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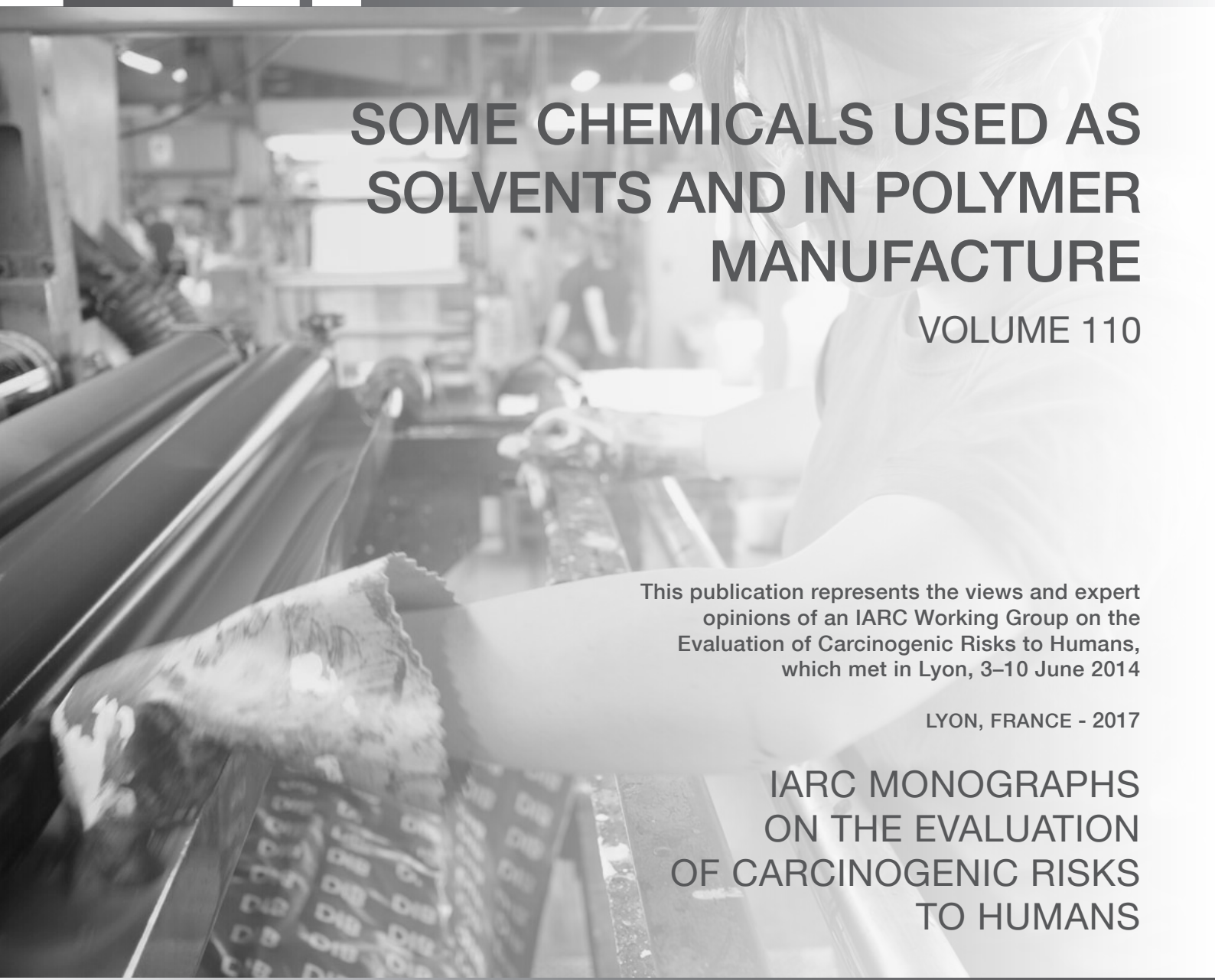


SOME CHEMICALS USED AS SOLVENTS AND IN POLYMER MANUFACTURE

VOLUME 110

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 3–10 June 2014

LYON, FRANCE - 2017

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1,2-DICHLOROPROPANE

1,2-Dichloropropane was reviewed previously by the Working Group in 1986, 1987, and 1998 (IARC, 1987, 1999). New data have since become available, and these have been incorporated, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

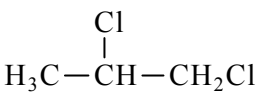
Chem. Abstr. Serv. Reg. No.: 78-87-5

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

IUPAC Systematic Name: 1,2-Dichloropropane

Synonyms: Propylene dichloride; propylene bichloride; propylene chloride; dichloro-1,2 propane; chloromethylchloride

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_3H_6Cl_2$

Relative molecular mass: 112.99

1.1.3 Chemical and physical properties of the pure substance

From OECD/SIDS (2003), unless otherwise specified

Description: Colourless liquid with a chloroform-like odour

Boiling point: 96.4 °C (94.0 to 96.8)

Melting point: –100.4 °C

Density: d_4^{25} 1.159 (O'Neil et al., 2006)

Solubility: Slightly soluble (2800 g/m^3) in water at 25 °C; soluble in alcohol, ethyl ether (Bingham & Cohrssen, 2012)

Volatility: Vapour pressure, 6.62 kPa at 25 °C; relative vapour density (air = 1), 3.9 (Verschueren, 2001)

Stability: Vapour is highly flammable and explosive

Octanol/water partition coefficient (P): log P, 1.99 (Verschueren, 2001)

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), 1 mg/m^3 = 4.62 ppm; calculated from: mg/m^3 = (relative molecular mass/24.47) × ppm.

Table 1.1 Methods for the analysis for 1,2-dichloropropane

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with acetone/ cyclohexane	GC/HECD	0.1 µg/sample	NIOSH (1994)
	Air collected in specially-prepared canister; desorb on cold trap	GC/MS GC/ECD GC/FID GC/PID	0.21 ppm NR NR NR	EPA (1999a)
	Analyte collected on sorbent tube; thermally desorb to GC	GC/MS GC/ECD GC/FID GC/PID	NR NR NR NR	EPA (1999b)
Water	Purge with inert gas and trap; desorb to GC	GC/PID GC/ECD GC/MS GC/MS	NR 0.03 µg/L 0.088 µg/L 0.018 µg/L	EPA(1988) EPA (1995a) EPA (2013) EPA (2009)
	Purge with inert gas and trap; desorb to GC	GC/MS	0.04 µg/L	EPA (1995b)
	Add internal standard (isotope labelled dichloromethane); with inert gas and trap; desorb to GC	GC/ MS	10 µg/L	EPA (1996c)
Liquid and solid wastes	Purge with inert gas and trap	GC/PID GC/HECD	NR 0.006 µg/L	EPA (1996b)
	Purge with inert gas and trap; and various other methods	GC/MS	5 µg/kg (soil/sediment) 500 µg/kg (wastes) 5 µg/L (groundwater)	EPA (1996a)

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

1.1.4 Technical products and impurities

Commercial 1,2-dichloropropane is marketed as a high-purity liquid (purity, 99–99.5%) for industrial use. Water and oxygenated organic impurities comprise a maximum of 0.05% and 0.1% of the product, respectively (Bayer AG, 1977). Trace amounts of chlorinated hydrocarbons of low relative molecular mass, such as chloropropenes and chloropropanes, are also present.

1.1.5 Analysis

Methods for the analysis of 1,2-dichloropropane have been reviewed by ATSDR (1989) and HSDB (2012). Selected methods for the analysis of 1,2-dichloropropane in various matrices are presented in Table 1.1. 1,2-Dichloropropane can be measured in the urine, blood, and exhaled air (ATSDR, 1989). There are no standardized analytical methods for the biological monitoring of exposure to 1,2-dichloropropane.

1.2 Production and use

1.2.1 Production

1,2-Dichloropropane, marketed as a solvent, is obtained as a by-product of the synthesis of propylene oxide by the chlorohydrin reaction (Mannsville Chemical Products Corp., 1984).

1,2-Dichloropropane is produced in North America, Europe, Asia, and South America. The total annual global production volume of 1,2-dichloropropane for 2001 was estimated to be 350 000 tonnes. In 2003, the estimated regional production percentages of 1,2-dichloropropane

were 64–69% in North America, 19–25% in Europe, 9–10% in South America, and 2–3% in Japan (OECD/SIDS, 2003).

Production of 1,2-dichloropropane in the USA decreased in the early 1980s since it was no longer used in paint strippers, furniture finishes, or as an insecticide (IARC, 1986; ATSDR, 1989; ACGIH, 2006). The amount manufactured and imported in countries of the European Union was between 1000 and 10 000 tonnes per year (ECHA, 2016). There were fewer data for the Asia–Pacific region, but the annual production of 1,2-dichloropropane in China was estimated as 45 000–68 000 tonnes (Chaoqun, 2008). In Japan, the annual production and import of 1,2-dichloropropane reported in 2011 was 1400 tonnes (METI, 2013).

1.2.2 Use

1,2-Dichloropropane is used primarily as a chemical intermediate in the production of other organic chemicals such as propylene, carbon tetrachloride, and tetrachloroethylene. It has been reported that co-product and raw material uses account for > 99.5% of the total production of 1,2-dichloropropane in the USA and Europe (OECD/SIDS, 2003).

Other uses for 1,2-dichloropropane include textile stain remover, oil and paraffin extractant, scouring compound, as a metal cleaner, and in insecticides (IARC, 1986). 1,2-Dichloropropane is used as a solvent or diluent in alkyd, acrylic, or polyurethane coatings and polyamide inks, as well as a metal degreaser in China (Chaoqun, 2008). According to the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) registration data, 1,2-dichloropropane is used in solvent-based degreasers and cleaning products, paint and stain removers, and glues and adhesives (ECHA, 2016).

1,2-Dichloropropane has been formulated with the active ingredient 1,3-dichloropropene for use as a grain and a soil fumigant, but has not been used in this way in the USA since 1989, or in the European Union since 2003. In Asia, the Organization for Economic Co-operation and Development (OECD) reports that soil fumigant use has been discontinued in Japan, but some agricultural uses may remain in other countries (OECD/SIDS, 2003).

In Japan, the major use of 1,2-dichloropropane is as a chemical intermediate, but it has also been used as cleaner in offset-printing processes (Kumagai et al., 2013). The use of 1,2-dichloropropane in the printing industry became common in Japan after the reduction in use of 1,1,1-trichloroethane because of the implementation of the Montreal Protocol and its amendment (UNEP, 2016). However, due to health concerns and legislative amendments, the use of 1,2-dichloropropane as a cleaning solvent in the printing industry has declined in Japan (MHLW, 2013a).

It is not known whether 1,2-dichloropropane has been used extensively in the printing industry in countries other than Japan. However, the United States Agency for Toxic Substances and Disease (ATDSR) toxicological profile for 1,2-dichloropropane, published in 1989, does not mention the use of 1,2-dichloropropane in the printing industry (ATSDR, 1989). Similarly, the WHO Environmental Health Criteria document on 1,2-dichloropropane, published in 1993, does not mention the use of 1,2-dichloropropane in the printing industry (IPCS, 1993).

1.3 Occurrence and exposure

1.3.1 Environmental occurrence

(a) Natural occurrence

1,2-Dichloropropane is not known to occur naturally.

(b) Air

Background concentrations of 1,2-dichloropropane in the air at isolated locations in the USA in 2003 were very low (mean, < 0.02 μg/m³) (McCarthy et al., 2006). Known environmental concentrations of 1,2-dichloropropane in the 1980s were summarized by WHO as: mean, 1.2 μg/m³ in Philadelphia, USA; between 0.02 and 0.04 μg/m³ after rain events in Portland, USA; and detectable at concentrations of 0.01–1.4 μg/m³ in a third of samples from 13 cities in Japan (IPCS, 1993).

(c) Water

Measurement of 1,2-dichloropropane in wells, groundwater, and surface water in the 1980s in the USA, the Netherlands, and Japan showed that 1,2-dichloropropane was only found in a minority of the water sources tested, and at concentrations that tended to be < 10 μg/L, although higher concentrations were occasionally reported (IPCS, 1993).

