma in the spleen and of Harderian gland adenoma in males; the incidence of Harderian gland adenoma was also significantly increased in males at the highest dose. There was a significant positive trend in the incidence of bronchioloalveolar carcinoma and bronchioloalveolar adenoma or carcinoma (combined) in males. There was a significant positive trend in the incidence of hepatocellular adenoma in male mice. In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma and bronchioloalveolar adenoma or carcinoma (combined). The incidence of bronchioloalveolar adenoma or carcinoma (combined) was also significantly increased at the highest dose in females. A significant positive trend in the incidence of hepatocellular adenoma was observed in females; with the incidence of hepatocellular adenoma being significantly increased at all doses (Ohnishi et al., 2013).

In the inhalation study that complied with GLP in male and female F344/DuCrj rats, there was a significant positive trend in the incidence of peritoneal mesothelioma in males, with the incidence being significantly increased at the highest dose. In males, there was a significant positive trend in the incidence of bronchioloalveolar adenoma, and the incidence was significantly increased at the intermediate dose. In female rats, there were no significant effects upon the incidence of neoplasms (Ohnishi et al., 2013).

In another well-conducted study in male and female B6C3F$_1$ mice exposed by inhalation, a significant positive trend in the incidence of lacrimal/Harderian gland adenoma or cystadenoma (combined) was observed in females. In male mice, there were no significant effects of treatment on the incidence of neoplasms (Quast et al., 1988).

In another well-conducted study in male and female Fischer 344 rats exposed by inhalation, a significant positive trend in the incidence of bilateral benign interstitial cell tumour of the testis was observed in males. In females, there was no significant effects of treatment on the incidence of neoplasms (Quast et al., 1988).

In the study in male and female Sprague-Dawley rats treated by oral administration (gavage), the incidence of all leukaemias (combination of various histological types) in a variety of organs and tissues was significantly increased in treated males. In female rats, there was no treatment-related effects. No increased incidence of neoplasms was observed in treated female rats (Maltoni et al., 1986).

Studies on oral administration of 1,1,1-trichloroethane administered by gavage to male and female B6C3F$_1$ mice and male and female Osborne-Mendel rats (NTP, 1977) were judged inadequate for the evaluation of the carcinogenicity of 1,1,1-trichloroethane in experimental animals.

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

(a) Absorption

Numerous studies have been published on the absorption of 1,1,1-trichloroethane in humans by either the dermal or inhalation routes of exposure. In general, all studies demonstrated rapid absorption, with many, especially the more recent studies, relating absorption to some measure of either 1,1,1-trichloroethane or one of its metabolites in either the urine or the blood. Dermal or percutaneous absorption is assessed either by direct application of 1,1,1-trichloroethane to the skin or by assessing dermal penetration of 1,1,1-trichloroethane vapours. Studies involving dermal absorption showed rapid absorption related to the type or condition of skin exposed, duration of exposure, and exposure concentration (Stewart & Dodd, 1964; Aitio et al., 1984; Poet et al., 2000). Several studies have been conducted on the percutaneous absorption of solvent vapours. Absorption was shown to be rapid for the vapour from several halogenated solvents, including 1,1,1-trichloroethane, with differences noted according to solvent lipid solubility, skin condition, and activity level of the participant (Riihimäki & Pfäffli, 1978; Wallace et al., 1989; Giardino et al., 1999). With volatile solvents such as 1,1,1-trichloroethane, absorption by the dermal route is very low when compared with inhalation (Giardino et al., 1999). Dermal absorption of 1,1,1-trichloroethane is considerably slower than that of other organic solvents, such as trichloroethylene, perchloroethylene [tetrachloroethylene], toluene, or xylene (Kezic et al., 2000, 2001).

Another focus of several studies on the absorption of 1,1,1-trichloroethane in humans exposed by inhalation has been to use measurements of 1,1,1-trichloroethane in exhaled breath, blood, or urine as surrogates for estimating the exposure dose. Droz et al. (1988) exposed participants to 1,1,1-trichloroethane at 200 ppm by inhalation for 6 hours and detected 1,1,1-trichloroethane in the breath up to 15 hours after exposure. Nagatoshi et al. (1994) monitored urinary excretion of various organic solvents, including 1,1,1-trichloroethane, and concluded that worker exposure was extremely small in factories that exercised proper control over toxic materials. [The Working Group noted that the nature of the controls, specifically whether protection against inhalation and dermal exposures was included, was unclear.] Nolan et al. (1984) used concentrations of 1,1,1-trichloroethane in both blood and exhaled air to validate inhalation exposure. They found that both measurements were

proportional to exposure and indicated that 25% of the administered 1,1,1-trichloroethane was absorbed during the 6-hour exposure. Tay et al. (1995) similarly found a good correlation between concentrations of 1,1,1-trichloroethane in end-of-shift exhaled air ($r = 0.81$) and venous blood samples ($r = 0.88$). Gill et al. (1991), Hajimiragha et al. (1986), and Monster & Houtkooper (1979) all found that blood concentrations of 1,1,1-trichloroethane provided an accurate assessment of inhalation exposure and absorption. Monster & Houtkooper (1979) directly compared the accuracy of measurements in the blood, urine, and exhaled air as an indication of exposure by inhalation to 1,1,1-trichloroethane, trichloroethylene, or perchloroethylene [tetrachloroethylene]. For all three solvents, blood concentrations of the parent compound gave the best estimates of exposure, although the advantages of using blood were very small compared with using exhaled air. Measuring solvent concentrations in the urine and exhaled air simultaneously did not significantly improve exposure estimates.

(b)   Distribution

Much of the absorbed 1,1,1-trichloroethane in humans is rapidly excreted in exhaled air as the unmetabolized parent compound (Gamberale & Hultengren, 1973). Caplan et al. (1976) analysed the tissue distribution of 1,1,1-trichloroethane in an otherwise healthy woman aged 40 years who had been accidentally poisoned by 1,1,1-trichloroethane. The deceased woman was found in a closed and poorly ventilated room in which paint, paint thinner, and towels soaked in those materials were found. There were paint stains on areas of the skin, suggesting that exposure was both by inhalation and the dermal route. By far the highest concentration of 1,1,1-trichloroethane was found in the brain (36 mg/100 mL), with markedly lower concentrations found in the kidney, liver, lung, blood, and bile (12, 5, 1, 2, and < 1 mg/100 mL, respectively).

Hajimiragha et al. (1986) concluded that their data on human exposures to volatile halogenated hydrocarbons agreed with those of Monster (1979) in that blood concentrations of 1,1,1-trichloroethane are determined by a complex equilibrium involving uptake, exhalation, and tissue storage, especially in adipose tissue. From the tissues, 1,1,1-trichloroethane is redistributed into the blood, and from the blood it is redistributed into alveolar air or undergoes biotransformation. Tissue depletion occurs quickly, with the exception of adipose tissue, from which depletion begins once blood concentrations decrease below a certain level as determined by the fat:blood partition coefficient of 1,1,1-trichloroethane. Consistent with the conclusion that 1,1,1-trichloroethane is stored and gradually released after repeated exposures, Seki et al. (1975) found that in printing-factory workers exposed solely to 1,1,1-trichloroethane at concentrations of up to 53 ppm, there was a linear relationship between total trichloro-compounds in the urine and environmental vapour concentrations. Towards the end of the work week, however, increased levels of urinary metabolites were generally noted, consistent with potential accumulation of 1,1,1-trichloroethane over the course of the work week. [The Working Group noted that the variability of measurements of urinary metabolites, such as in the study by Monster & Houtkooper (1979), suggests that some caution is needed in making conclusions about the accumulation of 1,1,1-trichloroethane.] The rapid initial distribution of 1,1,1-trichloroethane from blood into tissues and subsequent elimination, however, results in a weak correlation between clinical toxicity and blood concentrations (Meredith et al., 1989).

(c)   Metabolism

The metabolites of 1,1,1-trichloroethane are not unique to 1,1,1-trichloroethane and are also formed after exposure to trichloroethene [trichloroethylene] and tetrachloroethene

[tetrachloroethylene], although in different proportions (Fernández et al., 1977; Monster, 1986). Only a small fraction (< 10%) of the absorbed 1,1,1-trichloroethane is metabolized (ATSDR, 2006). Of the absorbed 1,1,1-trichloroethane, 2–5% is eliminated in the urine as trichloroethanol (half-life, 10–27 hours) and 1–2% as trichloroacetic acid (half-life, 70–85 hours), representing a minor elimination pathway (Humbert & Fernández, 1976; Monster, 1986; ATSDR, 2006). Nevertheless, urinary levels of trichloroethanol and trichloroacetic acid are well correlated with airborne exposures, indicating possibly useful biomarkers of current exposure (trichloroethanol) and weekly average exposure (trichloroacetic acid), in the absence of exposure to other chlorinated solvents (Imbriani et al., 1988; ATSDR, 2006).

As most of the pharmacokinetics data in humans for 1,1,1-trichloroethane show that only a limited amount of absorbed compound is metabolized (i.e. < 10%) (Monster, 1979), there is not an extensive amount of data available on rates of metabolism. Nonetheless, several studies in humans have demonstrated that trichloroethanol and trichloroacetic acid are the primary metabolites, with trichloroethanol being the more abundant one of the two (Nolan et al., 1984; Berode et al., 1990; Kawai et al., 1991; Pedrozo & Siqueira, 1996; Tomicic et al., 2011).

On the basis of similarities with the more widely studied solvent trichloroethylene and on experimental data from rodent studies (see Section 4.1.2(c)), Guengerich et al. (1991) concluded that the metabolism of 1,1,1-trichloroethane to trichloroethanol occurs primarily via human cytochrome P450 2E1 (CYP2E1). Supporting this suggestion are two studies that provided indirect evidence for the function of various CYP enzymes in the oxidation of 1,1,1-trichloroethane (Berode et al., 1990; Johns et al., 2006). These studies correlated the metabolism of 1,1,1-trichloroethane with that of other CYP2E1 substrates and showed that metabolism

of 1,1,1-trichloroethane is increased by ethanol consumption.

The major pathways for 1,1,1-trichloroethane metabolism, according to data from both human and experimental animal studies, are illustrated in Fig. 4.1. 1,1,1-Trichloroethane is oxidized by one of several CYP enzymes to form trichloroethanol, which subsequently undergoes either oxidation to trichloroacetic acid, or glucuronidation to form the corresponding glucuronide conjugate trichloroethanol–glucuronide (TCOG). Both metabolites are recovered in the urine, with the majority being trichloroethanol. Most of the metabolic flux is to trichloroethanol rather than trichloroacetic acid (Kawai et al., 1991). Other minor metabolites, including carbon dioxide and acetylene excreted in the exhaled air, have also been described (Tomicic et al., 2011). The potential implications of formation of acetylene from 1,1,1-trichloroethane are discussed in Section 4.2.1. It has been proposed that acetylene is formed from 1,1,1-trichloroethane via multiple steps of reductive dehalogenation that also involve CYP enzymes. Similar studies in experimental animal models that could provide additional support for this pathway are not available. The proposed scheme for this reductive metabolic pathway is shown in Fig. 4.2. [The Working Group noted that although this reductive pathway provides a chemical mechanism that could explain some of the adverse effects of 1,1,1-trichloroethane, its quantitative significance, especially in humans, is unclear.]

