1,2,3-TRICHLOROPROPANE

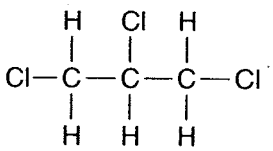
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 96-18-4
Chem. Abstr. Name: 1,2,3-Trichloropropane
IUPAC Systematic Name: 1,2,3-Trichloropropane
Synonyms: Allyl trichloride; glycerol trichlorohydrin; glyceryl trichlorohydrin; trichlorohydrin; trichloropropane

1.1.2 Structural and molecular formulae and relative molecular mass



$C_3H_5Cl_3$ Relative molecular mass: 147.43

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless to straw-coloured liquid with chloroform-like odour (Verschueren, 1983; United States National Institute for Occupational Safety and Health, 1994)

(*b*) *Boiling-point*: 156.8 °C (Lide, 1993)

(*c*) *Melting-point*: –14.7 °C (Lide, 1993)

(*d*) *Density*: 1.3889 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [4653], grating [10777]), nuclear magnetic resonance (proton [6769], C-13 [624]) and mass [814] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Slightly soluble in water (1.75 g/L); soluble in chloroform, diethyl ether and ethanol (Riddick *et al.*, 1986; American Conference of Governmental Industrial Hygienists, 1991; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 2 mm Hg [0.266 kPa] at 20 °C (Verschueren, 1983)

(*h*) *Reactivity*: Reacts with active metals, strong caustics and strong oxidizers (Sittig, 1985; United States National Institute for Occupational Safety and Health, 1994)

(*i*) *Octanol:water partition coefficient (P)*: log P, 1.98 (United States Agency for Toxic Substances and Disease Registry, 1992)

(*j*) *Conversion factor*: $mg/m^3 = 6.03 \times ppm$[1]

1.1.4 Technical products and impurities

1,2,3-Trichloropropane is available commercially at a purity of > 98–99.9% (Crescent Chemical Co., 1990; Fluka Chemical Corp., 1993; Aldrich Chemical Co., 1994; TCI America, 1994). The material tested by the United States National Toxicology Program (1993) contains the following impurities: 0.066% water, 0.14% unspecified chlorohexene, two unspecified chlorohexadienes (0.24 and 0.13%), several unidentified impurities (each < 0.1%) and 48 ppm [mg/L] total acidity (as hydrochloric acid) (Alessandri, 1993).

1.1.5 Analysis

Selected methods for the analysis of 1,2,3-trichloropropane are presented in Table 1.

Two gas chromatography/mass spectrometry (GC/MS) and two purge-and-trap GC methods for purgeable organic compounds, including 1,2,3-trichloropropane, are usually used for analysing aqueous samples (see also Table 1). The first method (EPA Method 524.1 and APHA/AWWA/WEF Method 6210C), involving use of a packed column, and similar purge-and-trap methods (EPA Method 502.1 and APHA/AWWA/WEF Method 6230C), involving detection by electrolytic conductivity or microcoulometric methods, are applicable for determining 1,2,3-trichloropropane in raw source water or in drinking-water at any stage of treatment. The second group of methods (EPA Method 524.2 and APHA/AWWA/WEF Method 6210D; EPA Method 502.2 and APHA/AWWA/WEF Method 6230D) is identical to the previous set, except that a capillary column is used. These methods are intended primarily for the detection of large numbers of contaminants at very low concentrations (Greenberg *et al.*, 1992).

Methods for the analysis of 1,2,3-trichloropropane in the exhaled air, urine, faeces, bile, major tissues and blood of rats have been described. The first method involved drawing dry air through a cage and into a trap filled with ethanol at –15 °C, followed by GC and electron capture detection. The second involved sample homogenization, extraction with hexane and analysis by GC with electron capture detection. Blood samples were added to water, and bile samples were added to ethanol before extraction (United States Agency for Toxic Substances and Disease Registry, 1992).

In a method for determining fumigants, including 1,2,3-trichloropropane, in citrus fruit (lemon, orange, grapefruit), samples were blended with water, distilled into cyclohexane in an apparatus for essential oils, cleaned-up on a Florisil column and analysed by GC with electron capture detection (Tonogai *et al.*, 1986).

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

Table 1. Methods for the analysis of 1,2,3-trichloropropane

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg/ sample	Eller (1994); US Occupational Safety and Health Administration (1990)
Water	Purge (inert gas); trap on suitable adsorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD or GC/MCD GC/MS	ND NR	US Environmental Protection Agency (1988)
	Purge and trap as above; desorb as vapour onto capillary gas chromatographic column	GC/PID-ECD GC/MS	0.02–0.4 µg/L 0.03–0.32 µg/L	US Environmental Protection Agency (1988)
Liquid and solid wastes	Purge (inert gas); trap on suitable adsorbent material; desorb as vapour onto packed gas chromatographic column	GC/ECD GC/MS	NR NR	US Environmental Protection Agency (1986a,b)