More recently, 1,2-dichloropropane has been found in 32 out of 324 samples of untreated ground water in Sicily, Italy, with the highest concentrations (up to 0.44 μg/L) being mainly located in plains where agricultural and industrial activity was most intense (Pecoraino et al., 2008). In the USA, 1,2-dichloropropane was detected in < 1% of 1207 samples of domestic well-water (Rowe et al., 2007). In three of these wells, the concentration of 1,2-dichloropropane exceeded the maximum contaminant level of 5 μg/L. In Cyprus, 1,2-dichloropropane was one of the most frequently detected volatile organic compounds contaminating surface water bodies, but concentrations were low (< 0.05 μg/L) (Fatta et al., 2007).

(d) Food

No data were available to the Working Group.

1.3.2 Occupational exposure

Occupational exposure to 1,2-dichloropropane may occur through inhalation and dermal contact. The main intake pathway is via the respiratory tract.

In small car-painting workshops in Italy, only one of the eight workshops investigated reported measurements of 1,2-dichloropropane that were above the level of detection (Vitali et al., 2006). In this particular shop, personal and stationary measurements of 5.3 mg/m³ were recorded during 5.5 hours of monitoring.

In another study in Italy, measurements of 1,2-dichloropropane in the breathing zone and the urine were reported for workers in plastic-product, paint-, and chemical-manufacturing industries (Ghittori et al., 1987). Most of the air concentrations were between 10 and 150 mg/m³, although two were > 400 mg/m³. Urinary concentrations (in μg/L) correlated very closely with the air concentrations.

Table 1.2 shows estimated levels of exposure to 1,2-dichloropropane (and dichloromethane) at a printing company in Osaka, Japan, following identification of a cluster of cancers of the biliary tract (cholangiocarcinoma) among company workers (Kumagai et al., 2013). The circumstances of exposure were quite specific in that the workers removed ink from rollers using volatile solvents between 300 and 800 times a day and the room had poor ventilation. There was co-exposure during several years to both dichloromethane and 1,2-dichloropropane (see the *Monograph* on Dichloromethane in the present volume). No exposure monitoring was undertaken at the time, so the Japanese National Institute of Occupational Safety and Health undertook a reconstruction experiment to estimate the exposure concentrations on the assumption that the exposure was proportional to the amount of chemical used. Additional details of the cluster investigation are given in Section 2 of this Monograph. Kumagai et al. (2013) reported

Table 1.2 Estimated exposure to 1,2-dichloropropane and dichloromethane of printers associated with cholangiocarcinoma clusters in Japan[a]

Location	Job classification and years	Number of workers	Estimated shift-TWA of dichloromethane (ppm)	Estimated shift-TWA of 1,2-dichloropropane (ppm)	Reference
Osaka	Proof printing (reconstruction)	50–100	130–360 at area estimate to the consumption at 0.938 L/h	60–210 at area estimate to the consumption at 0.812 L/h	JNIOSH (2012)
	1991–1993		80–210	120–430	Kumagai et al. (2013)
	1992–1998		190–540	100–360	
	1998–2006		NR	150–670	
Miyagi	Offset web printing 1992–2011	2	NR	80–170	Yamada et al. (2014) based on government survey data
Fukuoka	Offset web printing 1970–2008	3	0–150	62–200	Yamada et al. (2014) based on government survey data
				110–5200	Kumagai (2014)
Hokkaido	Proof printing 1985–1995	2	60–180	110–240	Yamada et al. (2014) based on government survey data
Aichi	Proof printing 1984–1995	1	240–6100	–	Kumagai (2014)

[a] The Working Group noted that the upper limits of these scenarios were estimated with the worst-case scenarios
h, hour; NR, not reported; ppm, parts per million; TWA, time-weighted average

that estimated concentrations of exposure to 1,2-dichloropropane in the proof-printing room were 120–430 ppm (mean, 220 ppm) [range, 416–1492 mg/m^3; mean, 763 mg/m^3] from 1991 to 1992/1993, 100–360 ppm (mean, 190 ppm) [range, 347–1249 mg/m^3; mean, 659 mg/m^3] from 1992/1993 to 1997/1998, and 150–670 ppm (mean, 310 ppm) [range, 520–2324 mg/m^3; mean, 1075 mg/m^3] from 1997/1998 to 2006. The front-room workers were estimated to be exposed to 1,2-dichloropropane at concentrations of 80 ppm [278 mg/m^3] from 1991 to 1992/1993, 70 ppm [243 mg/m^3] from 1992/1993, and 110 ppm [382 mg/m^3] from 1997/1998 to 2006 (Kumagai et al., 2013) (also see the *Monograph* on Dichloromethane, Section 1, Table 1.2, in the present volume).

A study of exposure to 1,2-dichloropropane by the Government of Japan showed that printers were still being exposed to 1,2-dichloropropane in 2012 (MHLW, 2013a).

1.3.3 Exposure of the general population

Very little information was available on exposure of the general population to 1,2-dichloropropane. Exposure may occur through inhalation of contaminated air, or through ingestion of contaminated water. In the United States National Health and Nutrition Examination Survey (NHANES) in 2003–2004, 1,2-dichloropropane was not detected in any of 1364 blood samples (CDC, 2009).

1.4 Regulations and guidelines

Limit values for occupational exposure to 1,2-dichloropropane in air vary from 10 ppm over 8 hours in Belgium, Ireland, Spain, and Japan, to 75 ppm over 8 hours in many other countries (Australia, Denmark, France, New Zealand, Singapore, Republic of Korea, Switzerland, USA).

Table 1.3 International limit values for occupational exposure to 1,2-dichloropropane

Country	Limit value, 8 hours	
	ppm	mg/m³
Australia	75	347
Belgium	10	47
Canada, Ontario	10	NR
Canada, Québec	75	347
Denmark	75	350
France	75	350
Hungary	NR	50
Ireland	10	46
Japan	10	NR
New Zealand	75	347
Poland	NR	50
Singapore	75	347
Republic of Korea	75	350
Spain	10	47
Switzerland	75	350
USA, Occupational Safety and Health Administration	75	350

NR, not reported; ppm, parts per million
From Working Environment Evaluation Standards (2013), IFA (2014)

Short-term limit values are 110 ppm in most jurisdictions (Table 1.3).

Dichloropropanes are included on the list of substances regulated under the European VOC Solvent Emissions Directive (European Commission, 1999; also described in Section 1.4 of the *Monograph* on Dichloromethane in the present volume.

In the USA, the Environmental Protection Agency (EPA) has regulated concentrations of 1,2-dichloropropane in drinking-water to < 5 ppb (EPA, 2014). WHO has set a provisional limit of 40 µg/L for 1,2-dichloropropane in drinking-water (WHO, 2011).

2. Cancer in Humans

Data on the association between cancer and exposure to 1,2-dichloropropane were available from several studies of cancer among printing workers in Japan (Kumagai et al., 2013; Kubo et al., 2014; Yamada et al., 2014), which were initiated after an unusual cluster of cholangiocarcinoma (cancer of the bile duct) was identified among workers in a printing plant in Osaka (Kumagai et al., 2013). Interpretation of these studies was challenging because the populations are small and workers were exposed not only to 1,2-dichloropropane, but also to more than 20 other chemicals, including dichloromethane, 1,1,1-trichloroethane, gasoline, kerosene and printing inks.

Three studies of broader groups of printing workers in Japan and other countries that were undertaken to follow up the initial findings in Japan, and that also reported data for cholangiocarcinoma were also reviewed (Okamoto et al., 2013; Vlaanderen et al., 2013; Ahrens et al., 2014). While previous studies have investigated cancer among printers (IARC, 1996), none have reported data for cholangiocarcinoma separately from all cancers of the liver, or provided data on 1,2-dichloropropane; these earlier studies on the printing industry were therefore not considered further by the Working Group.

2.1 Cholangiocarcinoma among printing workers in Japan

Three papers and a government report have presented findings concerning a cluster of cases of cholangiocarcinoma among workers at printing plants in Japan (Kumagai et al., 2013; MHLW, 2013a; Kubo et al., 2014; Yamada et al., 2014; see Table 2.1).

Table 2.1 Studies on cholangiocarcinoma and employment in the printing industry

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Japan							
Kumagai et al. (2013) Osaka, Japan, 1991–2011	62	Concentrations of 1,2-DCP and DCM estimated by simulation and mathematical modelling	Cholangiocarcinoma	All men	11	2900 (1100–6400)	Study initiated to investigate a cluster of cholangiocarcinoma in a single printing plant. Exposures were estimated but not used in the analysis. Women (n = 11) were excluded
MHLW (2013a) Osaka, Japan, 1991–2012	100	Concentrations of 1,2-DCP and DCM estimated by simulation and mathematical modelling	Cholangiocarcinoma	All workers	16	1226 (714–1963)	Follow-up investigation of the plant investigated by Kumagai et al. (2013), with more complete case finding and enumeration of the population. Women were included
Okamoto et al. (2013) Japan, 2009–2012	NR	Employment in the printing industry	Cholangiocarcinoma	All workers	76	1.28 (0.91–1.79)	Comparison of observed to expected insurance claims in "printing and related industry" to all other industries
			Intrahepatic (C22)		27	1.70 (0.91–3.15)	
			Extrahepatic (C24)		49	1.12 (0.75–1.69)	
			Cholangiocarcinoma	Men aged 30–49 yr	10	1.78 (0.63–5.00)	
			Intrahepatic (C22)		5	3.03 (0.52–17.56)	
			Extrahepatic (C24)		5	1.26 (0.34–4.71)	
Other countries							
Vlaanderen et al. (2013) Finland, Iceland, Norway, Sweden, 1961–2005	74 949	Job title	Intrahepatic cholangiocarcinoma (C22.1)	All printers and related workers, men	21	2.34 (1.45–3.57)	SIRs adjusted for country, age and period. Similar findings for women based on smaller numbers
				Typographers, men	11	2.01 (1.00–3.60)	
				Printers, men	6	3.54 (1.30–7.70)	
				Lithographers, men	2	3.91 (0.47–14.10)	

Table 2.1 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Vlaanderen et al. (2013) (cont.)			Extrahepatic cholangiocarcinoma (C23.9, C24.0, C24.1)	All printers and related workers, men	53	1.13 (0.85–1.48)	
				Typographers, men	34	1.09 (0.75–1.52)	
				Printers, men	9	1.37 (0.63–2.59)	
				Lithographers, men	0	0 (0.00–1.83)	
Ahrens et al. (2014) 9 European countries, 1995–1997	153 cases, 1421 population controls	Job title		Printing workers	5	2.42 (0.81–7.24)	ORs adjusted for country, birth year, gallstones and proxy interview
				Typesetters	3	5.78 (1.43–23.30)	

CI, confidence interval; DCM, dichloromethane; DCP, 1,2-dichloropropane; ICD, International Classification of Disease; OR, odds ratio; SIR, standardized incidence ratio; yr, year

2.1.1 *Workers at a printing plant in Osaka, Japan*

In a report on the initial investigation, Kumagai et al. (2013) described a cohort study of the relationship between occupational chemical exposure and incidence of cholangiocarcinoma (ICD10, C22.1, C24.0) among workers in the offset colour proof-printing section of a small printing company in Osaka, Japan. The study was initiated following the finding of a cluster of 11 cases of cholangiocarcinoma among workers in the printing section. The study population consisted of 62 men employed for at least 1 year between 1991 and 2006. Eleven women who were employed in the plant were excluded from the analysis as none had developed cholangiocarcinoma. Exposures were identified initially through worker interviews and company records. 1,2-Dichloropropane and dichloromethane had been used to remove ink from the transcription rubber roller (blanket), from approximately 1985 to 2006, and approximately 1985 to 1997, respectively. [The Working Group noted that a subsequent government investigation determined that exposure to dichloromethane had ended in 1996. A member of the Working Group involved with the Kumagai et al. (2013) study agreed that the government estimation was correct.]