(d)   Excretion

Excretion of 1,1,1-trichloroethane absorbed either dermally or via inhalation occurs by one of two mechanisms: exhalation of unmetabolized 1,1,1-trichloroethane, or urinary excretion of either 1,1,1-trichloroethane or its metabolites. For the latter, the urinary metabolites are primarily trichloroethanol and trichloroacetic acid, with the former being the predominant form. Studies on workers exposed to 1,1,1-trichloroethane have

Fig. 4.1 Scheme for oxidative metabolism of 1,1,1-trichloroethane
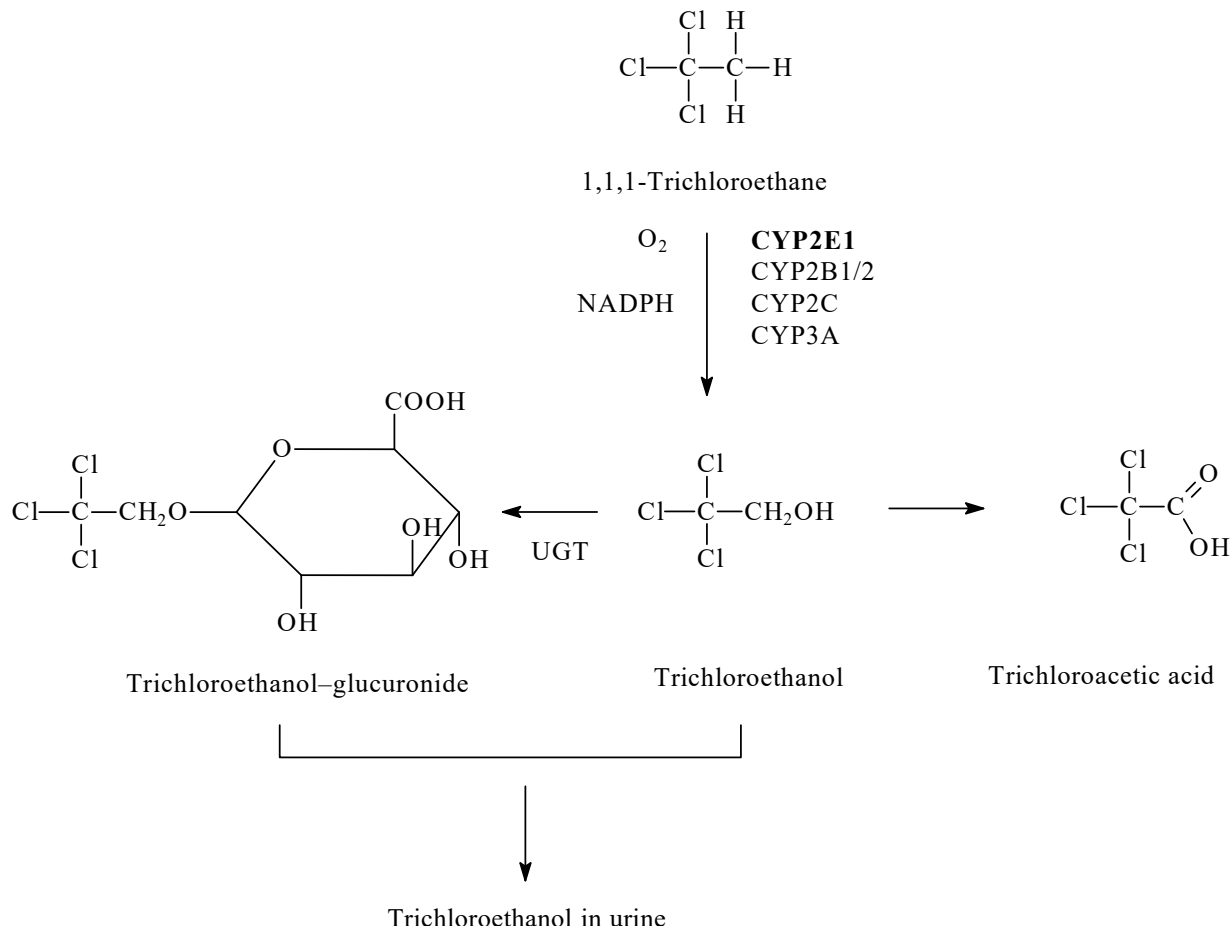
CYP, cytochrome P450; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form; UGT, uridine 5′-diphosphoglucuronyl-transferase.
The initial step in the oxidative metabolism of 1,1,1-trichloroethane is catalysed by one of several CYP enzymes, although most data suggest that CYP2E1 is the predominant active enzyme. The initial metabolite, trichloroethanol, has one of three fates: (1) further oxidation to trichloroacetic acid; (2) direct excretion into the urine; or (3) glucuronidation to form trichloroethanol–glucuronide. The glucuronide undergoes urinary excretion and is typically recovered as trichloroethanol.
Created by the Working Group.

focused for many years on validating measures that can be sensitive indicators or biomarkers of exposure. For example, Stewart et al. (1961) performed controlled human exposures to 1,1,1-trichloroethane vapour and showed an exponential decay curve for the concentration of 1,1,1-trichloroethane in exhaled air. Similar studies, such as those by Seki et al. (1975); Abe & Wakui (1984); Nolan et al. (1984); Hajimiragha et al. (1986); Imbriani et al. (1988); Gill et al. (1991);

Kawai et al. (1991); Laparé et al. (1995); Mizunuma et al. (1995); Tay et al. (1995); and Tomicic et al. (2011) have all shown the predominance of exhalation of unmetabolized 1,1,1-trichloroethane in the excretion of inhaled or absorbed 1,1,1-trichloroethane. Moreover, two of these studies (Nolan et al., 1984; Laparé et al., 1995) concluded that measurement of 1,1,1-trichloroethane concentration in exhaled air is the most reliable indicator of exposure and that measurement of urinary

Fig. 4.2 Proposed scheme for reductive dehalogenation of 1,1,1-trichloroethane
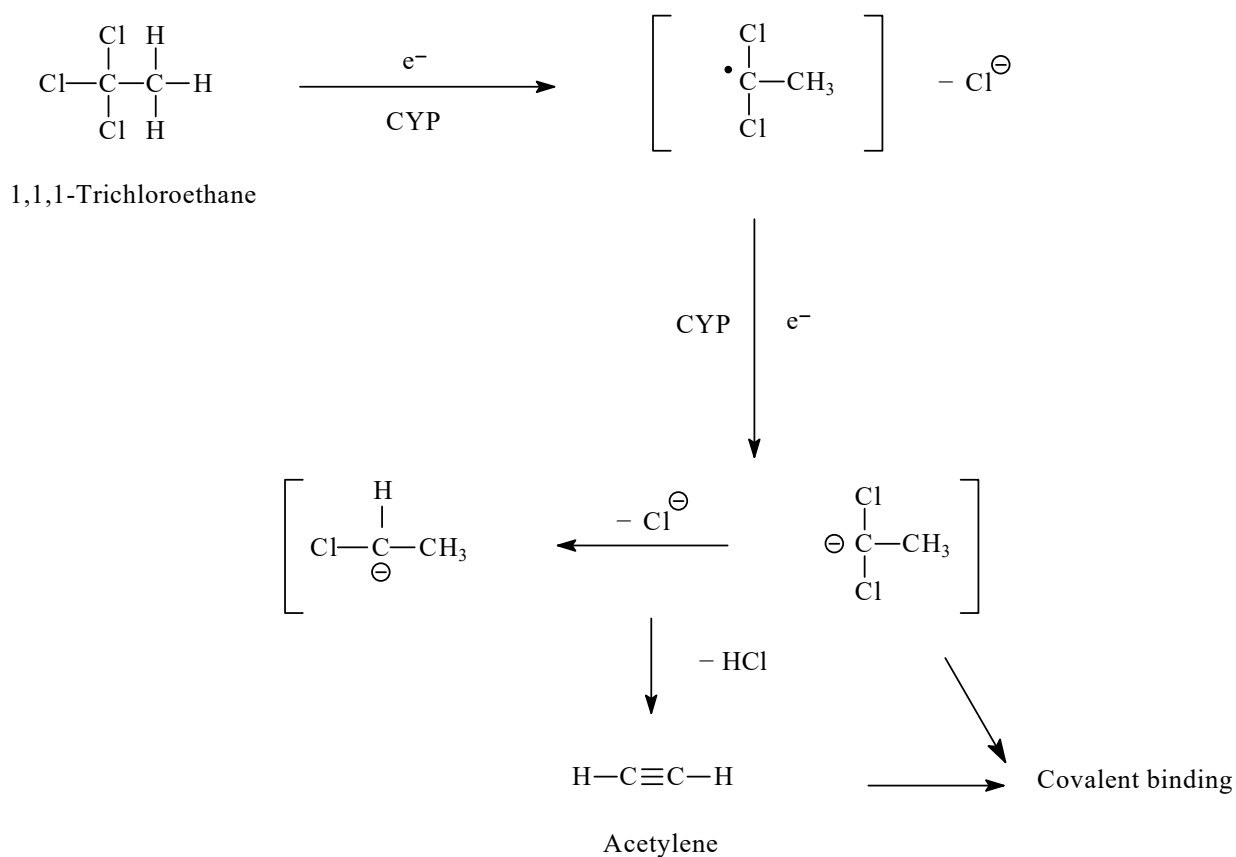
CYP, cytochrome P450.
The presumed pathway occurs under hypoxic or anaerobic conditions and involves formation of several electrophilic intermediates that are shown in square brackets. Studies indicate that the first two dehalogenation steps are dependent on reduced nicotinamide adenine dinucleotide phosphate (NADPH) and probably catalysed by CYP enzymes. The second set of reactive intermediates can either form covalent adducts with cellular nucleophiles or spontaneously lose HCl to form acetylene. The latter has been detected and can also form covalent adducts with cellular nucleophiles.
Created by the Working Group.

metabolites is subject to error and has the potential for significant individual variation. If urine is selected for monitoring exposure, parent chemical or total trichloro-compounds rather than specific metabolites are recommended by most of these studies. [The Working Group noted that this conclusion would seem to be inconsistent with that of Monster & Houtkooper (1979) discussed above in Section 4.1.1(a), who suggested that blood values correlated best with exposure

dose. As noted above, the strength of this conclusion was weak.]

4.1.2 Experimental systems

(a) Absorption

There were several studies on the absorption of 1,1,1-trichloroethane in animal models. For studies on dermal or percutaneous absorption, the guinea-pig is the most common model, whereas rats are primarily used for inhalation

studies. In addition to the characterization of chemical properties that facilitate absorption, the influence of occlusive agents, including gloves or barrier creams, has also been determined.

In a series of studies by Boman and colleagues (Boman et al., 1982, 1989, 1995; Boman & Wahlberg, 1986, 1989; Boman, 1989; Boman & Mellström, 1989; Mellström & Boman, 1992), the absorption of 1,1,1-trichloroethane through guinea-pig skin was characterized and compared with the absorption of other organic solvents, such as toluene or butanol. A key observation from all of these studies was that lipid solubility is a key determinant of the rate at which solvents are absorbed through the skin and that damage to the skin or the existence of barriers or occlusions can markedly affect the process of absorption. Morgan et al. (1991) studied dermal absorption in rats and concluded that absorption (as detected by the appearance of 1,1,1-trichloroethane in the blood) is rapid and can be significant even if only about 1% of the skin surface area is exposed.

Dallas et al. (1986, 1989) characterized the absorption of 1,1,1-trichloroethane in male Sprague-Dawley rats exposed to 1,1,1-trichloroethane at 50 or 500 ppm via inhalation. Absorption from the lungs was rapid, with substantial levels of 1,1,1-trichloroethane being detected in arterial blood within 2 minutes. Inhalation studies in mice exposed for 100 minutes to 1,1,1-trichloroethane at 3500 or 5000 ppm showed rapid uptake into the blood and brain, with near steady-state levels being reached after 40–60 minutes of exposure (You et al., 1994a). Accumulation of 1,1,1-trichloroethane in all tissues except fat was similar; maximal concentrations in fat were 20–30 times higher than those in other tissues (You et al., 1994b).

A study by Hobara et al. (1981) indicated systemic availability of 1,1,1-trichloroethane in dogs treated intravenously. 1,1,1-Trichloroethane was detected in exhaled breath within 1 minute, indicating rapid absorption.

(b) Distribution

As with studies in humans, assessments of the tissue distribution of 1,1,1-trichloroethane in experimental animals (rats, mice, and dogs) show accumulation predominantly in fat (Savolainen et al., 1977; Vainio et al., 1978; Savolainen, 1981). Schumann et al. (1982a) exposed male Fischer 344 rats and B6C3F$_1$ mice to [^{14}C]-labelled 1,1,1-trichloroethane at 150 or 1500 ppm for 6 hours and found a higher recovery of radio-label in fat than in either liver or kidney. They noted, however, that in both species, < 2% of the initial radiolabel remained after 24 hours, suggesting rapid excretion and little potential for bioaccumulation.

Besides the predominant, early accumulation of 1,1,1-trichloroethane in fat, other studies in rats (Westerberg & Larsson, 1982; Warren et al., 1998; and mice (Warren et al., 2000) have focused on distribution into the blood and brain. These studies showed rapid and concentration-dependent increases in 1,1,1-trichloroethane concentrations in both blood and brain after inhalation exposure, with concentrations in the brain being roughly twice those in the blood. In one study, You et al. (1994a) similarly found rapid distribution of 1,1,1-trichloroethane to the blood and brain. In another study, You et al. (1994b) also showed rapid distribution of 1,1,1-trichloroethane to the blood and several tissues besides brain. You & Dallas (1998) also noted that mice exhibited a greater capacity for 1,1,1-trichloroethane accumulation than did rats.