GC/FID, gas chromatography/flame ionization detection; ECD, electrolytic conductivity detection; MCD, microcoulometric detection; PID-ECD, photoionization detector in series with an electrolytic conductivity detector; ND, not determined; NR, not reported

1.2 Production and use

1.2.1 Production

1,2,3-Trichloropropane can be produced by chlorination of propylene (Sax & Lewis, 1987; see IARC, 1994a). Other reported methods for producing 1,2,3-trichloropropane include the addition of chlorine to allyl chloride (see IARC, 1987a), the reaction of thionyl chloride with glycerol and the reaction of phosphorus pentachloride with either 1,3- or 2,3-dichloropropanol. 1,2,3-Trichloropropane may also be produced in potentially significant amounts as a by-product of the production of other chemicals, including dichloropropene (a soil fumigant and nematocide; see IARC, 1987b), propylene chlorohydrin, propylene oxide (see IARC, 1994b), dichlorohydrin and glycerol (United States Agency for Toxic Substances and Disease Registry, 1992).

No data were available regarding recent production of 1,2,3-trichloropropane. The volume estimated to have been produced in 1977 in the United States was 21–110 million pounds (9.5–50 thousand tonnes) (United States Agency for Toxic Substances and Disease Registry, 1992). It is currently produced by one company each in Germany, Japan, the Russian Federation, the United Kingdom and the United States (United States International Trade Commission, 1992; Chemical Information Services, Inc., 1994).

1.2.2 Use

1,2,3-Trichloropropane was used in the past mainly as a solvent and extractive agent, including as a paint and varnish remover and as a cleaning and degreasing agent (Sax & Lewis, 1987). It is now used mainly as a chemical intermediate, for example, in the production of polysulfone liquid polymers, dichloropropene and hexafluoropropylene, and as a cross-linking agent in the synthesis of polysulfides (United States Agency for Toxic Substances and Disease Registry, 1992). These manufacturing processes generally occur in closed systems. 1,2,3-Trichloropropane is also found as an impurity in mixtures used as soil fumigants and fungicides, for instance, during the manufacture of the nematocide DD (a dichloropropane–dichloropropene mixture), which was introduced in 1942. Estimates of the amount of trichloropropanes in the DD mixture vary from 0.4 to 6–7% by weight (Oki & Giambelluca, 1987).

1.3 Occurrence

1.3.1 Natural occurrence

1,2,3-Trichloropropane is not known to occur as a natural product.

1.3.2 Occupational exposure

The National Occupational Exposure Survey conducted in the United States in 1981–83 indicated that 492 workers were potentially exposed to 1,2,3-trichloropropane (United States National Institute for Occupational Safety and Health, 1990). Any occupational exposure that occurred would probably result from inhalation and dermal contact. No data on occupational exposures were available to the Working Group.

1.3.3 Air

1,2,3-Trichloropropane was not detected in more than 400 samples of urban and rural air in Germany (von Düszeln *et al.*, 1982).

1.3.4 Water

1,2,3-Trichloropropane was found in groundwater in California (0.1–5 μg/L) and Hawaii (United States) as a result of use of pesticides in agriculture. It was detected in groundwater at two of 10 sites in an agricultural community in Suffolk County, New York, at concentrations of 6 and 10 μg/L and was found in 39% of 941 samples of groundwater in the United States, at a median concentration of 0.69 μg/L, an average concentration of 1.0 μg/L and a range of trace (below the detection limit) to 2.5 μg/L. It was found in groundwater at 0.71% of hazardous waste sites at a geometric mean concentration of 57.3 μg/L (United States Agency for Toxic Substances and Disease Registry, 1992). Concentrations of 0.3–2.8 μg/L were measured in well water on Oahu, Hawaii, probably as a result of the use and handling of the nematicide DD on pineapple plantations (Oki & Giambelluca, 1987).

Surface water from the Delaware River basin (United States) contained trichloropropane (unspecified isomer) at concentrations > 1 μg/L in 3% of the samples. Trichloropropane was also

found at unspecified concentrations in seawater of Narragansett Bay, RI (United States Environmental Protection Agency, 1989).

Drinking-water from a water plant in New Orleans, LA (United States), contained 1,2,3-trichloropropane at < 0.2 µg/L (Keith *et al.*, 1976). The compound was also detected in drinking-water in Ames, IA, but the concentrations were not reported (United States Environmental Protection Agency, 1989). It has also been detected in drinking-water in the Netherlands (Kool *et al.*, 1982).

1,2,3-Trichloropropane was found in 69 of 141 samples of sewage sludge from municipal sewage treatment plants in Michigan (United States) in 1980, at a median concentration of 0.35 mg/kg, an average of 1.07 mg/kg and a range of 0.005–19.5 mg/kg on a dry-weight basis (United States Agency for Toxic Substances and Disease Registry, 1992).

The half-life for evaporation of 1,2,3-trichloropropane from water was about 1 h (Dilling, 1977; United States Environmental Protection Agency, 1989). Experiments in showers showed that the fraction of 1,2,3-trichloropropane volatilized from tap water in the United States was around 20% (Tancrède *et al.*, 1992).