All 62 workers had been exposed to 1,2-dichloropropane and 35 of them had also been exposed to dichloromethane. Solvent concentrations were estimated in a subsequent government investigation (MHLW, 2013b) by experimentally reconstructing past conditions in the plant (JNIOSH, 2012), as described in the Kumagai et al. (2013) report. The estimated airborne concentrations in the proof-printing room (51 workers) were 100–670 ppm [462–3090 mg/m^3] for 1,2-dichloropropane, and 80–540 ppm [278–1870 mg/m^3] for dichloromethane. In the front room (11 workers), the airborne concentrations were estimated to be 70–110 ppm [323–508 mg/m^3] for 1,2-dichloropropane and 50–130 ppm [173–451 mg/m^3] for dichloromethane.

Diagnoses for the 11 cases of cholangiocarcinoma were verified, and vital status of the cohort was ascertained from 1991 until 2011. Fourteen workers who could not be traced were assumed to be alive at the end of 2011. Age at diagnosis of cholangiocarcinoma was 25–45 years, and age at death for the six deceased individuals was 27–46 years. The primary cancer site was the intrahepatic bile duct for five patients, and the extrahepatic bile duct for six patients. All patients had been exposed to 1,2-dichloropropane for 7–17 years, and diagnosed with cholangiocarcinoma 7–20 years after their first exposure. Ten patients were also exposed to dichloromethane for 1–13 years. Known risk factors for cholangiocarcinoma were investigated among the cases, but none were found, with the exception of one patient with a silent biliary stone. The standardized mortality ratio (SMR) for cholangiocarcinoma was 2900 (expected deaths, 0.00204; 95% confidence interval, CI: 1100–6400) for all male workers combined, relative to the Japanese male population.

Kubo et al. (2014) reported on a further investigation of 111 former or current workers at the same Osaka plant as Kumagai et al. (2013), based on data from a subsequent government investigation (MHLW, 2013b) and clinical records from several hospitals. This report included 88 men and 23 women employed at any time between 1981 and 2012. Ten former workers could not be followed up. By the end of 2012, the number of cases of cholangiocarcinoma among the workers reached 17, all diagnosed before age 45 years.

At least 22 chemicals were reported to have been used at the plant during the study period. Use of dichloromethane and 1,2-dichloropropane reportedly began 1991, and ended in 1996 for dichloromethane and in 2006 for 1,2-dichloropropane, according to an investigation by the Ministry of Health, Labour and Welfare (MHLW, 2013b). Of the 17 patients with

cholangiocarcinoma, all had been exposed to 1,2-dichloropropane, 11 had been exposed to dichloromethane, and eight had been exposed to 1,1,1-trichloroethane. The period of exposure to chlorinated organic solvents ranged from 6 to 16 years. The amounts of other chemicals used were lower and the exposure period was shorter. No rate ratios comparing exposed and unexposed workers were presented.

A report of findings by an expert group assembled by the Japanese Ministry of Health, Labour and Welfare (MHLW, 2013b) provided further details on the epidemiological and industrial hygiene investigations of the cluster of cholangiocarcinoma cases at the Osaka plant (Kumagai et al., 2013; Kubo et al., 2014). The report states that various inks and solvents were used at the plant, but investigation of exposures focused on dichloromethane and 1,2-dichloropropane following a decision by a workers' compensation panel. The numbers of workers exposed to 1,2-dichloropropane and dichloromethane were the same as reported by Kubo et al. (2014). The estimated standardized incidence ratio (SIR) for cholangiocarcinoma among all workers in the Osaka plant was 1226 (95% CI, 714–1963), based on 16 observed cases in 100 employees followed until 2012. A 17th case identified later was not included in the counts of the numbers of cases exposed to each agent or in the overall SIR. Separate SIRs according to exposure were not presented. The report also described another case of cholangiocarcinoma from a different plant in Aichi Prefecture, who was exposed to dichloromethane only.

[Members of the Working Group who had been involved in the studies confirmed that the cohort and the 17 cases of cholangiocarcinoma described in MHLW (2013a) were the same as described by Kubo et al. (2014), and that the 17th case was a worker who had been hired in 1997 and was therefore unlikely to have been exposed to dichloromethane. Interpretation of the findings about cholangiocarcinoma in Japanese printers in the Osaka plant was challenging because workers were exposed to multiple chemicals, and complete information about the cohort and the agents to which it was exposed was not available to the Working Group. Enumeration and follow-up of the cohort were incomplete, and female workers were omitted from the initial study by Kumagai et al. (2013), although included in the later follow-up by Kubo et al. (2014). In addition, past exposures were assessed using interviews, company records, and experimental simulation of historical working conditions, resulting in some discrepancies between the various reports with respect to the dates and levels of exposure (e.g. specific months during which use of dichloromethane was discontinued). However, Working Group members who had been involved in all three studies on this plant agreed with the conclusion of MHLW (2013a) regarding the data on last use of dichloromethane (1996). Information about the distribution of exposures in the full cohort was also not reported. No cases were observed among women. A member of the Working Group confirmed lower exposure levels and shorter employment among women. Despite the limitations of these studies on the Osaka plant, it was clear that the risk of cholangiocarcinoma among workers in this plant was astonishingly high, and the universal exposure to solvents at concentrations far above current international limit values, the specificity of the outcome, the young ages at diagnosis and death, and the absence of other established risk factors among the cases are consistent with an occupational cause. Because the original reports did not include risk estimates for specific exposures, the Working Group attempted to estimate SIRs for cholangiocarcinoma according to exposure to the principal solvents used at the Osaka plant. Using information on the numbers of workers exposed reported by Kumagai et al. (2013), and case descriptions and the overall SIR reported by (MHLW, 2013a), the Working Group estimated that 43% of workers were exposed only to

1,2-dichloropropane, giving 0.0057 expected cases until 2012. Based on the information in Kubo et al. (2014) and MHLW (2013a) (6 cases were exposed only to 1,2-dichloropropane), the Working Group estimated the SIR for exposure to 1,2-dichloropropane only to be 6/0.0057 = 1053 (95% CI, 386–2291) and the corresponding SIR for exposure to both 1,2-dichloropropane and dichloromethane as 1487 (95% CI, 742–2660). It was not possible to estimate an SIR for exposure to dichloromethane only, because all of the workers in Osaka were exposed to 1,2-dichloropropane. Although these estimates were clearly very crude, they suggested that the relative risk for 1,2-dichloropropane only was extremely high, and it was not possible to determine which agent was responsible for the relative risk in the group exposed to both 1,2-dichloropropane and dichloromethane. The Working Group noted that new cases continue to accumulate, with five cases identified in 2012 alone.]

2.1.2 *Workers at other printing plants in Japan*

Kumagai (2014) described two additional cases from two different printing plants (not the original one in Osaka). One case in Fukuoka was also described by Yamada et al. (2014) (see below), while the second case, from Aichi Prefecture, had been exposed to dichloromethane and 1,1,1-trichloroethane, but not to 1,2-dichloropropane [Working Group members confirmed that the case exposed to dichloromethane only was the same case without exposure to 1,2-dichloropropane reported by MHLW (2013a) from the Aichi Prefecture.]

Yamada et al. (2014) reported on six workers with cholangiocarcinoma from three small printing plants with fewer than 50 workers each in Miyagi, Fukuoka and Hokkaido, Japan; these plants were separate from the Osaka printing company described above. All six workers had been exposed to 1,2-dichloropropane for 10–16 years. Using mathematical models, working-environment concentrations of 1,2-dichloropropane in the printing rooms were estimated to be 17–180 ppm [79–830 mg/m^3], and estimated exposure concentrations during the ink-removal operation were 150–620 ppm [690–2900 mg/m^3]. Shift time-weighted average (TWA) values were estimated to be 75–240 ppm [350–1100 mg/m^3]. Four of the six workers had also been exposed to dichloromethane at estimated working-environment concentrations of 0–98 ppm [0–340 mg/m^3] in the printing rooms, and 0–560 ppm [0–1900 mg/m^3] during the ink-removal operation. The two other workers had dichloromethane exposures of < 1 ppm. Shift TWA concentrations of dichloromethane were estimated to be 0–180 ppm [0–620 mg/m^3]. Other chlorinated organic solvents were also used in the ink-removal operation, but none of these exposures was common to all patients. [The Working Group noted that this study showed that there were other small printing companies with exposures similar to the Osaka plant studied by Kumagai et al. (2013), in which multiple cases of cholangiocarcinoma occurred, all of whom had long-term, high-level exposure to 1,2-dichloropropane, in addition to other chemicals and inks.]

Okamoto et al. (2013) conducted a study in Japan to assess the occurrence of cancer of the bile duct among workers in the printing industry. Medical insurance claims for cancer of the bile duct from April 2009 to March 2012 were compared for workers in the printing industry and for age-standardized controls in all other industries, using the claims database of the Japan Health Insurance Association. This association insures workers of small–medium-sized employers of all industries, but does not include employees of the previously investigated Osaka printing company. Among men aged 30–49 years in the printing industry, an elevated "standardized prevalence rate ratio" (SPRR) was reported for total cancer of the bile duct (SPRR, 1.78; 95%

CI, 0.63–5.00; 10 cases). The SPRR was higher for cancer of the intrahepatic bile duct (SPRR, 3.03; 95% CI, 0.52–17.56; 5 cases). [The Working Group noted that some of the cases reported by Yamada et al. (2014) might have also been included in the study by Okamoto et al. (2013), and that the cancers of the biliary tract in this study may not have been confirmed histologically. The "printing and related industries" category that served as the exposed group was broad, and it was not clear which types of workplaces and exposures were included. Furthermore, the study covered only a 3-year period after the use of dichloromethane and 1,2-dichloropropane had ceased. The Working Group was also uncertain as to the precise definition of the measure of association used in this study, and noted that it may be possible to interpret the SPRR as the ratio of incident claim rates.]

2.2 Cholangiocarcinoma among printing workers outside Japan

Following reports of excess cholangiocarcinoma among printing workers in Japan (Kumagai et al., 2013), data from two international studies of occupational exposure were analysed to determine whether a similar association existed in other countries (see Table 2.1).

Vlaanderen et al. (2013) conducted a cohort study using a database of four Nordic countries (Finland, Iceland, Norway, and Sweden) set up by linking occupational information from censuses to national cancer registry data using personal identity codes. Estimates of exposure to specific solvents were not used in the analysis, but dicholoromethane was known to have been used in the printing industry (Kauppinen et al., 2009). For men, elevated risks of cancer of the liver (standardized incidence ratio, SIR, 1.35; 95% CI, 1.14–1.60; 142 cases) and intrahepatic cholangiocarcinoma (SIR, 2.34, 95% CI, 1.45–3.57; 21 cases) were seen. SIRs for cancer of the liver were especially high among printers (SIR, 2.22, 95% CI, 1.44–3.28; 25 cases) and lithographers (SIR, 2.38, 95% CI, 1.03–4.70; 8 cases), and SIRs for intrahepatic cholangiocarcinoma were elevated among typographers (SIR, 2.01, 95% CI, 1.00–3.60; 11 cases) and printers (SIR, 3.54, 95% CI, 1.30–7.70; 6 cases). SIRs for extrahepatic cholangiocarcinoma were not increased (SIR, 1.13, 95% CI, 0.85–1.48; 53 cases). SIRs for women followed a similar pattern, but the number of cases was low.

Ahrens et al. (2014) reported associations between cancers of the extrahepatic bile duct and printing occupations in a multicentric study of rare cancers in Europe. Adjusted odds ratios were 2.42 (95% CI, 0.81–7.24; 5 cases) and 5.78 (95% CI, 1.43–23.29; 3 cases) for ever employment in a printing occupation or as a typesetter, respectively.

[The Working Group noted that there was some potential for overlap between Vlaanderen et al. (2013) and Ahrens et al. (2014). These studies suggested that an excess risk of cholangiocarcinoma among printing workers may to some extent be generalizable beyond Japan, but the studies did not provide risk estimates for specific agents.]

3. Cancer in Experimental Animals

The carcinogenicity of 1,2-dichloropropane in experimental animals was reviewed previously by the Working Group (IARC, 1999).

3.1 Mouse

There was one study in male and female mice given 1,2-dichloropropane by oral administration (gavage), and one study in male and female mice given 1,2-dichloropropane by inhalation.