(c) Metabolism

(i) Non-human mammals in vivo

As noted in Section 4.1.1(c) and illustrated in Fig. 4.1, oxidative metabolism of 1,1,1-trichloroethane appears to be mediated by several CYP enzymes, although primarily by CYP2E1. 1,1,1-Trichloroethane has long been considered to be a relatively poor substrate for CYPs (Hake et al., 1960), especially compared with solvents

such as trichloroethylene (Dobrev et al., 2001) or *meta*-xylene (Tardif & Charest-Tardif, 1999). Despite a number of studies that conclude that metabolism plays a very minor role in the overall handling and disposition of 1,1,1-trichloroethane, several observations in rodents are consistent with a role for CYP-dependent metabolism, especially under certain conditions. For example, Blohm et al. (1985) exposed rats to 1,1,1-trichloroethane at 200 or 2000 ppm for several hours per day for nearly 3 months and found an increase in liver microsomal protein content and monooxygenase activity, indicating an increase in liver endoplasmic reticulum content. Kaneko et al. (1994) examined the effects of ethanol on the metabolism of either 1,1,1-trichloroethane or trichloroethylene to compare a "poorly metabolized" with a "highly metabolized" substance. Increases in the rate of metabolism of 1,1,1-trichloroethane to trichloroethanol were observed in ethanol-exposed rats, providing indirect evidence for the role of CYPs, particularly CYP2E1, in the metabolism of 1,1,1-trichloroethane.

Other studies have also provided indirect data supporting the role of CYPs in the metabolism of 1,1,1-trichloroethane. For example, Carlson (1981) exposed rabbits to 1,1,1-trichloroethane at 5600 ppm by inhalation and looked at the impact of pre-treatment with either phenobarbital (which induces multiple CYPs) or two broad CYP inhibitors on the oxidative metabolism of 1,1,1-trichloroethane. Pre-treatment with phenobarbital had a small effect in decreasing blood concentrations of 1,1,1-trichloroethane, whereas pre-treatment with the two CYP inhibitors decreased the metabolism of 1,1,1-trichloroethane, thus increasing blood concentrations of 1,1,1-trichloroethane. Bruckner et al. (2001) exposed male Sprague-Dawley rats to 1,1,1-trichloroethane at a range of doses by oral administration (gavage) and assessed the activities and expression of various CYPs. Induction of both CYP2E1 and CYP2B1/2 was observed. The metabolism of 1,1,1-trichloroethane was enhanced by pre-treatment with phenobarbital or ethanol, or by fasting. From these more direct data, the authors concluded that both CYP2E1 and CYP2B1/2 are involved in 1,1,1-trichloroethane metabolism.

Despite the various rodent studies with positive results that are consistent with a role for CYPs in the metabolism of 1,1,1-trichloroethane, there are a few studies in which the results are less clear. Savolainen et al. (1977) found that exposure to 1,1,1-trichloroethane for 5 days decreased the microsomal CYP content of rat liver, whereas exposure to trichloroethylene (for which metabolism by CYPs is much better characterized) increased the microsomal CYP content of rat liver. Toftgård et al. (1981) found that 1,1,1-trichloroethane had very modest or no effects on total CYP levels or activities, whereas other organic solvents, such as xylene, produced clearly significant increases. Wang et al. (1996) exposed rats to one of four solvents (including 1,1,1-trichloroethane) for 6 hours and assessed metabolic effects in the liver. Toluene, trichloroethylene, and benzene had marked effects on the activity of CYP-dependent enzymes and the expression of several CYP enzymes, whereas 1,1,1-trichloroethane had no effect on these processes. [The Working Group noted that the 6-hour exposure time was probably insufficient to observe all potential induction of CYPs or other drug-metabolizing enzymes, thus conclusions about the ability of 1,1,1-trichloroethane to induce CYP expression in this study would only be preliminary and based on a short exposure time.]

The metabolism of 1,1,1-trichloroethane has been compared to that of its isomer 1,1,2-trichloroethane and of trichloroethylene. Ikeda & Otsuji (1972) compared the excretion of trichloroethanol and trichloroacetic acid in rats or mice exposed by inhalation to 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, or 1,1,2,2-tetrachloroethane. All compounds except 1,1,2-trichloroethane generated significant amounts of urinary trichloroethanol and

trichloroacetic acid. [The Working Group noted that this finding would seem to contradict those of other studies that showed metabolism of 1,1,2-trichloroethane to be much faster than that of 1,1,1-trichloroethane.] Similar comparisons of the metabolism or effects on metabolism of 1,1,1-trichloroethane and *meta*-xylene (Tardif & Charest-Tardif, 1999) also supported the findings of relatively poor metabolism of 1,1,1-trichloroethane. In male Sprague-Dawley rats, co-exposure to both 1,1,1-trichloroethane and *meta*-xylene resulted in markedly lower excretion of urinary metabolites of 1,1,1-trichloroethane (i.e. trichloroethanol and trichloroacetic acid) than did exposure to 1,1,1-trichloroethane only.

Koizumi et al. (1983) exposed rats to 1,1,1-trichloroethane at 200, 400, or 800 ppm for 10 days and followed the conversion of 1,1,1-trichloroethane to trichloroethanol. While the amount of trichloroethanol produced increased markedly between 200 ppm and 400 ppm, the increase between 400 ppm and 800 ppm was much smaller, suggesting saturation of metabolism. In terms of species-dependent differences, it is estimated that the metabolism of 1,1,1-trichloroethane in mice is 2- to 3-fold that in rats on a body-weight basis (Schumann et al., 1982a, 1982b). Other studies, such as those conducted by Yoshida et al. (1998), further emphasize the modest role of metabolism versus excretion of unmetabolized 1,1,1-trichloroethane in overall disposition.

(ii)   *Non-human mammalian systems in vitro*

Lal et al. (1969) reported that 1,1,1-trichloroethane increased the hepatic oxidative metabolism of CYP substrates in vitro. [The Working Group noted that in this abstract no details were provided about the nature of CYP activities affected or the type of in vitro hepatic system used.] A study by Takano et al. (1988) also supported a role, albeit modest, for CYP in the metabolism of 1,1,1-trichloroethane. For example, although 1,1,1-trichloroethane increased the

rate of oxygen (O_2) consumption and hydrogen peroxide (H_2O_2) production in rat liver microsomes, the ratio of metabolism rate to O_2 consumption rate was very small (i.e. 0.011).

Van Dyke & Wineman (1971) examined the dechlorination of various chloroethanes and chloropropanes by hepatic microsomes from rat, rabbit, and guinea-pig. The rate of dechlorination of 1,1,2-trichloroethane by rat liver microsomes was about 20-fold that of 1,1,1-trichloroethane. While Takano et al. (1985) found CYP-dependent metabolism of 1,1,2-trichloroethane to be much faster than that of 1,1,1-trichloroethane, they emphasized that 1,1,1-trichloroethane should not be considered inert towards the mixed function oxidase system; they concluded that 1,1,1-trichloroethane binds to CYP, although only a small proportion of the bound molecules are metabolized.

While few studies are available in which a detailed analysis of the kinetics of CYP-dependent metabolism of haloalkanes was conducted, one study by Salmon et al. (1981) examined the microsomal de-chlorination of several chloroethanes, including 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trifluoro-2-chloroethane, and hexachloroethane. Of these seven compounds, 1,1,1-trichloroethane exhibited by far the lowest V_{max} (0.2 nmol/min per mg protein) with a K_m of 0.27 mM.

As noted in Section 4.1.1(c) and illustrated in Fig. 4.2, in addition to oxidative metabolism, 1,1,1-trichloroethane may also undergo reductive metabolism in hepatic microsomes to yield 1,1-dichloroethane (Thompson et al., 1985). The reaction was dependent on reduced nicotinamide adenine dinucleotide phosphate (NADPH) and occurred only under anaerobic conditions. [Thus, the role of reductive metabolism under most exposure conditions will probably be very minor.]

(d)   Excretion

The scientific literature on excretion of 1,1,1-trichloroethane for experimental animals resembles that for humans in terms of the number of published studies, major findings, and conclusions. For example, most of the absorbed 1,1,1-trichloroethane (94–98% in rats and 87–97% in mice) is recovered in exhaled air within 24 hours as unmetabolized 1,1,1-trichloroethane, with excretion of 1,1,1-trichloroethane being more rapid in mice than in rats (Schumann et al., 1982a, 1982b). Andoh et al. (1977) (cited in Yoshida et al, 1998) also reported that about 90% of the absorbed 1,1,1-trichloroethane was excreted by rats in exhaled air as the unchanged parent compound within 8 hours after intraperitoneal injection of 1,1,1-trichloroethane at 200 mg/kg bw.

Urinary excretion of metabolites (i.e. trichloroethanol and trichloroacetic acid) has also been assessed. Caperos et al. (1982) conducted a modelling study and concluded that urinary trichloroethanol level is a more sensitive indicator of exposure to 1,1,1-trichloroethane than is 1,1,1-trichloroethane level in the breath. They further noted that urinary trichloroacetic acid level is not a sufficiently sensitive or accurate indicator of exposure to 1,1,1-trichloroethane owing to the potential for variation with exposure concentrations.

Dallas et al. (1989), in their study on inhalation of 1,1,1-trichloroethane at 50 or 500 ppm for 2 hours in male Sprague-Dawley rats, found that concentrations of 1,1,1-trichloroethane in both blood and exhaled breath were directly proportional to exposure dose. By the end of the exposure period, one third to one half of the absorbed 1,1,1-trichloroethane was eliminated.

Hobara et al. (1981, 1982) investigated the toxicokinetics of 1,1,1-trichloroethane in one study and both 1,1,1-trichloroethane and 1,1,2-trichloroethane in a second study in dogs exposed by intravenous injection. Similar to findings in humans, mice, and rats, both compounds were rapidly available systemically and were detected in exhaled air within 1 minute.

Jakobson et al. (1982) dermally exposed anaesthetized guinea-pigs to a series of solvents and showed that elimination curves were nonlinear in all cases and corresponded to a kinetic model involving at least two compartments for 1,1,1-trichloroethane and the other solvents. [The Working Group noted that this contrasted with the simpler, linear relationships for elimination described for humans and rodents exposed by inhalation or intravenous injection. The complexities of cutaneous absorption and transient storage of solvent in fat may explain these differences.] Mortuza et al. (2018) analysed the toxicokinetics and elimination of trichloroethylene and 1,1,1-trichloroethane in male Sprague-Dawley rats exposed by gavage. While trichloroethylene exhibited nonlinear toxicokinetics, those for 1,1,1-trichloroethane were nearly linear.

In a study by Mitoma et al. (1985), male B6C3F$_1$ mice and Osborne-Mendel rats were exposed orally to 1,1,1-trichloroethane at two doses, the maximum tolerated dose (MTD) and ¼ MTD (rats, 3000 or 750 mg/kg bw, equal to 22.5 or 5.6 mmol/kg bw; and mice, 4000 or 1000 mg/kg bw, equal to 30.0 or 7.5 mmol/kg bw). 1,1,1-Trichloroethane was mostly eliminated as the parent compound in exhaled air (85–93% of the total administered dose) and metabolism only accounted for 4% or 6% of the total dose in rats and mice, respectively. Urinary metabolite profiles (for trichloroethanol and trichloroacetic acid) were similar in rats and mice.

4.2 Evidence relevant to key characteristics of carcinogens

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

(a) Humans

(i) Exposed humans

No studies on DNA adducts or protein adducts were available to the Working Group.

In a study in aircraft-maintenance personnel exposed to solvents that included 1,1,1-trichloroethane, Lemasters et al. (1999a) measured concentrations of parent 1,1,1-trichloroethane in the blood, urine, and exhaled breath, together with micronucleus formation and sister-chromatid exchange in peripheral blood lymphocytes over the course of 30 weeks of exposure. In participants who worked in the sheet metal shop, the frequency of sister-chromatid exchange was significantly higher after 30 weeks when compared with baseline levels. Micronucleus counts also increased significantly from 12 to 19.8 by 15 weeks but then decreased to near baseline by 30 weeks (see also Section 4.2.2). [The Working Group noted that although this study did not address the question of whether electrophilic intermediates are formed during 1,1,1-trichloroethane metabolism, the finding of an increased frequency of sister-chromatid exchange is consistent with such intermediates being formed. The Working Group also noted that this was a co-exposure to multiple solvents, and exposure characterization of the individual solvents was not presented for the participants undergoing genotoxicity assessments, thus a conclusion cannot be made regarding the genotoxic effects of only 1,1,1-trichloroethane in this study.]