See Table 3.1

Table 3.1 Studies of carcinogenicity with 1,2-dichloropropane in mice

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
NTP (1986) Mouse, $B6C3F_1$ (M) 104 wk	Oral administration (gavage) at a dose of 0, 125, or 250 mg/kg bw for 6 h/day, 5 days/wk 50 mice/group	Hepatocellular adenoma[a]: 7/50 (14%)*, 10/50 (20%), 17/50 (34%)** Hepatocellular carcinoma: 11/50 (22%), 17/50 (34%), 16/50 (32%) Hepatocellular adenoma or carcinoma (combined)[b]: 18/50 (36%)*, 26/50 (52%)[c], 33/50 (66%)**	*$P < 0.05$ (trend) **$P < 0.05$	Purity, > 99% Non-tumorous liver lesions were seen with an increased incidence in male mice at both dosing levels. Lesions included hepatomegaly, focal hepatocellular necrosis, and centrilobular necrosis
NTP (1986) Mouse, $B6C3F_1$ (F) 104 wk		Hepatocellular adenoma[a]: 1/50 (2%)*, 5/50 (10%), 5/50 (10%)** Hepatocellular carcinoma: 1/50 (2%), 3/50 (6%), 4/50 (8%) Hepatocellular adenoma or carcinoma (combined)[b]: 2/50 (4%)*, 8/50 (16%)**, 9/50 (18%)**	*$P < 0.05$ (trend) **$P < 0.05$	Purity, > 99% Mortality was increased in female mice at the highest dose
Matsumoto et al. (2013) Mouse, $B6D2F_1$ (M) 24 mo	Inhalation at a concentration of 0, 32, 80, or 200 ppm for 6 h/day, 5 days/wk 50 mice/group	Bronchiolo-alveolar adenoma: 5/50, 14/50*, 9/50, 12/50 Bronchiolo-alveolar carcinoma: 4/50, 6/50, 6/50, 8/50 Bronchiolo-alveolar adenoma or carcinoma (combined): 9/50, 18/50*, 14/50, 18/50* Histiocytic sarcoma: 1/50, 4/50, 7/50*, 0/50 Harderian gland adenoma: 1/50**, 2/50, 3/50, 6/50 Splenic haemangioma: 0/50, 1/50, 0/50, 1/50 Splenic haemangiosarcoma: 0/50, 3/50, 3/50, 5/50* Splenic haemangioma or haemangiosarcoma (combined): 0/50, 4/50, 3/50, 6/50* Mammary gland adenocarcinoma: 0/50, 0/50, 0/50, 1/50	*$P < 0.05$ **$P < 0.05$ (trend)	Purity, > 99.5%

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Matsumoto et al. (2013) Mouse, B6D2F$_1$ (F) 24 mo		Bronchiolo-alveolar adenoma: 1/50, 4/50, 4/50, 4/50 Bronchiolo-alveolar carcinoma: 1/50**, 1/50, 1/50, 4/50 Bronchiolo-alveolar adenoma or carcinoma (combined): 2/50**, 4/50, 5/50, 8/50* Histiocytic sarcoma: 0/50, 1/50, 0/50, 1/50 Harderian gland adenoma: 2/50, 2/50, 2/50, 2/50 Splenic haemangioma: 0/50, 0/50, 1/50, 0/50 Splenic haemangiosarcoma: 2/50, 0/50, 0/50, 0/50 Splenic haemangioma or haemangiosarcoma (combined): 2/50, 0/50, 1/50, 0/50 Mammary gland adenocarcinoma: 0/50, 0/50, 3/50, 1/50	*$P < 0.05$ **$P < 0.05$ (trend)	Purity, > 99.5%

[a] Historical controls (hepatocellular adenoma): males, 22/149 (14.7%); females, 8/148 (5.4%)

[b] Historical controls (hepatocellular adenoma or carcinoma, combined): males, 44/149 (29.5%); females, 11/148 (7.4%)

[c] As listed in the original report

F, female; h, hour; M, male; mo, month; ppm, parts per million; wk, week

3.1.1 Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 7–9 weeks) were given 1,2-dichloropropane (purity, > 99%) in corn oil by gavage at a dose of 0, 125, or 250 mg/kg bw per day, 5 days per week, for 103 weeks. Mortality was increased in females at the highest dose. The incidence of liver adenoma [hepatocellular adenoma] and liver adenoma or carcinoma (combined) [hepatocellular adenoma or carcinoma (combined)] in treated groups of males and females was higher than that in the concurrent control groups. Non-tumorous liver lesions were seen with an increased incidence in males at both dose levels, and included hepatomegaly, focal hepatocellular necrosis, and centrilobular necrosis (NTP, 1986).

3.1.2 Inhalation

Groups of 50 male and 50 female B6D2F$_1$ mice (age, 6 weeks) were given 1,2-dichloropropane at a concentration of 0 (control), 32, 80, or 200 ppm (v/v) by whole-body inhalation for 104 weeks (Matsumoto et al., 2013). Exposure to 1,2-dichloropropane significantly increased the incidences of bronchiolo-alveolar adenoma, and bronchiolo-alveolar adenoma or carcinoma (combined) in males. There was also a significant positive trend in the incidence of adenoma of the Harderian gland in males. The incidence of bronchiolo-alveolar adenoma or carcinoma (combined) was significantly increased in females. In addition, there was a significant positive trend in the incidence of bronchiolo-alveolar carcinoma in females. Non-neoplastic lesions, including atrophy and respiratory metaplasia of the olfactory epithelium, and of the submucosal gland epithelium of the nasal cavity or respiratory epithelium were also significantly increased in females. There was a significant increase in the incidence of histiocytic sarcoma in males at the intermediate dose, and a significant increase in the incidence of splenic haemangiosarcoma in males at the highest dose.

3.2 Rat

There was one study in male and female rats given 1,2-dichloropropane by oral administration (gavage), and one study in male and female rats given 1,2-dichloropropane by inhalation.

See Table 3.2

3.2.1 Oral administration

Groups of 50 male and 50 female F344/N rats (age, 7–9 weeks) were given 1,2-dichloropropane (purity, > 99%) in corn oil by gavage at a dose of 0, 62, or 125 mg/kg bw per day, 5 days per week, for 103 weeks (NTP, 1986). Female rats in the group at the highest dose demonstrated decreased survival, and male and female rats at the highest dose also showed decreased body weight. The incidence of adenocarcinoma of the mammary gland was significantly increased in females at the highest dose (1/50, 2/50, and 5/50 in the control, low-dose, and high-dose groups, respectively). The report noted that three of the five adenocarcinomas of the mammary gland in the female rats were of low-grade malignancy, and may represent a variant of fibroadenoma. [The Working Group accepted the data from this study because of the rigorous pathology peer review described in the report.] There were no effects on tumour incidence in male rats exposed to 1,2-dichloropropane.

3.2.2 Inhalation

Groups of 50 male and 50 female F344 rats (age, 6 weeks) were given 1,2-dichloropropane at a concentration of 0 (control), 80, 200, or 500 ppm by whole-body inhalation for 104 weeks (Umeda et al., 2010). At 2 years, there was a significant increase in the incidence of papilloma of the nasal cavity in male and female rats at the

Table 3.2 Studies of carcinogenicity with 1,2-dichloropropane in rats

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
NTP (1986) Rat, F344/N (M, F) 103 wk	Oral administration (gavage) at a dose of 0, 62, or 125 mg/kg bw for 6 h/day, 5 days/wk 50 rats/group	Mammary gland fibroadenoma: 15/50 (30%), 20/50 (40%), 7/50 (14%) Mammary gland adenocarcinoma: 1/50 (2%)*, 2/50 (4%), 5/50 (10%)**	*$P < 0.05$ (trend) **$P < 0.05$	Purity, > 99% [No effects on tumour incidences in males]
Umeda et al. (2010) Rat, F344 (M) 104 wk	Inhalation at a concentration of 0, 80, 200, or 500 ppm for 6 h/day, 5 days/wk 50 rats/group	Nasal cavity papilloma: 0/50*, 0/50, 3/50 (6%), 15/50 (30%)** Esthesioneuroepithelioma [olfactory neuroblastoma]: 0/50, 2/50 (4%), 1/50 (2%), 0/50	*$P \leq 0.01$ (trend) **$P \leq 0.01$	Purity, > 99.5%
Umeda et al. (2010) Rat, F344 (F) 104 wk	Inhalation at a concentration of 0, 80, 200, or 500 ppm for 6 h/day, 5 days/wk 50 rats/group	Nasal cavity papilloma: 0/50*, 0/50, 0/50, 9/50 (18%)** Esthesioneuroepithelioma [olfactory neuroblastoma]: 0/50, 0/50, 0/50, 0/50		

F, female; h, hour; M, male; ppm, parts per million; wk, week

highest dose. There were three cases of esthesioneuroepithelioma [olfactory neuroblastoma] in exposed males. [The olfactory neuroblastoma is an uncommon neoplasm of the sinonasal tract.]

The total incidence of nasal tumours increased in a concentration-dependent manner. The incidences of hyperplasia of the transitional cell epithelium and squamous cell hyperplasia of the respiratory epithelium in this 2-year study also increased in a concentration-dependent manner, and these lesions were morphologically different from the hyperplasia of the respiratory epithelium, including goblet cell metaplasia, observed in a 13-week experiment reported in the study article. [These hyperplastic lesions may be preneoplastic.] In the 2-year study, there were significantly increased incidences of atrophy and respiratory metaplasia of the olfactory epithelium, and inflammation and squamous cell metaplasia of the respiratory epithelium. [It is known that olfactory sensory neurons differ between species (rat versus mouse) in terms of tissue-selective toxicity (Zhuo et al., 1999; Bozza et al., 2002).]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Absorption

(a) Humans

In workers exposed to 1,2-dichloropropane in air, there was a linear correlation between concentration in the breathing zone and concentration in the urine, indicating systemic absorption via the respiratory tract (Ghittori et al., 1987). No direct data on the absorption of 1,2-dichloropropane in humans exposed by oral or dermal administration were available. However, systemic toxicities after ingestion indicate oral absorption through the gastrointestinal tract (Chiappino & Secchi, 1968; Perbellini et al., 1985, Pozzi et al., 1985).

An estimate of the human blood:air partition coefficient of 10.7 ± 0.5 was obtained in vitro, indicating that under equilibrium conditions, respiratory uptake of 1,2-dichloropropane from inhaled air would be expected to be similar to

that for chlorinated compounds such as chloroform and trichloroethylene, all of which have partition coefficients of around 10 (Sato & Nakajima, 1979).

(b) Experimental systems

Hutson et al. (1971) gave male and female rats an oral dose of radiolabelled 1,2-dichloropropane at 4–5 mg/kg bw. After 24 hours, 74–95% of the radiolabel was recovered in the urine or expired air. Similarly, Timchalk et al. (1991) gave male and female rats a single oral dose of radiolabelled 1,2-dichloropropane at 1 or 100 mg/kg bw, and 1 mg/kg bw daily for 8 days. After 48 hours, more than 80% of the radiolabel was recovered in the urine or expired air, with less than 10% in the faeces. These studies indicated near complete systemic absorption of 1,2-dichloropropane via the oral route.

Timchalk et al. (1991) exposed male and female rats to air containing radiolabelled 1,2-dichloropropane at a concentration of 5, 50, or 100 ppm for 6 hours. After 48 hours, 80% or more of the radiolabel was recovered in the urine and expired air, with less than 10% in the faeces, indicating near complete systemic absorption via the inhalation route.

No direct data were available on dermal absorption. However, systemic effects, including death, have been observed after dermal administration of 1,2-dichloropropane in rabbits, indicating systemic absorption through the skin (Smyth et al., 1969).

4.1.2 Distribution

(a) Humans

No data on tissue distribution of 1,2-dichloropropane in humans were available to the Working Group. Meulenberg & Vijverberg (2000) used empirical regression models to predict human tissue:air partition coefficients based on measured saline:air and oil:air partition coefficients. Based on these predictions, tissue:blood partition coefficients in humans were estimated to range from 0.9 (kidney) to 28 (fat), depending on the lipid content of the tissue. These values suggested that 1,2-dichloropropane would be widely distributed to tissues after systemic delivery.