(ii) Human cells in vitro

One study in human-derived cells indirectly addressed the question of the potential for formation of electrophilic metabolites from 1,1,1-trichloroethane (Doherty et al., 1996) (see also Section 4.2.2 on genotoxicity). In this comprehensive study, the authors investigated the ability of 13 chlorinated hydrocarbons, toluene, and *n*-hexane to induce micronucleus formation in the cytochalasin B-blocked micronucleus assay. Genetically engineered cell lines were used: (i) AHH-1 cells, a human lymphoblastoid cell line that natively possesses a relatively low level of CYP1A1 activity; (ii) h2E1 cells, a human lymphoblastoid cell line that possesses native CYP1A1 and contains a cDNA for CYP2E1; and (iii) MCL-5 cells, an AHH-1-derived cell line that stably expresses cDNAs encoding human CYP1A2, CYP2A6, CYP3A4, CYP2E1, and microsomal epoxide hydrolase and contains relatively high levels of native CYP1A1. Each cell line was exposed to three concentrations of each chemical. 1,1,1-Trichloroethane caused a relatively large increase in the ratio of mononucleated:binucleated cells in the two cell lines (h2E1 and MCL-5) that express high activities of CYP2E1. [The Working Group noted that, on the basis of these in vitro genotoxicity assays, 1,1,1-trichloroethane would be presumed to form an electrophilic metabolite. Cautions or limitations for this conclusion include the relatively high concentrations of 1,1,1-trichloroethane and other chemicals to which the cell lines were exposed, and the absence of any direct evidence showing formation of specific electrophilic and reactive intermediates.]

(b) Experimental systems

Compared with studies in humans or human-derived cells or tissues, there is not much evidence in experimental systems regarding the potential for the formation of electrophilic intermediates from 1,1,1-trichloroethane, although there are some studies that address this question more directly.

(i) Non-human mammals in vivo

Filser et al. (1982) exposed rats to various halogenated hydrocarbons under conditions of saturated metabolism and measured concentrations of the parent compound and acetone in exhaled breath. The authors proposed that acetonaemia was due to metabolism of the halogenated compounds to reactive epoxides. These epoxides are proposed to alkylate coenzyme A and thereby block the citric acid cycle. Exposure to many of the compounds studied, including vinyl chloride, vinyl bromide, vinyl fluoride, vinylidene fluoride, *cis-* and *trans*-1,2-dichloroethylene, trichloroethylene, perchloroethylene [tetrachloroethylene], methylene chloride [dichloromethane], chloroform, carbon tetrachloride, and 1,1,2-trichloroethane was associated with increased excretion of acetone. In contrast, no significant effect on acetone excretion was observed in rats exposed to either 1,1,1-trichloroethane or *n*-hexane. [The Working Group noted that neither 1,1,1-trichloroethane nor *n*-hexane form significant amounts of epoxides during their metabolism.]

In a study by Mitoma et al. (1985), male B6C3F$_1$ mice and Osborne-Mendel rats were exposed orally to 1,1,1-trichloroethane at two doses, the MTD and ¼ MTD (rats, 3000 or 750 mg/kg bw, equal to 22.5 or 5.6 mmol/kg bw; mice, 4000 or 1000 mg/kg bw, equal to 30.0 or 7.5 mmol/kg bw). In addition to assessing excretion and overall metabolism, dose-dependent liver protein binding was also demonstrated. This binding was detected at slightly greater levels in rats than in mice, indicating some formation of reactive electrophiles.

Turina et al. (1986) measured radiolabelling of DNA, RNA, and protein in various tissues from rats and mice exposed to [14C]-labelled 1,1,1-trichloroethane. A low level of DNA radiolabelling was detected in the liver. [The Working Group noted that the binding is typical of weak initiators.]

(ii) Non-human mammalian systems in vitro

Some evidence for the formation of electrophilic metabolites from 1,1,1-trichloroethane was provided in a study by Casciola & Ivanetich (1984), who assessed and compared the metabolism of multiple chloroethanes by rat hepatic nuclear CYP and by hepatic microsomes. [The Working Group noted that chloral hydrate is formed from the incubation of rat liver nuclei with 1,1,1-trichloroethane in the presence of NADPH, unlike in the main system in the endoplasmic reticulum. This would suggest the potential intermediate formation of an epoxide, as is the case for trichloroethylene; the quantitative significance of this pathway is unclear but is not likely to be very large.]

Maiorino et al. (1982) isolated liver microsomes from phenobarbital-induced rats and incubated them under a nitrogen atmosphere with 2 μmol of radiolabelled 1,1,1-trichloroethane and an NADPH-generating system. A low amount of protein binding (1.5 ± 0.7 nmol/mg protein) with 1,1,1-trichloroethane was detected. In comparison, protein binding (18.9 nmol/mg protein) at the same dose of 1,1,2-trichloroethane was more than 10-fold higher that for 1,1,1-trichloroethane. [The Working Group noted that these data indicate that although 1,1,1-trichloroethane can form electrophilic metabolites, its ability to do so is very modest compared with that of other, similar halogenated compounds.]

Takano et al. (1988) provided evidence for a low rate of CYP-dependent metabolism of 1,1,1-trichloroethane in rat liver microsomes. There was no detectable increase in the formation of malondialdehyde in incubations of 1,1,1-trichloroethane with rat liver microsomes (see Section 4.2.3), suggesting little in the way of formation of electrophilic or oxidizing metabolites.

As described in Sections 4.1.1(c) and 4.1.2(c) and illustrated in Fig. 4.2, reductive de-chlorination of 1,1,1-trichloroethane is expected to yield

multiple electrophilic and reactive intermediates and ultimately to produce acetylene (Thompson et al., 1985). [The Working Group noted that such a reaction, however, should occur under severely hypoxia or anaerobic conditions. Hence, this is not likely to be a quantitatively significant pathway under most conditions.]

Turina et al. (1986) also detected covalent binding of [^{14}C]-labelled 1,1,1-trichloroethane in microsomes from various tissues isolated from rats and mice. Like for the in vivo exposures described above, labelling of microsomal proteins was low, although CYP-dependent binding was shown for liver microsomes and was less clear for lung microsomes.

4.2.2 Is genotoxic

(a) Humans

(i) Exposed humans

See Table 4.1.

A study on aircraft-maintenance workers at a United States Air Force base investigated the correlation between measurements of the internal dose (i.e. in breath, blood, and urine) of solvents including 1,1,1-trichloroethane, and genotoxic effects in peripheral blood lymphocytes (Lemasters et al., 1999a). The results of the preliminary exposure assessment (pilot study) of industrial hygiene air samples and internal dose measurements in eight existing employees indicated that, of the solvents measured, 1,1,1-trichloroethane was present at the highest breath concentrations, specifically in the two sheet metal workers tested, in whom 1,1,1-trichloroethane was measured at 8.9 and 23.0 ppb in exhaled breath. The results of the subsequent genotoxicity assessment in a separate cohort of new hires in the sheet metal shop indicated small, but statistically significant increases ($P = 0.003$) in the frequency of sister-chromatid exchange after 30 weeks of exposure. There were significant increases ($P = 0.03$) in the frequency of micronucleus formation after 15 weeks of exposure compared with unexposed individuals; however, there was no significant difference at 30 weeks. [The Working Group noted that this was a co-exposure to multiple solvents, and exposure characterization of the individual solvents was not presented for the participants undergoing genotoxicity assessments; thus, a conclusion could not be made regarding the genotoxic effects of only 1,1,1-trichloroethane in this study.]

(ii) Human cells in vitro

See Table 4.2.

1,1,1-Trichloroethane induced an increase in DNA damage as assessed by the comet assay in erythroid progenitor cells derived from human umbilical cord blood (Irvin-Barnwell et al., 2021).

1,1,1-Trichloroethane did not induce unscheduled DNA synthesis in HeLa cells in either the presence or absence of metabolic activation (Martin & McDermid, 1981).

An investigation into the genotoxicity of chlorinated hydrocarbons in metabolically competent human cells reported that 1,1,1-trichloroethane induced a significant increase in the frequency of both kinetochore-positive and kinetochore-negative micronuclei in AHH-1, h2E1, and MCL-5 cells (Doherty et al., 1996) (see Section 4.2.1). [The results indicate that 1,1,1-trichloroethane has both clastogenic and aneugenic activity.]

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3.

In a multigenerational study, mice in the F_0 generation were given drinking-water containing 1,1,1-trichloroethane, then mated to produce the F_1 generation. Some F_1 treated animals were also given drinking-water containing 1,1,1-trichloroethane and mated to produce the F_2 generation. Untreated F_1 and F_2 generation males were used for a dominant lethal study. No evidence of dominant lethal mutations was observed in either the F_1 or the F_2 generation (Lane et al., 1982).

Table 4.1 Genetic and related effects of 1,1,1-trichloroethane in exposed humans

End-point	Biosample type	Location, setting, study design	Exposure level and number of exposed and controls	Results[a]	Covariates controlled	Comments	Reference
Micronucleus formation	Peripheral blood lymphocytes	USA, Air Force base/cross-sectional	6 exposed (exposure not measured), 8 controls	(+)	Smoking, number of caffeinated beverages per day	No exposure characterization in participants undergoing genotoxicity assessment; small sample size; study participants exposed to mixture of solvents and fuel fumes	Lemasters et al. (1999a)
Sister-chromatid exchange	Peripheral blood lymphocytes	USA, Air Force base/cross-sectional	6 exposed (exposure not measured), 8 controls	(+)	Smoking, number of caffeinated beverages per day	No exposure characterization in participants undergoing genotoxicity assessment; small sample size; study participants exposed to mixture of solvents and fuel fumes	Lemasters et al. (1999a)

[a] (+), positive in a study of limited quality.

Table 4.2 Genetic and related effects of 1,1,1-trichloroethane in human cells in vitro

End-point	Tissue, cell type	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA strand breaks (comet assay)	Cord blood, erythroid progenitor cells	+	NT	10 nM [1.335 ng/mL]	Purity, NR	Irvin-Barnwell et al. (2021)
Unscheduled DNA synthesis	HeLa S3 cells	–	–	100 µg/mL (−S9); 100 µg/mL (+ phenobarbital-induced rat S9)	Purity, NR	Martin & McDermid (1981)
		NT	–	100 µg/mL (+ 3-methylcholanthrene-induced rat S9)		
Micronucleus formation	AHH-1 cells h2E1 cells MCL-5 cells	+ + +	NT NT NT	2.5 mM [333.5 µg/mL]	Purity, NR	Doherty et al. (1996)

AHH-1, a human lymphoblastoid cell line; h2E1, a human lymphoblastoid cell line which possesses native CYP1A1 and contains a cDNA for CYP2E1; HIC, highest ineffective concentration; LEC, lowest effective concentration; MCL-5, an AHH-1-derived cell line that stably expresses cDNAs encoding human CYP1A2, CYP2A6, CYP3A4, CYP2E1, and microsomal epoxide hydrolase, and contains relatively high levels of native CYP1A1; NR, not reported; NT, not tested; S9, 9000 × g supernatant.
[a] +, positive; –, negative.