(b) Experimental systems

In rats exposed to 1,2-dichloropropane by inhalation, reported peak blood concentrations were 0.06 (0.06), 0.92 (1.00), and 3.87 (4.55) μg/g in males (females) exposed at 5, 50 and 100 ppm, respectively, indicating systemic delivery of 1,2-dichloropropane in blood via the circulatory system (Timchalk et al., 1991). No sex differences were found; peak concentrations were similar in males and females. No direct data on tissue distribution of 1,2-dichloropropane were available to the Working Group. However, Gargas et al. (1989) reported measured tissue:blood partition coefficients in the range of 0.64 (muscle) to 27 (fat), suggesting that 1,2-dichloropropane is widely distributed to tissues after systemic delivery.

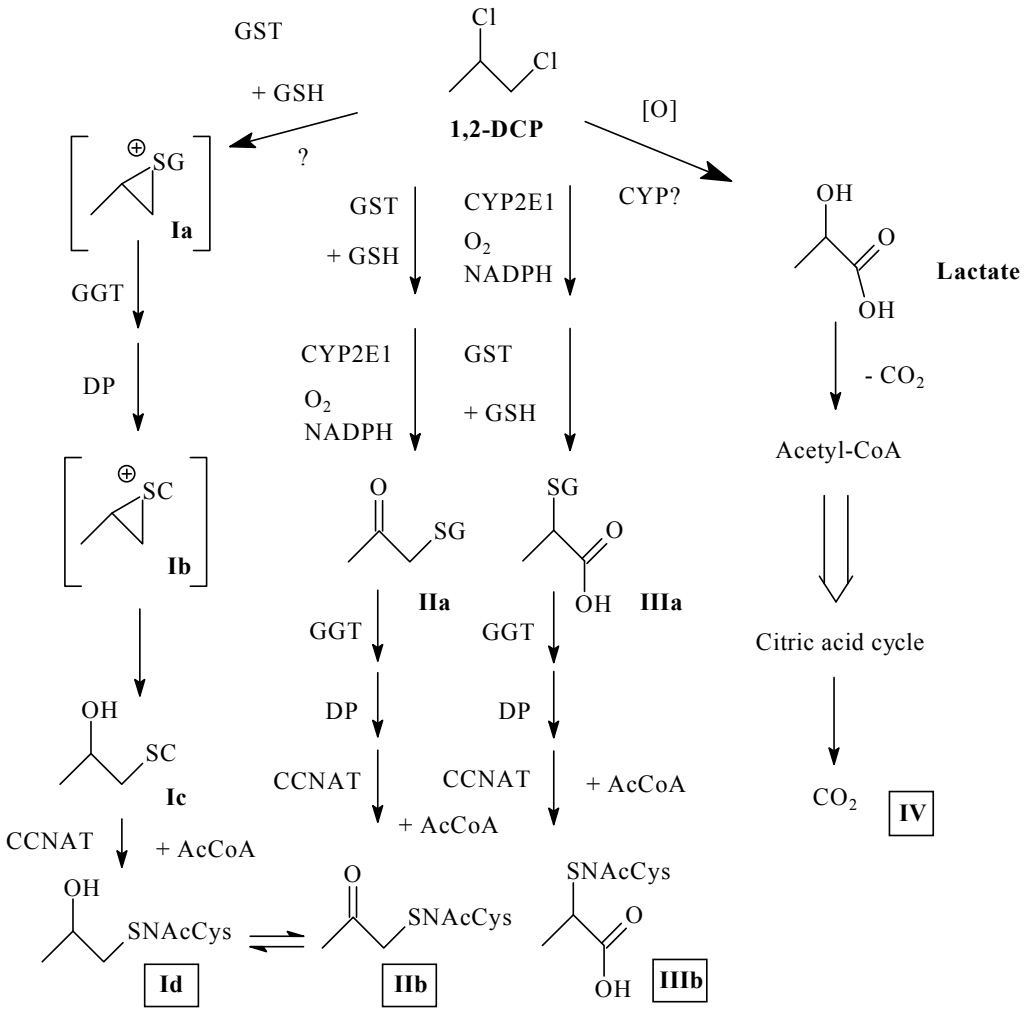
4.1.3 Metabolism

(a) Overview

There are four pathways for the metabolism of 1,2-dichloropropane (summarized in Fig. 4.1). The two best-characterized of these four pathways involve sequential action of cytochrome P450 (CYP) and glutathione *S*-transferase (GST); the other two pathways are less well characterized with respect to the enzymes involved, but do produce metabolites that have been isolated and identified. Some metabolites have been isolated (indicated in Fig. 4.1 by rectangles around their number designations), while others are presumed to occur based on the known chemistry of similar haloalkanes.

1,2-Dichloropropane undergoes sequential GST-mediated conjugation with glutathione (GSH) and then oxidative dehalogenation by cytochrome P450 (CYP) (or vice versa), to generate two GSH conjugates (see Fig. 4.1;

Fig. 4.1 Pathways for the metabolism of 1,2-dichloropropane



Adapted from Timchalk et al. (1991) and Bartels & Timchalk (1990)
Known and proposed pathways for the metabolism of 1,2-DCP (1,2-dichloropropane). Names of metabolites that have been recovered and identified are indicated in rectangles, whereas those that are chemically unstable and reactive are indicated in parentheses. Metabolites: Ia and Ib, glutathione (GSH) and cysteine-containing episulfonium ions; Ic, *S*-(2-hydroxypropyl)-L-cysteine; Id, *N*-acetyl-*S*-(2-hydroxypropyl)-L-cysteine; IIa, *S*-(2-oxopropyl)glutathione; IIb, *N*-acetyl-*S*-(2-oxopropyl)-L-cysteine; IIIa, *S*-(1-carboxylethyl)glutathione; IIIb, *N*-acetyl-*S*-(1-carboxyethyl)-L-cysteine; IV, carbon dioxide. Other abbreviations: AcCoA, acetyl-coenzyme A; CCNAT, cysteine conjugate *N*-acetyltransferase; CYP, cytochrome P450; DP, dipeptidase; GGT, γ-glutamyltransferase; GST, glutathione *S*-transferase

metabolites IIa [S-(2-oxopropyl)glutathione] and IIIa [*S*-(1-carboxyethyl)glutathione]). Guengerich et al. (1991) showed that CYP2E1 is very active in the metabolism of 1,2-dichloropropane and similar halogenated alkanes of low relative molecular mass, including dichloromethane. The two GSH conjugates are processed by the standard reaction pathway in the kidneys (Lash et al., 1988) to form the corresponding mercapturates (Fig. 4.1; metabolites IIb [*N*-acetyl-*S*-(2-oxopropyl)-L-cysteine] and IIIb [*N*-acetyl-*S*-(1-carboxyethyl)-L-cysteine]). In addition to these two mercapturates, which have been identified in the urine of rats exposed to 1,2-dichloropropane (Bartels & Timchalk, 1990), metabolite IIb (*N*-acetyl-*S*-(2-oxopropyl)-L-cysteine) can

be reduced to form metabolite Id (*N*-acetyl-*S*-(2-hydroxypropyl)-L-cysteine) (also called 2-hydroxypropyl-mercapturic acid), which has also been identified in the urine of rats exposed to 1,2-dichloropropane.

Alternatively, GSH conjugation of 1,2-dichloropropane has also been suggested to form an episulfonium ion (Fig. 4.1; metabolite Ia [GSH-containing episulfonium ion]), which should undergo spontaneous hydrolysis to produce the cysteine conjugate (Fig. 4.1; metabolite Ic [*S*-(2-hydroxypropyl)-L-cysteine]). This can in turn undergo *N*-acetylation to form metabolite Id [*N*-acetyl-*S*-(2-hydroxypropyl)-L-cysteine]. Metabolite Id has been identified in the urine of rats exposed to 1,2-dichloropropane, but this does not constitute definitive proof for this pathway, since it is also formed through sequential CYP–GST metabolism, as described previously. Based on studies with isotope-labelled 1,2-dichloropropane, Bartels & Timchalk (1990) have determined that formation of the mercapturate Ia through a GST-only pathway is negligible, and that it is most likely that the sequential CYP–GST pathway predominates.

A fourth presumed fate of 1,2-dichloropropane is oxidative dechlorination that leads to formation of lactate, and ultimately release of carbon dioxide. While this pathway is presumed to occur as indicated in Fig. 4.1, with carbon dioxide being detected as derived in part from 1,2-dichloropropane, the mechanism for conversion of 1,2-dichloropropane to lactate has not been determined (while a CYP enzyme is expected to be involved, this has not yet been demonstrated).

The CYP2E1 and GST reactions occur primarily in the liver, which is very efficient at excreting GSH conjugates (Fig. 4.1, metabolites Ia, IIa, and IIIa) into the bile. Because the biliary tract is a significant site of gamma-glutamyltransferase (GGT) and dipeptidase activities, some of the excreted GSH conjugates will be converted to the corresponding cysteine conjugates. These undergo enterohepatic and renal–hepatic circulation, ultimately forming the mercapturates (Fig. 4.1, metabolites Id, IIb, and IIIb). The GSH-conjugation reaction also occurs in the kidney, although the renal activity of CYP2E1 is relatively low, especially in humans. Formation of reactive episulfonium ions (Fig. 4.1, metabolites Ia and Ib) can occur via GSH conjugation, especially at higher concentrations of 1,2-dichloropropane when CYP2E1 is saturated. When this reaction occurs in the liver, excretion of these reactive metabolites into the biliary tract may be partly responsible for toxicity of 1,2-dichloropropane in the liver and/or the biliary tract.

(b) Humans or human-derived tissues

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

The only published study of the metabolism of 1,2-dichloropropane in human-derived tissues was that of Guengerich et al. (1991), which demonstrated the key role of CYP2E1 in the metabolism of several small halogenated hydrocarbons. 1,2-Dichloropropane was found to be one of the better substrates among the chemicals tested with purified human liver CYP2E1 and human liver microsomes. Thus, while trichloroethane and chlorzoxazone were metabolized by the purified human liver CYP2E1 at rates of 1.6 and 3 nmol of product formed/minute per nmol CYP, respectively, the rate of metabolism of 1,2-dichloropropane was 1.1 nmol of product formed/minute per nmol CYP. This rate compared quite favourably to that of purified CYP2E1 with trichloroethylene, which was only slightly lower at 0.97 nmol of product formed/minute per nmol CYP. Further evidence that the metabolism of 1,2-dichloropropane by human liver microsomes is predominantly mediated by CYP2E1 came from studies of immunoinhibition with specific antibodies to CYP2E1.

(c) Experimental systems

Almost all of the published studies on 1,2-dichloropropane metabolism were either in vivo in rats or in various in-vitro preparations from rat liver tissue. Publications are listed in chronological order.

(i) In vivo

Hutson et al. (1971) exposed rats to ^{14}C-labelled 1,2-dichloropropane by stomach tube and examined products in the urine, faeces, and expired air for 96 hours. A relatively high proportion of the administered dose (approximately 20%) was recovered as carbon dioxide in the expired air during the first 24 hours. Little apparent difference was detected between males and females over the 96-hour collection period.

Jones & Gibson (1980) treated male Sprague-Dawley rats with 1,2-dichloropropane by either single intraperitoneal injection or daily oral dosing for 4 days. *N*-Acetyl-*S*-(2-hydroxypropyl)-L-cysteine (Fig. 4.1; metabolite Id) was the major urinary metabolite recovered over 96 hours. Another significant, although relatively minor, metabolite was β-chlorolactate; this finding provides support for carbon dioxide formation via the metabolic route shown in Fig. 4.1.

Timchalk et al. (1991) studied pharmacokinetics and metabolism in male and female Fischer 344 rats given ^{14}C-labelled 1,2-dichloropropane by oral administration or inhalation. By either route, metabolism was rapid, with three urinary mercapturates identified (Fig. 4.1; metabolites Id, IIb, IIIb), and radiolabelled carbon dioxide detected in expired air. As would be expected, the liver contained the highest proportion of radiolabel after oral exposure.