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Dominant lethal mutations	Mouse, ICR Swiss	F_1 mating generation F_2 mating generation	– –	5.83 mg/mL (1000 mg/kg bw per day) (F_0 generation) 5.83 mg/mL (1000 mg/kg bw per day) (F_1 generation)	F_0 generation exposed in drinking-water for 5 wk F_1 generation exposed in drinking-water for 11 wk	Purity, 97% (3% *para*-dioxane)	Lane et al. (1982)
Micronucleus formation	Mouse, B6C3F$_1$ (M, F)	Peripheral blood normochromatic erythrocytes	+/– –	80 000 ppm	13 wk oral exposure with feed containing microencapsulated 1,1,1-trichloroethane	Purity, > 99%; Positive trend test, but no significance relative to controls in males; n = 5 per group	NTP (2000)
Micronucleus formation	Mouse, NMRI (M, F)	Bone marrow polychromatic erythrocytes	(–)	2000 mg/kg bw	Intraperitoneal ×2 (at 0 and 24 h)	Purity, NR; 2 males and 2 females per group; bone marrow exposure not determined	Gocke et al. (1981)
Micronucleus formation	Mouse, B6C3F$_1$ (NR)	Bone marrow polychromatic erythrocytes	(+) (–) (–)	80% LD$_{50/7}$ (sampled at 48 and 72 h) 80% LD$_{50/7}$ (sampled at 72 h) 80% LD$_{50/7}$ (sampled at 36, 48, and 60 h)	Intraperitoneal ×2 (at 0 and 24 h) or ×1 (last test only)	Purity, NR; n = 4–5 per group; doses, NR; described as percentage of LD$_{50/7}$ (i.e. the dose required to kill 50% of animals within 7 days); statistical method based on historical control data, not on concurrent control; positive response only observed at 72 h time point in first experiment; bone marrow exposure not determined	Salamone et al. (1981)
Micronucleus formation	Mouse, CD-1 (M, F)	Bone marrow polychromatic erythrocytes	(–)	0.032 mg/kg bw	Intraperitoneal ×2 (at 0 and 24 h)	Purity, NR; 2 males and 2 females; bone marrow exposure not determined	Tsuchimoto et al. (1981)

bw, body weight; F, female; LD, lethal dose; LED, lowest effective dose; HID, highest ineffective dose; M, male; NR, not reported; ppm, parts per million; wk, week.

[a] –, negative; +/–, equivocal; (+) or (–), positive or negative in a study of limited quality.

1,1,1-Trichloroethane elicited equivocal and negative responses for micronucleus formation in peripheral blood lymphocyes in male and female mice, respectively, after exposure to feed containing 1,1,1-trichloroethane for 13 weeks (NTP, 2000).

Negative responses and one weak positive response were observed in the bone marrow micronucleus assay in mice (Gocke et al., 1981; Salamone et al., 1981; Tsuchimoto et al., 1981).

Evidence of oxidative stress-induced DNA damage in mice treated with 1,1,1-trichloroethane was also observed and is discussed in more detail in Section 4.2.3 (Al-Griw et al., 2016).

(ii) Non-human mammalian cells in vitro

See Table 4.4.

1,1,1-Trichloroethane in either the liquid or vapour phase did not induce unscheduled DNA synthesis in cultured hepatocytes from rats (Althaus et al., 1982; Shimada et al., 1985; Milman et al., 1988). 1,1,1-Trichloroethane induced unscheduled DNA synthesis in cultured hepatocytes from male mice (Milman et al., 1988).

1,1,1-Trichloroethane exposure yielded five negative gene-mutation responses in the mouse lymphoma assay in the absence of metabolic activation and three positive and four negative responses in the presence of metabolic activation (Mitchell et al., 1988; Myhr & Caspary, 1988). [The Working Group noted that the positive responses in the presence of metabolic activation were inconsistent.]

1,1,1-Trichloroethane induced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of metabolic activation, but not in the presence of metabolic activation (Galloway et al., 1987). Equivocal responses were observed in the chromosomal aberration assay in Chinese hamster lung fibroblast (CHL/IU) cells (JETOC, 2005).

One negative response and one equivocal response were observed for sister-chromatid exchange induction in CHO cells in the absence of metabolic activation and an equivocal response and a negative response were observed in the presence of metabolic activation (Perry & Thomson, 1981; Galloway et al., 1987).

(iii) Non-mammalian experimental systems

See Table 4.5.

1,1,1-Trichloroethane elicited a negative response in the sex-linked recessive lethal *Basc* test in *Drosophila melanogaster* after the assessment of three successive broods (Gocke et al., 1981).

The genotoxicity of 1,1,1-trichloroethane was assessed in two plant systems. Chromosome aberrations were significantly induced in onion (*Allium cepa*) root tip cells in the *Allium* anaphase-telophase test (Rank & Nielsen, 1994). Conversely, 1,1,1-trichloroethane in the vapour phase did not yield a significant mutagenic effect in the *Tradescantia* stamen hair bioassay (Schairer & Sautkulis, 1982).

1,1,1-Trichloroethane did not induce reverse mutations in *Saccharomyces cerevisiae* (Mehta & von Borstel, 1981). 1,1,1-Trichloroethane (US EPA standard, free of epoxide preservative) weakly induced deletions at the highest concentration tested in the deletion recombination assay; however, 1,1,1-trichloroethane containing 0.05% 1,2-epoxybutane as a stabilizer elicited a stronger response (Brennan & Schiestl, 1998). 1,1,1-Trichloroethane did not induce mitotic gene conversion in *S. cerevisiae* in strains JD1 or D7 (Sharp & Parry, 1981a; Zimmermann & Scheel, 1981). 1,1,1-Trichloroethane did not induce mitotic crossing-over in *S. cerevisiae* in strains T1 or T2, or in the rep-test in strains T4 and T5 (analogous to the rec-test in *B. subtilis*) (Kassinova et al., 1981). A repair assay using wild-type and *rad* strains of *S. cerevisiae* demonstrated that 1,1,1-trichloroethane does not cause relative growth inhibition in repair-deficient yeast, thus indicating a lack of genotoxicity (Sharp & Parry, 1981b). 1,1,1-Trichloroethane did not induce

Table 4.4 Genetic and related effects of 1,1,1-trichloroethane in non-human mammalian cells in vitro

End-point	Species, cell type	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Rat, primary hepatocytes	–	NT	7.5 μM (– pyridines)	Purity, NR	Althaus et al. (1982)
		–	NT	7.5 μM (+ pyridines)		
Unscheduled DNA synthesis	Rat, primary hepatocytes	–	NT	0.1% in air (non-stabilized)	Modified vapour-phase exposure performed in an exposure chamber; both non-stabilized (purity, 99.8%) and stabilized (purity, 94.10%, with 5.65% stabilizer mixture containing butylene oxide) 1,1,1-trichloroethane were tested	Shimada et al. (1985)
		–	NT	0.1% in air (stabilized)		
Unscheduled DNA synthesis	Rat, primary hepatocytes	–	NT	NR	Modified vapour-phase exposure performed in an exposure chamber	Milman et al. (1988)
Unscheduled DNA synthesis	Mouse, primary hepatocytes	+	NT	NR	Modified vapour-phase exposure performed in an exposure chamber	Milman et al. (1988)
Gene mutation, $Tk^{+/-}$	Mouse, L5178Y/$Tk^{+/-}$ lymphoma cells	–	+	400 nL/mL (–S9); 31.3 nL/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Myhr & Caspary (1988)
		–	+	400 nL/mL (–S9); 200 nL/mL (+Aroclor 1254-induced rat S9)		
		–	–	400 nL/mL (–S9); 400 nL/mL (+Aroclor 1254-induced rat S9)		
		NT	–	400 nL/mL (+ uninduced rat S9)		
Gene mutation, $Tk^{+/-}$	Mouse, L5178Y/$Tk^{+/-}$ lymphoma cells	–	(+)	0.51 μL/mL (–S9); 0.64 μL/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Mitchell et al. (1988)
		–	–	0.51 μL/mL (–S9); 0.51 μL/mL (+Aroclor 1254-induced rat S9)		
		NT	–	0.51 μL/mL (+Aroclor 1254-induced rat S9)		
Chromosomal aberrations	Chinese hamster, ovary cells (CHO)	+	–	160 μg/mL (–S9); 5000 μg/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Galloway et al. (1987)

Table 4.5 Genetic and related effects of 1,1,1-trichloroethane in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Drosophila melanogaster, Berlin K (wildtype and *Basc*)	Sex-linked recessive lethal mutations	–	NT	25 mM [3335 µg/mL]	Purity, NR	Gocke et al. (1981)
Allium cepa	Chromosome aberrations	+	NT	175 µM [23.3 µg/mL]	24 h exposure; purity, NR	Rank & Nielsen (1994)
Tradescantia, clone 4430	Forward mutation	–	NT	5170 ppm [28 × 103 mg/m³]	Vapour-phase-exposure; 6 h exposure; purity, NR	Schairer& Sautkulis (1982)
Saccharomyces cerevisiae, T4/T5	DNA damage	–	NT	Concentration, NR (rep-test with strains T4 and T5)	Purity, NR	Kassinova et al. (1981)
Saccharomyces cerevisiae, 197/2d (wildtype and *rad*)	DNA damage	–	–	750 µg/mL (−S9); 750 µg/mL (+Aroclor 1254-induced rat S9)	Performed in stationary cells; purity, NR	Sharp & Parry (1981b)
Saccharomyces cerevisiae XV185-14C	Reverse mutation	–	–	1111 µL/mL (−S9); 1111 µL/mL (+S9)	Purity, NR	Mehta & von Borstel (1981)
Saccharomyces cerevisiae, RS112	Deletion	(+)	NT	5.35 mg/mL (US EPA standard free of epoxide preservative)	Purity, NR	Brennan & Schiestl 1998
		+	NT	4.01 mg/mL (stabilized with 0.05% 1,2-epoxybutane)		
Saccharomyces cerevisiae, JD1	Mitotic gene conversion	–	–	750 µg/mL (−S9); 750 µg/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Sharp & Parry (1981a)
Saccharomyces cerevisiae, D7	Mitotic gene conversion	–	–	2 µL/mL [2600 µg/mL] (−S9); 2 µL/mL (+S9)	One concentration tested; purity, NR	Zimmermann & Scheel (1981)
Saccharomyces cerevisiae, T1 and T2	Mitotic crossing-over	–	–	100 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Kassinova et al. (1981)
Saccharomyces cerevisiae, D61.M	Aneuploidy Aneuploidy	– –	NT NT	5330 µg/mL (cold interruption) 5990 µg/mL (standard incubation)	Purity, 99%	Whittaker et al. (1990)
Saccharomyces cerevisiae, D6	Aneuploidy	–	–	750 µg/mL (−S9); 750 µg/mL (+Aroclor 1254-induced rat S9)	Purity, NR	Parry & Sharp (1981)
Aspergillus nidulans, P1	Mitotic malsegregation	–	NT	0.1% v/v in medium (~1320 µg/mL)	Purity, > 99%	Crebelli et al. (1988)
Salmonella typhimurium, BA13 and BAL13	Forward mutation	–	–	74.96 µM (−S9); 74.96 µM (+Aroclor 1254-induced rat S9)	Pre-incubation protocol; purity, 97%	Roldán-Arjona et al. (1991)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium, TM677	Forward mutation	–	–	1000 µg/mL (−S9); 1000 µg/mL (+ phenobarbital-induced rat S9)	Purity, NR	Skopek et al. (1981)
		NT	–	1000 µg/mL (+Aroclor 1254-induced rat S9)		
Salmonella typhimurium, TA92, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	(–)	(–)	2000 µg/plate (−S9); 2000 µg/plate (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	Brooks & Dean (1981)
Salmonella typhimurium, TA97 and TA98	Reverse mutation	(+)	(+)	10 µg/plate (−S9); 10 µg/plate (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Strobel & Grummt (1987)
Salmonella typhimurium, TA98, TA1537 and TA1538	Reverse mutation	–	–	10% in air (−S9); 10% in air (+Aroclor 1254-induced rat S9) (non-stabilized)	Plate incorporation assay, modified vapour-phase exposure Non-stabilized, purity, 99.8%; stabilized, purity, 94.1% (5.65% stabilizer)	Shimada et al. (1985)
		–	–	10% in air (−S9); 10% in air (+Aroclor 1254-induced rat S9) (stabilized)		
Salmonella typhimurium, TA98	Reverse mutation	–	–	1.0 mL in desiccator (−S9); 1.0 mL in desiccator (+Aroclor 1254-induced rat S9)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, NR	Nestmann et al. (1980)
Salmonella typhimurium, TA98 and TA1537	Reverse mutation	–	–	5% in air for 24 h (−S9); 5% in air for 24 h (+S9)	Vapour-phase exposure; purity, 99%; results observed in 2 replicate experiments	JETOC (2005)
Salmonella typhimurium, TA98, TA100, TA1535, and TA1537	Reverse mutation	(–)	(–)	Concentrations, NR (−S9; + rat S9)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, 97–99%	Milman et al. (1988)
		NT	(–)	Concentrations, NR (−S9; + mouse S9)		
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	(–)	(–)	2000 µg/plate (−S9); 2000 µg/plate (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Rowland & Severn (1981)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	(–)	(–)	1000 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Falck et al. (1985)