Bartels & Timchalk (1990) treated male and female Fischer 344 rats with radiolabelled 1,2-dichloropropane as a single oral dose at 100 mg/kg bw in corn oil, and measured metabolites in urine. As noted above, these studies were the first to demonstrate the recovery of three different mercapturates in vivo (Fig. 4.1; metabolites Id, IIb, and IIIb). Based on isotope labelling, Bartels & Timchalk (1990) also found no evidence of the pathway involving formation of an episulfonium ion being active.

Timchalk et al. (1991) followed up these studies with a more detailed analysis of the metabolism of ^{14}C-labelled 1,2-dichloropropane by exposing Fischer 344 rats both orally and by inhalation. Distribution of radioactivity in rats exposed to 1,2-dichloropropane at 5, 50, or 100 ppm by inhalation showed the predominance of urine as a route of recovery of metabolites. The concentration of carbon dioxide in expired air increased with 1,2-dichloropropane at 5 to 50 ppm, but decreased at 100 ppm, suggesting saturation of the metabolic pathway through lactate and the citric acid cycle. No sex-specific differences in pharmacokinetics or metabolism by either the oral or inhalation exposure route were observed.

(i) In vitro

The earliest study of the metabolism of 1,2-dichloropropane in vitro used rat liver microsomes (Van Dyke & Wineman, 1971). These authors examined the dechlorination of a series of chloroethanes and propanes. The dechlorination reaction was shown to require NADPH and oxygen, and be inducible by phenobarbital and benzo[*a*]pyrene, but not by methylcholanthrene. These results implicated the CYP monooxygenase system. However, this study also showed that a factor present in the supernatant was necessary for optimal activity. Among six different chlorinated propanes examined as substrates during the course of a 30-minute incubation, 1,1,2-trichloropropane was by far the best substrate (41% dechlorination). Of the dichlorinated propanes, 1,1-dichloropropane was by far the best substrate (25% dechlorination), whereas 1,2-dichloropropane was only a slightly better substrate than 2,2-dichloropropane (6% versus 2.5% dechlorination).

The dependence on a factor present in the supernatant for an optimal dechlorination reaction rate for 1,2-dichloropropane and the other chloropropanes was subsequently shown to be due to a requirement for GSH. Before isolation of mercapturates as the primary metabolites of 1,2-dichloropropane, Trevisan et al. (1989, 1993) and Imberti et al. (1990) showed an association between toxicity caused by 1,2-dichloropropane in rats and GSH status, and that exposure to 1,2-dichloropropane leads to depletion of GSH. Trevisan et al. (1993) further showed that blockage of oxidative metabolism with carbon monoxide prevented GSH depletion in the rat kidney, demonstrating the importance of the GSH-conjugation reaction in the metabolism of 1,2-dichloropropane.

Tornero-Velez et al. (2004) compared the kinetics of metabolism in rat liver microsomes of various dichlorinated and dibrominated alkanes, with carbon-chain lengths ranging from two to four. In general, metabolism was fastest with higher chain length and the presence of bromine rather than chlorine. 1,2-Dichloropropane exhibited a catalytic efficiency (i.e. V_{max}/K_m) that was approximately 25% of that of the most efficiently catalysed substrate, which was 1,3-dichloropropane.

Although most studies in mammals have suggested that CYP2E1 is the primary CYP enzyme that metabolizes 1,2-dichloropropane through the oxidative pathway, other CYPs also exhibit activity. For example, Lefever & Wackett (1994) studied the oxidation of several polychlorinated ethanes and 1,2-dichloropropane by cytochrome $P450_{CAM}$, which is now known as CYP101. Oxidation activity was highest with the more highly chlorinated ethanes (e.g. hexachloroethane and pentachloroethane); 1,2-dichloropropane was oxidized to chloroacetone at a rate that was only 25% of that of these two highly chlorinated ethanes and was only 5% of that of camphor. Nonetheless, these data suggest the possibility that other CYPs besides CYP2E1 may metabolize 1,2-dichloropropane.

4.1.4 Excretion

(a) Humans

Ghittori et al. (1987) measured 1,2-dichloropropane in the urine of men exposed occupationally, indicating that excretion of the parent compound occurs in urine.

(b) Experimental systems

In experimental animals, 1,2-dichloropropane is eliminated primarily as metabolites in urine and expired carbon dioxide, with lesser amounts expired as volatile organic compounds, and excreted in the faeces (Hutson et al., 1971; Timchalk et al., 1991). At 24 hours after oral administration in rats, Hutson et al. (1971) reported that 80–90% of the administered dose was eliminated in the faeces, urine, and expired air, of which urine accounted for 50.2%, carbon dioxide accounted for 19.3%, and expired volatiles accounted for 23.1%. Similarly, in rats exposed orally or by inhalation, Timchalk et al. (1991) reported 37–65% recovery in the urine, or 18–40% recovery in expired air, depending on dose. The amount expired as volatile organic compounds increased with dose or concentration, and in all cases the majority of the expired volatile organic material was found to be unchanged 1,2-dichloropropane (Timchalk et al., 1991). This dose-dependency is consistent with dose-dependent saturation of 1,2-dichloropropane metabolism (Timchalk et al., 1991). Overall, elimination is fairly rapid, with the majority of the administered dose excreted in the first 24 hours after exposure (Hutson et al., 1971; Timchalk et al., 1991).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

See Table 4.1

The genetic toxicology of 1,2-dichloropropane has been reviewed previously by the Working Group (IARC, 1999). There is evidence for induction of base-pair mutation in two studies in *Salmonella typhimurium* (TA100, TA1535 [De Lorenzo et al., 1977, Principe et al., 1981]), with and without an exogenous metabolic system, but not in a third study (Haworth et al., 1983). Stolzenberg & Hine (1980) tested 1,2-dichloropropane at a lower dose, which may explain the negative results in that study. Results were negative in TA1537, TA1538, TA98, and TA1978 strains (De Lorenzo et al., 1977; Principe et al., 1981; Haworth et al., 1983). Results were also negative in one study in *Streptomyces coelicolor* (Principe et al., 1981). 1,2-Dichloropropane induced weak mutagenic effects, but no chromosomal effects in *Aspergillus nidulans* (Principe et al., 1981; Crebelli et al., 1984). It did not induce sex-linked recessive lethal mutation in *Drosophila melanogaster* (Woodruff et al., 1985). In Chinese hamster ovary cells in culture, 1,2-dichloropropane induced sister-chromatid exchange and chromosomal aberration, both with and without exogenous metabolic activation (Galloway et al., 1987; von der Hude et al., 1987).

The acute toxicity and mutagenicity of halogenated aliphatic compounds was assessed in a test for somatic mutation and recombination in *Drosophila melanogaster* (wing spot test). Compared with several structurally related compounds, the median lethal concentration (LC_{50}) of 1,2-dichloropropane was high (14.4 µg/L). At ½ LC_{50}, slight but statistically significant positive effects in terms of wing-spot number frequencies were noted (Chroust et al., 2007).

1,2-Dichloropropane was not mutagenic in the dominant-lethal assay in rats in a study by EPA (1989) in which male Sprague-Dawley rats were exposed to drinking-water containing 1,2-dichloropropane at a concentration of 0.024%, 0.10%, or 0.24% (w/v) for 14 weeks. The positive control, cyclophosphamide (100 mg/kg bw, single oral dose), induced a significant dominant lethal effect in the same study (EPA, 1989).

Male B6C3F_1 and *Gpt* Delta C57BL/6J mice were exposed to 1,2-dichloropropane (0, 150, 300, or 600 ppm), dichloromethane (400, 800, or 1600 ppm), or combinations of both solvents (1,2-dichloropropane plus dichloromethane at 150 plus 400 ppm and 300 plus 800 ppm), by inhalation (6 hours per day, 5 days per week, for 6 weeks for each agent, or for 4 weeks for the combination, respectively). Genotoxicity was assessed by *Pig-a* gene mutation and assays for micronucleus formation in peripheral blood, and by *Gpt* mutation and comet assays in the liver. *Pig-a* mutation frequencies and micronucleus incidences were not significantly increased by any exposure. In the liver, DNA damage as measured by the comet assay (tail intensity) was increased in a dose-dependent manner by 1,2-dichloropropane (being significant at 300 ppm), but not by dichloromethane (Suzuki et al., 2014). There was a significant increase in comet tail intensity at a lower dose of 1,2-dichloropropane (150 ppm) after co-exposure with dichloromethane (400 ppm) (Suzuki et al., 2014). *Gpt* mutations were not induced after exposure to 1,2-dichloropropane at 300 ppm, but were significantly increased after co-exposure to 1,2-dichloropropane (300 ppm) and dichloromethane (800 ppm) (Suzuki et al., 2014). [The Working Group noted that a plausible explanation for this result was that co-exposure to dichloromethane leads to saturation of CYP2E1, leading to greater bioactivation of 1,2-dichloropropane through the GSH pathway.]

4.3 Biochemical and cellular effects

In-vitro experiments using renal cortical slices from the kidneys of male Wistar rats showed that exposure to 1,2-dichloropropane caused loss of organic anion accumulation (a

Table 4.1 Studies of genotoxicity with 1,2-dichloropropane

Test system	Results[a]		Concentration[b] (LEC or HIC)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, reverse mutation	+	+	5 000	De Lorenzo et al. (1977)
Salmonella typhimurium TA100, reverse mutation	–	–	565	Stolzenberg & Hine (1980)
Salmonella typhimurium TA100, reverse mutation	+	+	2 900	Principe et al. (1981)
Salmonella typhimurium TA100, reverse mutation	(+)	–	5 000	Haworth et al. (1983)
Salmonella typhimurium TA1535, reverse mutation	+	+	5 000	De Lorenzo et al. (1977)
Salmonella typhimurium TA1535, reverse mutation	+	+	2 900	Principe et al. (1981)
Salmonella typhimurium TA1535, reverse mutation	(+)	–	5 000	Haworth et al. (1983)
Salmonella typhimurium TA1537, reverse mutation	–	–	5 800	Principe et al. (1981)
Salmonella typhimurium TA1537, reverse mutation	–	–	1 666	Haworth et al. (1983)
Salmonella typhimurium TA1538, reverse mutation	–	–	5 800	Principe et al. (1981)
Salmonella typhimurium TA98, reverse mutation	–	–	5 800	Principe et al. (1981)
Salmonella typhimurium TA98, reverse mutation	–	–	5 000	Haworth et al. (1983)
Salmonella typhimurium TA1978, reverse mutation	–	–	25 000	De Lorenzo et al. (1977)
Streptomyces coelicolor, forward mutation	–	NT	58 000	Principe et al. (1981)
Aspergillus nidulans, genetic crossing-over	–	NT	17 400	Crebelli et al. (1984)
Aspergillus nidulans, forward mutation	(+)	NT	58 000	Principe et al. (1981)
Drosophila melanogaster, sex-linked recessive lethal mutations	–	NR	7200 ppm, inhalation	Woodruff et al. (1985)
Chinese hamster ovary cells, sister-chromatid exchange, in vitro	+	+	113	Galloway et al. (1987)
Chinese hamster lung fibroblast V79 cells, sister-chromatid exchange, in vitro	+	+	370	von der Hude et al. (1987)
Chinese hamster ovary cells, chromosomal aberration, in vitro	(+)	(+)	660	Galloway et al. (1987)
Drosophila melanogaster larvae, wing spot test	+	NA	7.7 µg/L air	Chroust et al. (2007)
Male Sprague-Dawley rats, dominant-lethal assay	–[c]	NA	0.24% in drinking-water, 14 wk[d]	EPA (1989)

Table 4.1 (continued)