Table 4.5   (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	**With metabolic activation**			
Salmonella typhimurium, TA98, TA100, and TA1537	Reverse mutation	(–)	(–)	5000 µg/plate (–S9); 5000 µg/plate (+Aroclor 1254-induced mouse S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	MacDonald (1981)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	(–)	(–)	2500 µg/plate (–S9); 2500 µg/plate (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Trueman (1981)
Salmonella typhimurium, TA98, TA100, TA1535, and TA1537	Reverse mutation	(–) NT	(–) (–)	10 000 µg/plate (–S9); 10 000 µg/plate (+ rat S9); 3333 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	Haworth et al. (1983)
		(–) NT	(–) (–)	3333 µg/plate (–S9); 3333 µg/plate (+ rat S9); 3333 µg/plate (+ hamster S9)		
Salmonella typhimurium, TA98	Reverse mutation	(–) NT	(–) (–)	1000 µg/plate (–S9); 3333 µg/plate (+ rat S9); 1000 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	NTP (2000)
		(–) NT	(–) (–)	10 000 µg/plate (–S9); 10 000 µg/plate (+ rat S9); 10 000 µg/plate (+ hamster S9)		
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	(–)	(–)	1000 µg/mL(–S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; Mutascreen test; purity, NR	Falck et al. (1985)
Salmonella typhimurium, TA98, TA1535, and TA1537	Reverse mutation	(–)	(–)	500 µg/mL (–S9); 500 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; microtiter fluctuation test; purity, NR	Gatehouse (1981)
Salmonella typhimurium, TA100	Reverse mutation	+	+	1000 µL in desiccator (–S9); 1000 µL in desiccator (+Aroclor 1254-induced rat S9)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, NR	Simmon et al. (1977)
Salmonella typhimurium, TA100	Reverse mutation	+ –	+ NT	150 mg/L in air (–S9); 150 mg/L in air (+Aroclor 1254-induced rat S9) (Fisher Co.); 210 mg/L in air (Aldrich Co.)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, 97%	Nestmann et al. (1984)

Table 4.5   (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	**With metabolic activation**			
Salmonella typhimurium, TA100	Reverse mutation	+	+	10% in air (−S9); 10% in air (+Aroclor 1254-induced rat S9) (non-stabilized)	Plate incorporation assay modified vapour-phase exposure; non-stabilized, purity, 99.8%; stabilized, purity, 94.1% (5.65% stabilizer)	Shimada et al. (1985)
		+	+	2.5% in air (−S9); 10% in air (+Aroclor 1254-induced rat S9) (stabilized)		
Salmonella typhimurium, TA100	Reverse mutation	+	+	5% in air for 24 h (−S9); 5% in air for 24 h (+S9)	Vapour-phase exposure; purity, 99%; results observed in 2 replicate experiments	JETOC (2005)
Salmonella typhimurium, TA100 and TA1535	Reverse mutation	+	+	1.0 mL in desiccator (−S9); 1.0 mL in desiccator (+Aroclor 1254-induced rat S9)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, NR	Nestmann et al. (1980)
Salmonella typhimurium, TA100 and TA1535	Reverse mutation	+	+	2000 µL in desiccator (−S9); 2000 µL in desiccator (+Aroclor 1254-induced rat S9)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, NR	Gocke et al. (1981)
Salmonella typhimurium, TA100	Reverse mutation	(+)	(−)	1000 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Strobel & Grummt (1987)
Salmonella typhimurium, TA100	Reverse mutation	(−) NT (−) NT	(−) (−) (−) (−)	10 000 µg/plate (−S9); 10 000 µg/plate (+ rat S9); 10 000 µg/plate (+ hamster S9); 3333 µg/plate (−S9); 3333 µg/plate (+ rat S9); 1000 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	Haworth et al. (1983)
Salmonella typhimurium, TA100	Reverse mutation	(−) NT (−) NT	(−) (−) (−) (−)	1000 µg/plate (−S9); 3333 µg/plate (+ rat S9); 1000 µg/plate (+ hamster S9); 10 000 µg/plate (−S9); 10 000 µg/plate (+ rat S9); 10 000 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	NTP (2000)
Salmonella typhimurium, TA104	Reverse mutation	(−)	(+)	1000 µg/mL (−S9); 10 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Strobel & Grummt (1987)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	**With metabolic activation**			
Salmonella typhimurium, TA1535	Reverse mutation	+	+	80 mg/L in air (−S9); 80 mg/L in air (+Aroclor 1254-induced rat S9) (Fisher Co.)	Plate incorporation assay modified in sealed desiccators to allow vapour-phase exposure; purity, 97%	Nestmann et al. (1984)
		+	NT	210 mg/L in air (Aldrich Co.)		
Salmonella typhimurium, TA1535	Reverse mutation	+	+	10% in air (−S9); 10% in air (+Aroclor 1254-induced rat S9) (non-stabilized)	Plate incorporation assay in sealed dessicator to allow modified vapour-phase exposure; non-stabilized, purity, 99.8%; stabilized, purity, 94.1% (5.65% stabilizer)	Shimada et al. (1985)
		+	+	2.5% in air (−S9); 2.5% in air (+Aroclor 1254-induced rat S9) (stabilized)		
Salmonella typhimurium, TA1535	Reverse mutation	+	+	0.1% in air for 24 h (−S9); 0.5% in air for 24 h (+S9)	Vapour-phase exposure; purity, 99%; results of two replicate experiments	JETOC (2005)
		+	+	0.5% in air for 24 h (−S9); 0.5% in air for 24 h (+S9)		
Salmonella typhimurium, TA1535, TA1537, and TA1538	Reverse mutation	(−)	(−)	10 000 µg/plate (−S9); 10 000 µg/plate (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Richold & Jones (1981)
Salmonella typhimurium, TA1535 and TA1537	Reverse mutation	(−) NT	(−) (−)	10 000 µg/plate (−S9); 10 000 µg/plate (+ rat S9); 10 000 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	Haworth et al. (1983)
		(−) NT	(−) (−)	1000 µg/plate (−S9); 3333 µg/plate (+ rat S9); 3333 µg/plate (+ hamster S9)		
Salmonella typhimurium, TA1535 and TA1537	Reverse mutation	(−) NT	(−) (−)	1000 µg/plate (−S9); 3333 µg/plate (+ rat S9); 1000 µg/plate (+ hamster S9)	Not vapour-phase exposure; pre-incubation protocol; purity, NR	NTP (2000)
		(−) NT	(−) (−)	10 000 µg/plate (−S9); 10 000 µg/plate (+ rat S9); 10 000 µg/plate (+ hamster S9)		
Salmonella typhimurium, TA1535/pSK1002	DNA damage SOS (*umu*) induction assay	−	−	666 µg/mL		Nakamura et al. (1987)
Escherichia coli, WP2 *uvrA*/pKM101	Reverse mutation	−	−	5% in air for 24 h (−S9); 5% in air for 24 h (+S9)	Vapour-phase exposure; purity, 99%; results observed in 2 replicate experiments	JETOC (2005)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Escherichia coli, WP2 *uvrA*	Reverse mutation	(−)	(−)	1000 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; microtiter fluctuation test; purity, NR	Gatehouse (1981)
Escherichia coli, WP2 *uvrA*	Reverse mutation	(−)	(−)	1000 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; standard plate incorporation; purity, NR	Falck et al. (1985)
Escherichia coli, WP2 *uvrA*	Reverse mutation	(−)	(−)	1000 µg/mL (−S9); 1000 µg/mL (+Aroclor 1254-induced rat S9)	Not vapour-phase exposure; Mutascreen test; purity, NR	Falck et al. (1985)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; ppm, parts per million; S9, 9000 × *g* supernatant from liver; US EPA, United States Environmental Protection Agency.

[a] +, positive; −, negative; +/−, equivocal; (+) or (−), positive or negative in a study of limited quality.

chromosome loss (Whittaker et al., 1990) or aneuploidy in *S. cerevisiae* (Parry & Sharp, 1981).

1,1,1-Trichloroethane did not induce mitotic malsegregation in *Aspergillus nidulans* strain P1 (Crebelli et al., 1988).

1,1,1-Trichloroethane gave negative results in the L-arabinose resistance (Ara) forward-mutation assay in *Salmonella typhimurium* both in the presence and absence of metabolic activation (Roldán-Arjona et al., 1991). A negative response was also observed in the 8-azaguanine resistance forward-mutation assay in *S. typhimurium* in both the presence and absence of metabolic activation (Skopek et al., 1981).

With a modified vapour-phase exposure protocol in a sealed exposure chamber, 1,1,1-trichloroethane induced reverse mutations in *S. typhimurium* strains TA100 and TA1535, but not in TA98, TA1537, or TA1538 (Shimada et al., 1985). In this study, it was observed that 1,1,1-trichloroethane stabilized with 5.65% butylene oxide yielded a higher potency and magnitude of response than did 1,1,1-trichloroethane with a purity of 99.8%. [The Working Group noted that this study highlights the confounding nature of contaminating "stabilizer" additives.] Similarly, mostly positive responses in TA100 and TA1535 were observed in studies that used a modified vapour-phase exposure in a sealed desiccator to assess mutagenicity in *S. typhimurium* (Simmon et al., 1977; Nestmann et al., 1980; Gocke et al., 1981; Nestmann et al., 1984; JETOC, 2005). 1,1,1-Trichloroethane induced reverse mutations in TA100 in both the presence and absence of metabolic activation (Simmon et al., 1977). Using the vapour-phase exposure approach, 1,1,1-trichloroethane did not induce reverse mutations in TA98 but did induce reverse mutations in TA100 and TA1535 (Nestmann et al., 1980). In another vapour-phase exposure study, positive responses were observed in *S. typhimurium* strains TA100 and TA1535 with 1,1,1-trichloroethane obtained from one source, whereas a negative response and a less potent

positive response were observed in TA100 and TA1535, respectively, with 1,1,1-trichloroethane from a different source (Nestmann et al., 1984). [The Working Group noted that these differences may be attributed to minute, undetermined differences in chemical composition between the two sources of 1,1,1-trichloroethane.] A positive response in TA100 and TA1535 was observed after vapour-phase exposure in a sealed desiccator (Gocke et al., 1981). In another study using vapour-phase exposures, positive responses were observed for *S. typhimurium* strains TA100 and TA1535 both with and without metabolic activation, whereas negative responses were observed for *Escherichia coli* strain WP2 *uvrA*/pKM101 and *S. typhimurium* strains TA98 and TA1537, both with and without metabolic activation (JETOC, 2005). One bacterial reverse-mutation study employing a sealed desiccator for vapour-phase exposure reported negative responses in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, both with and without metabolic activation (Milman et al., 1988). [The Working Group noted that these studies demonstrate the importance of using modified vapour-phase exposure to assess the mutagenicity of 1,1,1-trichloroethane. The Working Group also noted that *S. typhimurium* strains TA100 and TA1535, which are both used to measure base substitution, are the strains that are most sensitive to 1,1,1-trichloroethane-induced mutagenicity.]

1,1,1-Trichloroethane generally did not induce reverse mutations in the standard plate-incorporation assay. Negative results were observed in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, and in *E. coli* strain WP2 *uvrA* when following the standard plate-incorporation protocol (MacDonald, 1981; Richold & Jones, 1981; Rowland & Severn, 1981; Trueman, 1981; Falck et al., 1985). One study, however, yielded positive responses in *S. typhimurium* strains TA97, TA98, TA100, and TA104 following the standard plate-incorporation protocol (Strobel & Grummt, 1987). Similarly,

1,1,1-trichloroethane did not induce reverse mutations in the pre-incubation assay in *S. typhimurium* strains TA92, TA98, TA100, TA1535, TA1537, and TA1538, either with or without metabolic activation (Brooks & Dean, 1981; Haworth et al., 1983; NTP, 2000). 1,1,1-Trichloroethane also did not induce reverse mutations in the Mutascreen automated assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, and in *E. coli* strain WP2 *uvrA* (Falck et al., 1985). 1,1,1-Trichloroethane gave negative results in the microtiter fluctuation test in *S. typhimurium* strains TA98, TA1535, and TA1537, and in *E. coli* strain WP2 *uvrA* (Gatehouse, 1981).

1,1,1-Trichloroethane did not induce *umu* gene expression in *S. typhimurium* strain TA1535/pSK1002 in either the presence or absence of metabolic activation (Nakamura et al., 1987).

4.2.3 Induces oxidative stress

(a) Humans

No studies were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

A study analysing the relationship between hepatotoxicity and free radical production found that, while 1,1,1-trichloroethane at a dose of 5 mmol/kg bw administered orally to rats caused mild hepatotoxicity, as measured by a weak, but significant increase in serum glutamic--pyruvic transaminase (GPT) activity, it did not lead to an increase in free radical concentrations (Xia & Yu, 1992).