Test system	Results[a]		Concentration[b] (LEC or HIC)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Male B6C3F$_1$ mice, *Pig-a* mutant frequencies, blood, in vivo	–	NA	600 ppm (6 h/day, 5 days/wk, 6 wk), inhalation	Suzuki et al. (2014)
Male B6C3F$_1$ mice, micronucleus formation, reticulocytes, in vivo	–	NA	600 ppm (6 h/day, 5 days/wk, 6 wk), inhalation	Suzuki et al. (2014)
Male B6C3F$_1$ mice, DNA damage liver (comet assay, tail intensity, in vivo)	+	NA	300 ppm (6 h/day, 5 days/wk, 6 wk), inhalation	Suzuki et al. (2014)
Male B6C3F$_1$ mice, DNA damage liver (comet assay, tail intensity, in vivo)	+	NA	150 ppm (6 h/day, 5 days/wk, 6 wk), inhalation, with co-exposure to dichloromethane at 400 ppm	Suzuki et al. (2014)
Transgenic, *gpt* Delta C57BL/6J mice, gene mutation, Gpt in liver	–	NA	300 ppm (6 h/day, 5 days/wk, 4 wk), inhalation	Suzuki et al. (2014)
Transgenic *gpt* Delta C57BL/6J mice, gene mutation, Gpt in liver	+	NA	300 ppm (6 h/day, 5 days/wk, 4 wk) with co-exposure to dichloromethane at 800 ppm, inhalation	Suzuki et al. (2014)

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

[b] LEC, lowest effective concentration; HIC, highest ineffective concentration; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw per day

[c] Statistically significant increase was observed after 1 week of breeding in preimplantation losses and resorption rate at 0.024% and 0.24% treated group (not in 0.10 mid-dose) compared to concurrent controls. However, data from the second week showed no treatment-related statistical difference from concurrent controls

[d] 0.024%, 0.10%, 0.24% w/v continuous 14-week treatment corresponded to time-weighted average daily dosage of 28, 91, and 162 mg/kg bw per day, respectively

NA, not applicable; NT, not tested; wk, week

measure of renal function), release into the incubation medium of tubular enzymes, aspartate aminotransferase (AST) and lactate dehydrogenase, depletion of GSH, and increase in concentrations of malondialdehyde (Trevisan et al., 1993). Acivicin and aminooxyacetic acid, inhibitors of GGT and the cysteine conjugate β-lyase, respectively, partially prevented loss of organic anion accumulation (*p*-aminohippurate) and increases in malondialdehyde induced by exposure to 1,2-dichloropropane, suggesting that toxicity is at least partially related to the cysteine conjugate. Alpha-ketobutyrate, an activator of the cysteine conjugate β-lyase, enhanced the effects of 1,2-dichloropropane, suggesting that the toxicity of 1,2-dichloropropane is partially due to nephrotoxic thioalkanes formed from the cysteine conjugate activated by the β-lyase.

Another study investigated the effect of testosterone on the nephrotoxicity of 1,2-dichloropropane in naïve males, females, and castrated males with testosterone replacement (Odinecs et al., 1995). The nephrotoxicity was evaluated by measuring accumulation of an organic anion (*p*-aminohippurate) and release of AST into the incubation medium in renal cortical slices prepared from animals with differing hormonal status. 1,2-Dichloropropane decreased accumulation of *p*-aminohippurate by renal cortical slices and increased release of AST. This effect was the largest in the slices obtained from naïve male rats. Males were more susceptible

than females to the decreases in *p*-aminohippurate accumulation and increases in release of AST caused by exposure to 1,2-dichloropropane. Castration of males had a protective effect against the changes in *p*-aminohippurate uptake and AST release, but pretreatment with testosterone significantly increased the susceptibility of females for effects on *p*-aminohippurate accumulation only. This study showed that greater susceptibility to 1,2-dichloropropane-induced nephrotoxicity in males can be explained by CYP activity in the kidney, as treatment with testosterone leads to an increase of CYP activity in the kidneys of female and castrated males.

4.4 Organ toxicity

4.4.1 Liver

(a) Humans

Several studies show evidence for liver toxicity in humans exposed to 1,2-dichloropropane. A case report of a worker using stain-remover containing 1,2-dichloropropane described liver injury (indicated by elevations in AST and alanine aminotransferase (ALT), and reduced prothrombin activity). Hepatic biopsy revealed acute centrolobular necrosis characterized by pyknosis and a few "cellular shadows" (Lucantoni et al., 1992). Three cases of intoxication with 1,2-dichloropropane (one by ingestion, two by inhalation) were reported to present with clinical features of severe liver damage evident from elevation of serum enzymes (Pozzi et al., 1985).

Kumagai et al. (2014) reported indications of liver damage both during and after exposure to 1,2-dichloropropane in 10 printing workers later diagnosed with cholangiocarcinoma. Values for erythrocytes, haemoglobin, haematocrit (erythrocyte volume fraction), total cholesterol, triglycerides, and fasting plasma glucose were within the standard ranges during exposure to 1,2-dichloropropane for almost all patients, but GGT levels exceeded the standard range for six patients. Two of these six patients were diagnosed with cholangiocarcinoma during exposure, and the other four patients were diagnosed 1–9 years after termination of exposure. The remaining four patients had GGT levels that were within the standard range during exposure, but had increased GGT levels thereafter, and were diagnosed with cholangiocarcinoma 4–10 years after termination of exposure. AST and ALT levels were also elevated in exposed workers.

(b) Experimental systems

(i) Rats

In 13-week and 2-year studies in male and female F344 rats exposed to 1,2-dichloropropane by inhalation, absolute and relative liver weights were significantly increased in female rats exposed at 500 ppm and above, and swelling of centrilobular hepatocytes was observed in male and female rats exposed at 2000 ppm (Umeda et al., 2010). Centrilobular hepatic fatty degeneration with atrophy and necrosis of the liver was found in studies of shorter duration in rats (Heppel et al., 1946).

In studies in Sprague-Dawley rats given 1,2-dichloropropane by gavage for up to 13 weeks, morphological changes were reported in the liver, including moderate cytoplasmic condensation, necrosis of centrilobular hepatocytes, and mixed inflammatory cell infiltration (Bruckner et al., 1989). Another 13-week study in male and female F344N rats treated by oral gavage found centrilobular congestion of the liver, hepatic fatty changes, and centrilobular necrosis (NTP, 1986). Daily dosing of rats with 1,2-dichloropropane for 4 weeks resulted in a dose-dependent increase in the incidence of focal liver necrosis and steatosis (Trevisan et al., 1989).

Treatment of rats with buthionine sulfoximine, a glutathione-depleting agent, increased lethality of 1,2-dichloropropane (2 mL/kg bw, by gavage), while administration of *N*-acetylcysteine,

a glutathione precursor, decreased toxicity (Imberti et al., 1990).

(ii) Mice

In a 13-week study in B6D2F$_1$/Crlj mice given 1,2-dichloropropane by inhalation, swelling of centrilobular hepatocytes was found to be significantly increased in both male and female mice exposed at 300 ppm and above (Matsumoto et al., 2013). Other pathological observations included necrosis, fatty change, vacuolic change, and mineralization of centrilobular hepatocytes. Total bilirubin, AST, ALT, and lactate dehydrogenase were increased in male and female mice exposed at 400 ppm. Alkaline phosphatase activity was significantly increased in male mice exposed at 300 ppm and above. A study in C3H mice exposed to 1,2-dichloropropane at 400 ppm for up to 37 days (4–7 hours/day) found moderate to marked congestion and fatty degeneration of the liver, extensive centrilobular coagulation and necrosis of the liver. Some of the observations were made post mortem in mice that died during treatments (Heppel et al., 1948).

Several long-term bioassays in mice exposed to 1,2-dichloropropane by inhalation reported signs of liver histopathology (Heppel et al., 1946; Matsumoto et al., 2013). Dose-dependent increases in the incidences of hepatomegaly and hepatic necrosis (focal, not otherwise specified, and centrilobular combined) were also found in male mice, but not females, given 1,2-dichloropropane by gavage for 2 years, (NTP, 1986).

(iii) Other species

In a study by Heppel and colleagues, rabbits and dogs were exposed to 1,2-dichloropropane via inhalation (Heppel et al., 1946). Few animals were examined in each of these species, usually one per group. Mild steatosis was observed in two rabbits exposed for 1 or 2 weeks. Post-mortem (death due to 1,2-dichloropropane exposure at 1000 ppm for up to 96 days) pathological evaluation of the liver in dogs showed moderate to marked fatty degeneration of the liver. In a follow-up study in dogs treated with 1,2-dichloropropane at lower concentrations (400 ppm, 134 exposures, 4–7 hours per exposure) via inhalation, slight haemosiderosis was observed in the liver of one dog (Heppel et al., 1948).

4.4.2 Kidney

(a) Humans

Several case studies reported that exposure to 1,2-dichloropropane may cause acute renal failure in humans (Pozzi et al., 1985; Lucantoni et al., 1992; Fiaccadori et al., 2003).

(b) Experimental systems

(i) Rats

In male and female F344/DuCrj rats exposed to 1,2-dichloropropane for 13 weeks or 2 years, no exposure-related kidney lesions were reported (Umeda et al., 2010). In rats exposed to 1,2-dichloropropane for between 2 and 140 days, no kidney histological changes were observed (Heppel et al., 1948). No apparent nephrotoxicity was observed in male Sprague-Dawley rats treated with 1,2-dichloropropane by gavage for 1 day, 10 days, or 13 weeks (Bruckner et al., 1989), or in male and female F344 rats treated by gavage for 13 weeks or 2 years (NTP, 1986).

As mentioned above (see Section 4.3), in-vitro studies in which rat renal cortical slices were exposed to 1,2-dichloropropane showed that a depletion in GSH occurs, and that it can be prevented by carbon monoxide. It was also shown that the loss of organic anion accumulation (*p*-aminohippurate) can be partially inhibited by acivicin and aminooxyacetic acid, which are inhibitors of GGT and β-lyase activities, respectively (Trevisan et al., 1993).

(ii) Mice

Kidney toxicity has been observed in several studies in mice. In B6D2F1/Crlj mice exposed to 1,2-dichloropropane by inhalation for 2 years,

basophilic changes in the proximal tubules and mineralization of the cortex were reported in males (Matsumoto et al., 2013). No kidney pathology was found at the 13-week time-point in this study. Two additional studies in mice reported fatty degeneration of the kidney after a single lethal dose, or repeated dosing for 2–4 weeks (Heppel et al., 1946, 1948). In studies in male and female B6C3F$_1$ mice treated by gavage, no exposure-related lesions were reported in the kidney at either 13 weeks or 2 years (NTP, 1986).

(iii) Other species

In a study in guinea-pigs killed 6–8 months after exposure to 1,2-dichloropropane by inhalation for up to 4 months, renal cortical scarring, extensive renal fibrosis and amyloidosis, tubular atrophy and fatty degeneration alternating with dilated and occasionally cystic tubules were reported in some exposed animals (Heppel et al., 1948). A study in dogs exposed to 1,2-dichloropropane for up to 4 months observed scattered granulomatous lesions in the kidney, with no demonstrable acid-fast bacilli (Heppel et al., 1948).

4.4.3 Central nervous system

Depression of the central nervous system was reported in humans exposed to 1,2-dichloropropane at high concentrations (Perbellini et al., 1985; Imberti et al., 1987; Lucantoni et al., 1992). Depression of the central nervous system was observed in adult male Sprague-Dawley rats given 1,2-dichloropropane by gavage for 1 day, 10 days, or 13 weeks (Bruckner et al., 1989).

4.4.4 Haematotoxicity

Haemolytic anaemia has been observed in humans in two case reports of exposure to 1,2-dichloropropane (Pozzi et al., 1985; Lucantoni et al., 1992).

In experimental animals, haemolytic anaemia, accompanied by pathological changes of the spleen, was observed in B6D2F$_1$ mice and F344/DuCrj rats exposed to 1,2-dichloropropane by inhalation for 13 weeks (Umeda et al., 2010; Matsumoto et al., 2013), and in Sprague-Dawley rats exposed by gavage for 13 weeks (Bruckner et al., 1989).

4.4.5 Skin

In a case series of 10 subjects with contact allergic dermatitis, all demonstrated a positive response to 1,2-dichloropropane (Baruffini et al., 1989). In another case report, a woman exposed occupationally to 1,2-dichloropropane reported hand dermatitis that receded after changing work (Grzywa & Rudzki, 1981).