Tabatabaei & Abbott (1999) measured the generation of 2,3-dihydroxybenzoic acid (2,3-DHBA) as a marker of oxidative stress, since 2,3-DHBA is generated after hydroxyl radical attack on salicylate and can be measured with high sensitivity by liquid chromatography-mass spectrometry. They found that in rats pre-treated with salicylate then given 1,1,1-trichloroethane at 700 mg/kg bw via intraperitoneal injection, mean maximal plasma 2,3-DHBA concentrations increased 6.4-fold compared with saline-treated controls (Tabatabaei & Abbott, 1999).

Hepatotoxicity, as demonstrated by a heavily congested central vein, blood sinusoids, leukocytic infiltration, and hepatocellular apoptosis, was observed in young (i.e. age 3–5 weeks) Swiss albino mice given 1,1,1-trichloroethane at 100 and 400 µg/kg bw by intraperitoneal injection twice per week for 3 weeks. Internucleosomal DNA fragmentation was identified by histopathology, and increased levels of lipid peroxidation were measured by the quantification of thiobarbituric acid-reactive substances (TBARS), thus indicating DNA damage caused by oxidative stress (Al-Griw et al., 2016).

In one study on the transgenerational hepatic effects of 1,1,1-trichloroethane in Swiss albino mice, young (i.e. age ~3 weeks) females in the F_0 generation were given 1,1,1-trichloroethane at 100 µg/kg bw by intraperitoneal injection twice per week for 3 weeks and bred at age 10 weeks. An increase in adult-onset liver abnormalities was observed in both F_0 female mice and F_1 (offspring) mice, increased signs of lipid peroxidation, as measured by TBARS, in the livers of both the F_0 and F_1 mice, and increased nitric oxide and protein carbonyl content (i.e. biomarkers of oxidative stress) in the livers of F_1 mice (Al-Griw et al., 2017).

(ii) Non-human mammalian cells in vitro

A study in cardiac myocytes isolated from neonatal rats did not find any evidence that 1,1,1-trichloroethane at up to 1 and 4 mM enhanced H_2O_2-induced oxidative injury as measured by release of TBARS during lipid peroxidation and loss of lactate dehydrogenase through damaged sarcolemma membranes, respectively (Toraason et al., 1994).

Electron spin resonance spectroscopy coupled to the spin trapping technique was used to

investigate the formation of free radicals in cultured primary hepatocytes from rats pre-treated with phenobarbital. The results revealed that 1,1,1-trichloroethane at 2.5 μL/mL induced the formation of free radicals in cultured primary rat hepatocytes under both normoxic and hypoxic conditions (Tomasi et al., 1984).

1,1,1-Trichloroethane did not induce lipid peroxidation, as measured by TBARS, in either bovine pulmonary arterial endothelial cells or in rabbit aortic smooth muscle cells at concentrations ranging from 0.6% to 4% v/v. An increase in lipid peroxidation was observed in endothelial cells treated with both 1,1,1-trichloroethane and Fe(III)ADP and in smooth muscle cells treated with 1,1,1-trichloroethane and either Fe(III)ADP or Fe(II)ADP. These increases significantly exceeded the effects observed in cells treated with Fe(III)ADP or Fe(II)ADP alone (Tse et al., 1990). [The Working Group noted that this study indicated evidence of synergistic oxidative-stress activity with iron and 1,1,1-trichloroethane.]

(iii)   Acellular systems in vitro

The effects of 1,1,1-trichloroethane on CYP-dependent mixed-function oxidation by rat liver microsomes was studied by determination of the rates of O_2 consumption, H_2O_2 production, 1,1,1-trichloroethane metabolism, and spectral change in CYP. After incubation with phenobarbital-induced rat liver microsomes, 1,1,1-trichloroethane increased rates of O_2 consumption and H_2O_2 production, but metabolism was minimal. 1,1,1-Trichloroethane bound to CYP caused a type I spectral change. No increase in TBARS was observed. Together, the results indicate that 1,1,1-trichloroethane is not metabolized by CYP-dependent mixed-function oxidation, but rather that it has an uncoupling effect on the enzymes and causes futile O_2 consumption and H_2O_2 production (Takano et al., 1988). [The Working Group noted that this study provides a potential mechanism for the induction of oxidative stress by 1,1,1-trichloroethane.]

4.2.4 Induces chronic inflammation

(a)   Humans

(i)   Exposed humans

Muttray et al. (1999) exposed 12 healthy, non-smoking students to 1,1,1-trichloroethane at 20 and 200 ppm for 4 hours in an exposure chamber, using a crossover study design. Concentrations of interleukin (IL) 1β, IL6, and IL8 were significantly elevated, and prostaglandin E_2 was unchanged in nasal secretions after exposure to 1,1,1-trichloroethane at 200 ppm, indicating the initiation of a subclinical inflammatory response. [The Working Group noted that the results presented in this study represent an acute inflammatory response.]

(ii)   Human cells in vitro

No studies were available to the Working Group.

(b)   Experimental systems

(i)   Non-human mammals in vivo

Chronic inflammation was observed in the kidneys of male rats exposed to feed containing microencapsulated 1,1,1-trichloroethane at 10 000 ppm or more for 13 weeks (NTP, 2000).

In an investigation into the relative effects of 1,1,1-trichloroethane on liver and kidney function in Swiss-Webster mice exposed via a single intraperitoneal injection, liver changes consistent with inflammation were reported; these are described in more detail in Section 4.3 (Klaassen & Plaa, 1966). [The Working Group noted that the results presented in this study represent an acute inflammatory response.]

(ii)   Non-human mammalian cells in vitro

In an in vitro study in mouse embryo fibroblasts, 1,1,1-trichloroethane at up to 100 μM did not have any effect on the induction of interferon α or β (Sonnenfeld et al., 1983). [The Working Group noted that the results presented in this

study may not be relevant to a chronic inflammatory response.]

4.2.5 Alters cell proliferation, cell death, or nutrient supply

(a) Humans

No studies were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

In a chronic study, groups of 50 male and 50 female Osborne-Mendel rats and B6C3F$_1$ mice were given 1,1,1-trichloroethane in corn oil by oral administration at two dose levels on 5 days per week for 78 weeks. Rats received doses of 750 or 1500 mg/kg bw per day, and mice were given time-weighted average doses of 2807 or 5615 mg/kg bw per day. The 1,1,1-trichloroethane used had a purity of 95% with 3% *para*-dioxane [1,4-dioxane]. No signs of altered cell proliferation, cell death, or nutrient supply were observed (NTP, 1977).

In a chronic inhalation study, cortical hyperplasia was observed in the adrenal glands at slightly increased incidence in female Fischer 344 rats exposed to 1,1,1-trichloroethane at 3200 ppm compared with the controls. Urine analysis in the last week of the 2-year exposure period demonstrated increased frequency of ketone bodies in male mice at 3200 ppm (Ohnishi et al., 2013). [The Working Group noted that the results of this study provide evidence of increased cellular proliferation (e.g. hyperplasia) and altered nutrient supply (e.g. the presence of ketone bodies in the urine of male mice).]

Two studies noted that 1,1,1-trichloroethane did not induce significant effects on either the initiation (at 9.9 mmol/kg bw, the MTD) or promotion (at 7.4 mmol/kg bw) of liver foci in Osborne-Mendel rats when increased γ-glutamyltranspeptidase activity was used as a marker

for putative preneoplastic lesions (Story et al., 1986; Milman et al., 1988).

(ii) Non-human mammalian cells in vitro

No studies were available to the Working Group.

4.2.6 Evidence relevant to other key characteristics

(a) Humans

Regarding immunosuppression, the effects of 1,1,1-trichloroethane on the immune function of natural killer, natural cytotoxic, and natural P815 killer cells isolated from human liver were assessed in vitro by measuring the tumoricidal activity of the exposed immune cells against K562 human erythroleukaemia, WEHI-164 mouse fibrosarcoma, and P815 mouse mastocytoma cells, respectively. 1,1,1-Trichloroethane had no significant effect on the immune function of the natural killer, natural cytotoxic, and natural P815 killer cells (Wright et al., 1994).

(b) Experimental systems

Regarding immunosuppression, the effects of single and multiple 3-hour exposures to 1,1,1-trichloroethane at 350 ppm were evaluated in CD-1 mice by monitoring changes in their susceptibility to experimentally induced *Streptococcus* aerosol infection and pulmonary bactericidal activity against inhaled *Klebsiella pneumoniae*. Neither single nor 5 day repeated exposures to 1,1,1-trichloroethane had any effect on mortality or bactericidal activity (Aranyi et al., 1986).

Regarding the modulation of receptor-mediated effects, increased butyrylcholinesterase activity is associated with depleted testosterone. After continuous exposure by inhalation at 625 ppm for 30 days, 1,1,1-trichloroethane did not increase plasma butyrylcholinesterase levels in male NMRI mice, thus no evidence of receptor-mediated effects was observed (Kjellstrand

et al., 1985). Inhalation of 1,1,1-trichloroethane at 3500 ppm for 30 minutes led to decreased plasma levels of corticosterone and increased hypothalamic corticotropin-releasing factor in male Sprague-Dawley rats. Inhalation of 5000 ppm 1,1,1-trichloroethane for 30 minutes led to decreased plasma corticosterone and plasma adrenocorticotropic hormone levels, but no change in adrenocorticotropic hormone or corticotropin-releasing factor levels in the hypothalamus, hippocampus, or frontal cortex in rats. These results indicate a suppression of hypothalamic-pituitary-adrenal axis activity (Pise et al., 1998).

Regarding immortalization, 1,1,1-trichloroethane at 99 and 990 μM induced transformation in Fischer rat embryo cells (F1706). These transformed cells produced undifferentiated fibrosarcomas in inoculated newborn Fischer rats (Price et al., 1978). Syrian hamster embryo cells exposed to 1,1,1-trichloroethane at vapour concentrations of 8–23 μg/cm³ for 20 hours experienced significantly enhanced transformation by SA7 adenovirus. Conversely, exposure to the liquid did not enhance transformation (Hatch et al., 1983). 1,1,1-Trichloroethane induced a positive dose-dependent transformation response in BALB/c-3T3 cells exposed in sealed glass chambers in two separate studies (Tu et al., 1985; Milman et al., 1988). [The Working Group noted that the available studies suggest that 1,1,1-trichloroethane is capable of immortalizing cells in vitro.]

4.2.7 High-throughput in vitro toxicity screening data evaluation

The analysis of the in vitro bioactivity of the agents reviewed in *IARC Monographs* Volume 130 was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al.,

2018). 1,1,1-Trichloroethane was one of thousands of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes of the US EPA and the United States National Institutes of Health. Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is publicly available (US EPA, 2021d). A supplementary table (Annex 2, Supplementary material for Section 4, Mechanistic Evidence, web only; available from: https://publications.iarc.fr/611) contains a summary of the findings (including the assay name, the corresponding key characteristic, the resulting "hit calls" both positive and negative, and any reported caution flags) for 1,1,1-trichloroethane. The results were generated with the software "kc-hits" (key characteristics of carcinogens – high-throughput screening discovery tool) (available from: https://gitlab.com/i1650/kc-hits) using the US EPA ToxCast and Tox21 assay data and the curated mapping of key characteristics to assays available at the time of the evaluations performed for the present monograph. Findings and interpretations from these high-throughput assays for 1,1,1-trichloroethane are discussed below.

After mapping against the key characteristics of carcinogens, the ToxCast/Tox21 database contained 111 assays in which 1,1,1-trichloroethane was tested. Of these, it was found to be active in only one assay corresponding to a loss of HEK293 cell viability, in which it exhibited a half-maximal activity concentration (AC_{50}) of 57.50 μM. However, this assay was reported with a caution flag: less than 50% active and borderline activity (US EPA, 2021d). [The Working Group noted that this result is not relevant to the carcinogenicity of the chemical.]

4.3 Other relevant evidence

Groups of 10 male and 10 female F344/N rats and B6C3F$_1$ mice were given feed containing microencapsulated 1,1,1-trichloroethane at a

concentration of 5000, 10 000, 20 000, 40 000, or 80 000 ppm for 13 weeks. Relative and absolute liver weights in female rats were decreased at the highest dose. Male rats at 10 000 ppm or greater exhibited a spectrum of non-neoplastic kidney lesions, including renal tubule casts and renal tubule degeneration, consistent with hyaline droplet nephropathy (NTP, 2000).

In chronic inhalation studies, male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to 1,1,1-trichloroethane at 150, 500, or 1500 ppm for 6 hours per day, 5 days per week, for 2 years. Very slight microscopic hepatic effects, such as an accentuation of the normal hepatic lobular pattern and smaller hepatocytes with altered cytoplasmic staining around the portal vein, were seen in the liver of male and female rats at 1500 ppm and necropsied at 6, 12, and 18 months (Quast et al., 1988).

In a short-term renal toxicity study in male F344/N rats, 1,1,1-trichloroethane administered by gavage at a dose of 0.62 or 1.24 mmol/kg bw per day once daily for 21 days did not lead to hyaline droplet nephropathy, although clinical pathology suggested renal injury, and urinary protein output and aspartate aminotransferase activity were higher than in the controls (NTP, 1996).

An investigation into the relative effects of chlorinated hydrocarbons on liver and kidney function in Swiss-Webster mice exposed via a single intraperitoneal injection noted that 1,1,1-trichloroethane caused less severe liver dysfunction than did the other chlorinated hydrocarbons tested, as measured by sulfobromophthalein retention and serum GPT determination, and did not cause renal dysfunction, as measured by phenolsulfonephtalein excretion. Enlargement of hepatocytes with portal lymphocytic infiltration and vacuolation and slight necrosis were noted in the livers of animals treated with lethal concentrations of 1,1,1-trichloroethane. No microscopic changes were observed in the kidneys (Klaassen & Plaa, 1966).

5. Summary of Data Reported

5.1 Exposure characterization

1,1,1-Trichloroethane is a High Production Volume chlorinated hydrocarbon that was widely used in the 1970s and 1980s for cold cleaning and vapour degreasing of metal parts and machinery such as printing presses, printed circuit boards, plastic moulds, and many other appliances in a variety of industries including metalworking, printing, chemicals, plastics, and in numerous workplaces, such as garages. 1,1,1-Trichloroethane was also used in various other applications and products, including aerosol products, adhesives, coatings and inks, and textiles. Starting in the late 1990s, use of 1,1,1-trichloroethane was gradually phased out because of its capacity to deplete stratospheric ozone; however, it continued to be a major feedstock material for other hydrochlorofluorocarbon products, and had more minor but essential uses, such as for medical devices and aviation safety testing.

1,1,1-Trichloroethane is readily released into the environment from fugitive air emissions, and to surface water and soil, and leachates from landfills, during the production and use of both industrial and consumer products. Once in the environment, 1,1,1-trichloroethane can migrate far from its source of origin because of its long half-life, and has been measured at varying levels in urban, rural, and indoor air samples; in surface water and groundwater samples; and in soil, and waste samples. Historically, it was also present in a variety of food products, drinking-water, and many household products.

Occupational exposure to 1,1,1-trichloroethane may occur during its manufacture and during its use in a variety of industries. In these diverse workplaces, 1,1,1-trichloroethane is taken up via all routes, but inhalation is the major route of exposure. 1,1,1-Trichloroethane can be quantified in biological samples, and its metabolites

trichloroethanol and trichloroacetic acid have been quantified in blood, end-exhaled air, and urine samples from exposed humans. The number of exposed workers, however, is likely to be substantially lower now than in the 1970s to 1990s.

The general population was also probably exposed to low levels of 1,1,1-trichloroethane in the 1970s to 1990s because of widespread use. 1,1,1-Trichloroethane was present in blood samples of participants in earlier National Health and Nutrition Examination Surveys (1988–1994, NHANES III); however, more recent surveys since 2005 have not detected 1,1,1-trichloroethane in the blood, indicating diminished exposures. Implementation of the Montreal Protocol has resulted in significant decline in the production and use of 1,1,1-trichloroethane, which has caused reduction in environmental contamination and significant reduction in human exposure.

5.2 Cancer in humans

The available evidence on cancer in humans consisted of two cohort studies, five nested case–control studies, and sixteen population-based case–control studies, with most of these having been published since the previous evaluation of 1,1,1-trichloroethane by the *IARC Monographs* programme. These studies examined occupational exposure to 1,1,1-trichloroethane and the risk of lymphatic and haematopoietic malignancies, cancers of the kidney and urinary bladder, breast, and brain and nervous system, as well as melanoma of the skin and cancers of the digestive tract, bone, lung, cervix, prostate, and testis. There were also two case studies on cholangiocarcinoma and ampullary carcinoma.

Among the studies on multiple myeloma, some statistically significant positive, although imprecise, associations with ever-exposure to 1,1,1-trichloroethane were observed in two cohort studies with very small numbers of exposed cases; in one of the studies, the positive finding was observed among female but not male cohort members. There was also a statistically significant positive association with ever-exposure to 1,1,1-trichloroethane in a case–control study, based on 36 exposed cases. The association remained in sensitivity analysis reassigning jobs with low confidence in the assessment to the unexposed category. Odds ratios were elevated across most categories of exposure duration, unlagged cumulative exposure, and cumulative exposure with a 10-year lag, although no evidence of a positive trend with increasing exposure category was observed. Overall, the Working Group considered that a positive association between exposure to 1,1,1-trichloroethane and multiple myeloma was credible; however, in view of the small numbers of exposed participants, potential misclassification in exposure assessment, and potential selection bias, systematic or random errors could not be ruled out with reasonable confidence.

Among studies on other cancer types, there were few positive findings and the available studies in humans were not sufficiently informative to permit a conclusion to be drawn about the presence or absence of a causal association owing to the small numbers of exposed participants (particularly for highly exposed participants), potential misclassification in exposure assessment, and potential selection bias, information bias, or other methodological sources of bias.

5.3 Cancer in experimental animals

Treatment with 1,1,1-trichloroethane caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in two species.

1,1,1-Trichloroethane was administered by inhalation in one study in male and female Crj:BDF$_1$ mice. In males, 1,1,1-trichloroethane caused an increase in the incidence of malignant lymphoma in the spleen, bronchioloalveolar carcinoma, and bronchioloalveolar adenoma or

carcinoma (combined). In females, 1,1,1-trichloroethane caused an increase in the incidence of bronchioloalveolar adenoma or carcinoma (combined).

1,1,1-Trichloroethane was administered by inhalation in one study in F344/DuCrj rats. In males, 1,1,1-trichloroethane caused an increase in the incidence of peritoneal mesothelioma.

1,1,1-Trichloroethane was administered by oral administration (gavage) in one study in Sprague-Dawley rats. In males, 1,1,1-trichloroethane caused an increase in the incidence of leukaemia (the combination of various histological types) in a variety of organs and tissues.

5.4   Mechanistic evidence

1,1,1-Trichloroethane is rapidly absorbed in humans after either dermal/percutaneous exposure or inhalation, as confirmed by measurements of 1,1,1-trichloroethane in blood or exhaled air. Once absorbed, 1,1,1-trichloroethane is distributed primarily into the brain and adipose tissue, with significantly lower amounts in other tissues. Most pharmacokinetic data in humans indicate that < 10% of absorbed 1,1,1-trichloroethane is metabolized. Multiple cytochrome P450s (CYPs) can metabolize 1,1,1-trichloroethane to trichloroethanol and trichloroacetic acid, although CYP2E1 is believed to be the primary enzyme involved. 1,1,1-Trichloroethane is a relatively poor substrate for CYP-dependent oxidative metabolism compared with other organic solvents. Elimination of 1,1,1-trichloroethane occurs by either exhalation of unmetabolized 1,1,1-trichloroethane in the breath, or excretion of either unmetabolized 1,1,1-trichloroethane or the metabolites trichloroethanol or trichloroacetic acid in the urine. Most of the absorbed 1,1,1-trichloroethane (~90% in humans, ~95% in rats) is excreted as unmetabolized 1,1,1-trichloroethane rather than as metabolites. Studies on the absorption, distribution, metabolism, and excretion of 1,1,1-trichloroethane in experimental systems (including in rats, mice, guinea-pigs, and dogs) generally support the findings in humans and human-derived cells or tissues, although rates are faster in these systems than in humans.

Overall, the mechanistic evidence for 1,1,1-trichloroethane regarding the key characteristics of carcinogens ("is electrophilic or metabolically activated", "is genotoxic", "induces oxidative stress", "induces chronic inflammation", "modulates receptor-mediated effects" "causes immortalization", and "alters cell proliferation, cell death, or nutrient supply") is suggestive but incoherent across different experimental systems. There were no studies in humans with exposure specifically attributable to 1,1,1-trichloroethane.

There is suggestive indirect evidence for the formation of electrophilic metabolites from 1,1,1-trichloroethane in human cells in vitro. In experimental systems, there is suggestive evidence for DNA and protein binding. Consequences suggesting the formation of an electrophilic intermediate from 1,1,1-trichloroethane occur at exposure levels that are lower than for most other characterized halogenated solvents. There is suggestive evidence indicating that 1,1,1-trichloroethane is genotoxic under specific test conditions. Positive responses were obtained in comet and micronucleus-formation assays in human cells in vitro, but results were generally negative in non-human mammalian systems in vivo, and incoherent across other experimental systems in vitro. Positive responses were observed in 2 out of 10 genotoxicity studies in non-human mammalian cells in vitro, with the remaining studies yielding negative or equivocal results. Using a modified vapour-phase exposure protocol, 1,1,1-trichloroethane gave positive results for mutagenicity in two strains of *Salmonella typhimurium*.

Regarding the key characteristics "induces oxidative stress", "induces chronic inflammation", "modulates receptor-mediated effects", and "causes immortalization", there is suggestive

mechanistic evidence. 1,1,1-Trichloroethane induced oxidative stress in rodents and in mammalian experimental systems in vitro. 1,1,1-Trichloroethane also induced chronic inflammation in the kidney of rats. The results of one study indicated that 1,1,1-trichloroethane suppressed hypothalamic–pituitary–adrenal axis activity in rats, but no receptor-mediated effects were observed in another study in mice. Four studies indicated that 1,1,1-trichloroethane was capable of immortalizing rodent cells in vitro. Regarding the key characteristic "alters cell proliferation, cell death, or nutrient supply", there is suggestive but incoherent mechanistic evidence for 1,1,1-trichloroethane. In one study, exposure to 1,1,1-trichloroethane induced cortical hyperplasia in the adrenal gland of female rats and an increase in the frequency of ketone bodies in the urine of male mice, but in another chronic study in rodents, no alterations in cell proliferation, cell death, or nutrient supply were observed. 1,1,1-Trichloroethane also had no effect on either the initiation or promotion of rat liver foci in two studies. Regarding the key characteristic "is immunosuppressive", 1,1,1-trichloroethane had no effects in two studies. 1,1,1-Trichloroethane was largely inactive in the assay battery of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of 1,1,1-trichloroethane. Positive associations have been observed between exposure to 1,1,1-trichloroethane and multiple myeloma.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,1,1-trichloroethane.

6.3 Mechanistic evidence

There is *limited mechanistic evidence.*

6.4 Overall evaluation

1,1,1-Trichloroethane is *probably carcinogenic to humans (Group 2A).*

6.5 Rationale

The Group 2A evaluation for 1,1,1-trichloroethane is based on *limited evidence* for cancer in humans and *sufficient evidence* for cancer in experimental animals.

The evidence was *limited* that exposure to 1,1,1-trichloroethane causes multiple myeloma in humans. There were some statistically significant positive, although imprecise, associations between ever-exposure to 1,1,1-trichloroethane and multiple myeloma observed in two cohort studies with very small numbers of exposed cases. There was also a statistically significant positive association between ever-exposure to 1,1,1-trichloroethane and multiple myeloma in a case–control study. Odds ratios were elevated across most categories of exposure duration and cumulative exposure, but no evidence of a positive trend with increasing exposure category was observed. While positive associations were seen in the body of evidence, the small numbers of exposed participants, and concerns regarding potential misclassification in exposure assessment and potential selection bias meant that chance and bias could not be ruled out with reasonable confidence. The evidence for cancer at other sites in humans was *inadequate*: there

were few positive findings and the available studies were not sufficiently informative to permit a conclusion to be drawn about the presence or absence of a causal association.

The *sufficient evidence* for cancer in experimental animals is based on an increased incidence of either malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in two species.

The mechanistic evidence was *limited* as the findings regarding the key characteristics of carcinogens across experimental systems, including in some studies using human cells in vitro, were suggestive, but incoherent.

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