No data on experimental animals were available to the Working Group.

4.4.6 Respiratory system

No data on humans were available to the Working Group.

In mice exposed to 1,2-dichloropropane by inhalation for 13 weeks, treatment-related metaplasia and atrophy of the nasal cavity epithelium, and necrosis of the olfactory epithelium, were reported in males and females (Matsumoto et al., 2013). In rats exposed to 1,2-dichloropropane by inhalation for 13 weeks or 2 years, hyperplasia of the respiratory epithelium, and atrophy of the olfactory epithelium occurred in males and females (Umeda et al., 2010).

4.4.7 Adrenal gland

No data on humans were available to the Working Group.

In a study in rats exposed to 1,2-dichloropropane by inhalation for 13 weeks, the incidence of fatty changes in the adrenal gland was statistically significant in females (Umeda et al., 2010). In a study in dogs exposed by inhalation, marked congestion, atrophy, pigmentation and focal necrosis of the zona reticularis of the

adrenal gland was reported in one dog (Heppel et al., 1946).

4.5 Susceptible populations

4.5.1 Polymorphisms

No publications were available that had directly assessed the effects of 1,2-dichloropropane in potentially susceptible populations. However, the dependence of toxicity on the metabolism of 1,2-dichloropropane by CYP2E1 and GST suggests that genetic polymorphisms in these enzymes will modulate individual susceptibility to 1,2-dichloropropane. Specifically, it is expected that higher activities of CYP2E1 and certain GST isoforms would promote greater toxicity after exposure to 1,2-dichloropropane. Regarding the GST-dependent metabolism of 1,2-dichloropropane, the function of specific isoforms has not been determined.

4.5.2 Life stage

No studies providing data related to life-stage susceptibility to the carcinogenic effects of 1,2-dichloropropane were available to the Working Group.

4.6 Mechanistic considerations

Limited information was available on the toxicokinetics of 1,2-dichloropropane. However, the available data suggested that 1,2-dichloropropane behaves similarly to other halogenated alkanes, and is metabolized by CYP and GST-mediated conjugation with GSH. Available toxicokinetic data indicated that metabolism is extensive, with excretion of multiple urinary metabolites indicating that multiple metabolic pathways are active (Timchalk et al., 1991).

The best-studied metabolic pathways involve GSH conjugation in combination with CYP, leading to mercapturates that are excreted in the urine; GSH-conjugation alone, which may lead to formation of reactive metabolites; or CYP alone, which leads to formation of carbon dioxide that is exhaled. CYP2E1 plays a major role in CYP-mediated metabolism (Guengerich et al., 1991), although the evidence suggests that other CYPs can also be involved (Lefever & Wackett, 1994). Under conditions of higher exposure when CYP2E1 is saturated, it is plausible that GSH-only metabolism would predominate, but this has not been demonstrated. Alternatively, saturation of CYP without a shift to GSH-only metabolism would lead to increased excretion of the parent compound, which has been observed in rats (Timchalk et al., 1991). Moreover, a shift to GSH-only metabolism would lead to a change in the proportion of urinary mercapturates, but no such change was observed with increasing dose (Timchalk et al., 1991). Finally, based on isotope-labelling, Bartels & Timchalk (1990) found no evidence for activity of the GSH-only pathway. Overall, the Working Group concluded that, while plausible, there was insufficient direct evidence for the activity of a GSH-only pathway, leading to formation of reactive metabolites.

No data on the genotoxicity of 1,2-dichloropropane or its metabolites in humans were available to the Working Group. In experimental systems in vivo, no dominant-lethal effect was observed in one study (EPA, 1989). In another in-vivo study, no increases in the frequency of *Pig-a* mutation or micronucleus formation were observed with exposure to 1,2-dichloropropane, but DNA damage as measured by the comet assay was increased in a dose-dependent manner, with increases occurring at lower levels of exposure to 1,2-dichloropropane under conditions of co-exposure to dichloromethane (Suzuki et al., 2014). Genotoxicity with 1,2-dichloropropane has been observed in vitro, including mutation in *Salmonella*, and sister-chromatid exchanges in Chinese hamster ovary and lung fibroblast V79 cells, and chromosomal aberrations in Chinese hamster ovary cells, where results did not depend

on the presence or absence of exogenous metabolic activation (De Lorenzo et al., 1977; Principe et al., 1981; Galloway et al., 1987; von der Hude et al., 1987). While there is some evidence for genotoxicity with 1,2-dichloropropane in vivo and in vitro, the genotoxicity database contains mixed results and is not extensive.

1,2-Dichloropropane causes hepatic and renal toxicity, including fatty degeneration and necrosis, in humans (Perbellini et al., 1985; Pozzi et al., 1985; Lucantoni et al., 1992; Fiaccadori et al., 2003) and in experimental systems (Heppel et al., 1946, 1948; NTP, 1986). Damage is often extensive, and sometimes fatal. Haemolytic anaemia as a result of 1,2-dichloropropane exposure has also been consistently reported in studies in humans and experimental animals (Heppel et al., 1946; Pozzi et al., 1985; Lucantoni et al., 1992; Umeda et al., 2010; Matsumoto et al., 2013). Nasal, but not lung, toxicity has been reported in mice and rats exposed to 1,2-dichloropropane via inhalation, with effects observed including desquamation of the olfactory epithelium (Umeda et al., 2010; Matsumoto et al., 2013).

No direct data on susceptibility were available to the Working Group.

5. Summary of Data Reported

5.1 Exposure data

1,2-Dichloropropane is a synthetic, chlorinated solvent that is a by-product of the manufacture of propylene oxide. 1,2-Dichloropropane is used primarily as a chemical intermediate in the production of other organic chemicals, such as propylene, carbon tetrachloride, and tetrachloroethylene. It is also used as solvent in several uses including paint stripping. Until 2012, it was used as a printing-press cleaner in Japan. There are no data as to whether it has been used for this purpose in other countries. 1,2-Dichloropropane was formerly used as one component of a grain and soil fumigant, although this use is no longer permitted in Europe and the USA. Inhalation is the primary route of exposure in occupational settings, and dermal contact can also occur. Occupational exposures of > 1 g/m^3 have been estimated. Little information is available on exposure of the general population to 1,2-dichloropropane from environmental sources, but environmental air concentrations are likely to be very low.

5.2 Human carcinogenicity data

Investigations into the carcinogenicity of 1,2-dichloropropane were prompted by the recognition of a cluster of 17 cases of cancer of the biliary tract (identified histologically as cholangiocarcinoma) in a small offset-printing plant in Osaka, Japan. Subsequently, epidemiological and occupational hygiene investigations identified seven additional cases from four other small printing plants in Japan. Age of death or diagnosis for these cases was about 20–60 years; cancers of the biliary tract usually occur at later ages in the general population. Based on the results from the Osaka plant alone, the estimated relative risk for this rare and generally fatal cancer is extraordinarily high. Most workers at these plants were exposed to both dichloromethane and 1,2-dichloropropane at levels well above current international limit values, as well as to other solvents and inks. No studies of the association of cancer in humans with exposure to 1,2-dichloropropane in other countries or industries were available to the Working Group.

The exposure distribution of the full cohort in the Osaka plant was not described, but in the follow-up of about 100 workers until 2012, 17 cases were observed, of which 6 had no known exposure to dichloromethane. The Working Group estimated relative risks of approximately 900 for exposure to 1,2-dichloropropane. Seven additional cases of cancer of the bile duct were identified in subsequent reports from other

Japanese printing plants. Of these, one case was exposed to high levels of dichloromethane without exposure to 1,2-dichloropropane. The other six cases were all exposed to 1,2-dichloropropane, four to both dichloromethane and 1,2-dichloropropane, and two to 1,2-dichloropropane with only negligible exposure to dichloromethane (< 1 ppm).

Given the rarity of the outcome, the young ages at diagnosis, the absence of other known risk factors among the cases, and the very high relative risk, as well as the specificity and apparent intensity of the exposures, the finding of a large excess of cancer of the biliary tract among the printing workers is extremely unlikely to be the result of chance and very unlikely to be due to bias or confounding.

5.3 Animal carcinogenicity data

There were two studies of carcinogenicity with 1,2-dichloropropane in mice: one study of oral administration (gavage) in males and females, and one study of inhalation in males and females. 1,2-Dichloropropane increased the incidences of hepatocellular adenoma and/or carcinoma in male and female mice after oral administration, of bronchiolo-alveolar adenoma and/or adenocarcinoma in male and female mice exposed by inhalation, and of splenic haemangiosarcoma in male mice exposed by inhalation. 1,2-Dichloropropane induced histiocytic sarcoma and Harderian gland adenoma in male mice exposed by inhalation.

There were two studies of carcinogenicity with 1,2-dichloropropane in rats: one study of oral administration (gavage) in male and female rats and one study of inhalation in males and females. 1,2-Dichloropropane increased the incidence of adenocarcinoma of the mammary gland in female rats after oral administration, and of papilloma of the nasal cavity in male and female rats exposed by inhalation, and probably induced rare olfactory neuroblastoma in the nasal cavity of male rats exposed by inhalation.

5.4 Mechanistic and other relevant data

1,2-Dichloropropane is a volatile lipophilic compound that is readily absorbed after oral, inhalation, or dermal exposure. After absorption, 1,2-dichloropropane is extensively distributed systemically, and metabolized to mercapturates excreted in the urine and in carbon dioxide in exhaled breath. Multiple pathways involving cytochrome P450 (CYP) and glutathione *S*-transferase-mediated conjugation with glutathione (GSH), both individually and in combination, may be responsible for the metabolism of 1,2-dichloropropane. Metabolites formed through the combination of GSH conjugation and CYP oxidation, or through CYP alone, do not appear to be reactive. The pathway involving GSH conjugation alone is plausible, based on similarities to other halogenated hydrocarbons such as trichloroethylene and methyl chloride, and may lead to formation of reactive, genotoxic metabolites. However, there is no direct evidence for the activity of the GSH conjugation-only pathway for 1,2-dichloropropane.

Genotoxicity with 1,2-dichloropropane has been observed in vitro in some mammalian (e.g. Chines hamster ovary cells) and non-mammalian systems (some strains of *Salmonella*), as well as in some in-vivo experiments in mice. No data on genotoxicity in humans or human-derived cells were available. While there was some evidence of genotoxicity in vivo and in vitro, the data were mixed and limited in extent.

1,2-Dichloropropane causes hepatic and renal toxicity, and haemolytic anaemia, in humans and rodents. Nasal, but not lung, toxicity has been reported in mice and rats exposed to 1,2-dichloropropane via inhalation. These data suggest that the hepatic, renal, haematopoietic,

and respiratory systems are potential target tissues. Non-genotoxic mechanisms of carcinogenesis have not been identified.

Overall, given that there was some evidence for genotoxicity, the Working Group considered that the mechanistic evidence for 1,2-dichloropropane carcinogenesis is *moderate*.

6. Evaluation

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of 1,2-dichloropropane. 1,2-Dichloropropane causes cancer of the biliary tract (confirmed as cholangiocarcinoma).

The major challenge in evaluating the occurrence of cancer in the Japanese printing plants was to determine whether the observed excess of cholangiocarcinoma could be attributed to a specific agent, measured or unmeasured. Workers were exposed to numerous chemicals, but 1,2-dichloropropane was known to be common to all except one of the 24 cases of cholangiocarcinoma. Moreover, 6 of the cases had no exposure to dichloromethane and the Working Group's estimate of the relative risk for these cases was extremely high. Based on this evidence, the majority of the Working Group concluded that 1,2-dichloropropane is the causative agent responsible for the large excess of cholangiocarcinoma among the workers exposed to 1,2-dichloropropane, but not dichloromethane. However, a minority of the Working Group concluded that the association between 1,2-dichloropropane and cancer of the biliary tract was credible, but the role of exposure to other agents, principally dichloromethane, could not be separated with complete confidence, and noted that most of the evidence came from studies in a single plant.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

1,2-Dichloropropane is *carcinogenic to humans (Group 1).*

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