1.3.5 Soil

1,2,3-Trichloropropane was reported to have a half-life of 2.7 days in a silt loam and a sandy loam (Anderson *et al.*, 1991). An unspecified isomer of trichloropropane was reported to be relatively easily decomposed by microbes in activated sludge (United States Environmental Protection Agency, 1989).

In the study described above in California and Hawaii, 1,2,3-trichloropropane was found in soil samples at levels of 0.2–2 ppb [µg/kg]. It was found at a depth of at least 10 feet [3.05 m] in soil profiles in Hawaii (Cohen *et al.*, 1987).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines in several countries are given in Table 2.

2. Studies of Cancer in Humans

No data were available to the Working Group.

Table 2. Occupational exposure limits and guidelines for 1,2,3-trichloropropane

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1991	60	TWA; skin notation
Belgium	1991	60	TWA; skin notation
Denmark	1991	300	TWA
Finland	1993	300	TWA
		450	STEL
Germany	1993	None	Carcinogenic to animals
Netherlands	1994	60	TWA; skin notation
Russian Federation	1991	2	STEL
Switzerland	1991	300	TWA
		1500	STEL
United Kingdom	1993	300	TWA
		450	STEL
USA			
ACGIH	1994	60	TWA; skin notation
NIOSH	1994	None	Potential carcinogen
OSHA	1994	300	TWA

From ILO (1991); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); United Kingdom Health and Safety Executive (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); United States Occupational Safety and Health Administration (1994). TWA, time-weighted average; STEL, short-term exposure limit

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 Mouse

Groups of 60 male and 60 female B6C3F1 mice, six weeks of age, were administered 1,2,3-trichloropropane (purity, > 99%) in corn oil by gavage at doses of 0 (vehicle control), 6, 20 or 60 mg/kg bw on five days per week for 104 weeks. Four to 10 mice per group were removed for histopathological evaluation at 15 months. Survival of treated mice was significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were: 42 control males and 41 control females and 18 males at the low dose and 13 females at the low dose; none of the animals at the middle or high doses survived. Histopathological evaluation revealed increased incidences (life-table test or logistic regression analysis) of neoplasms of the forestomach, liver and Harderian gland in males and females and neoplasms of the oral mucosa and uterus in females (see Table 3). The incidence of focal hyperplasia of the forestomach epithelium was increased in treated mice, occurring in 8/52 control males, 29/51 at

Table 3. Incidences of neoplastic lesions in B6C3F1 mice during gavage with 1,2,3-trichloropropane for two years

Site and tumour type	Males				Females			
	Vehicle control	6 mg/kg bw	20 mg/kg bw	60 mg/kg bw	Vehicle control	6 mg/kg bw	20 mg/kg bw	60 mg/kg bw
Forestomach								
Squamous-cell papilloma	3/52	28/51 $p < 0.001$	22/54 $p < 0.001$	33/56 $p < 0.001$	0/50	23/50 $p < 0.001$	18/51 $p < 0.001$	29/55 $p < 0.001$
Squamous-cell carcinoma	0/52	40/51 $p < 0.001$	50/54 $p < 0.001$	51/56 $p < 0.001$	0/50	46/50 $p < 0.001$	49/51 $p < 0.001$	49/55 $p < 0.001$
Papilloma or carcinoma	3/52	50/51 $p < 0.001$	53/54 $p < 0.001$	55/56 $p < 0.001$	0/50	48/50 $p < 0.001$	50/51 $p < 0.001$	54/55 $p < 0.001$
Liver								
Hepatocellular adenoma	11/52	18/51 $p = 0.073$	21/54 $p = 0.028$	29/56 $p < 0.001$	6/50	9/50	8/51	31/55 $p < 0.001$
Hepatocellular carcinoma	4/52	11/51 $p = 0.015$	5/54	3/56	1/50	3/50	0/51	2/55
Adenoma or carcinoma	13/52	24/51 $p = 0.008$	24/54 $p < 0.007$	31/56 $p < 0.001$	7/50	11/50	8/51	31/55 $p < 0.001$
Harderian gland, adenoma	1/52	2/51	10/54 $p = 0.002$	11/56 $p = 0.008$	2/50	6/50	7/51	10/55 $p = 0.06$
Oral mucosa								
Squamous-cell papilloma					1/50	0/50	1/51	0/55
Squamous-cell carcinoma					0/50	0/50	1/51	5/55 $p = 0.006$
Papilloma or carcinoma					1/40	0/50	2/51	5/55 $p = 0.006$
Uterus								
Stromal polyp					0/50	2/50	1/51	6/54
Endometrial adenoma or adenocarcimoma					0/50	5/50	3/51	9/54 $p = 0.030$

From United States National Toxicology Program (1993)

p values are given for incidences that are significantly greater than those of controls on the basis of life-table tests or logistic regression analysis (adjusted for survival)

the low dose, 27/54 at the middle dose and 34/56 at the high dose; and in 10/50 control females, 15/50 at the low dose, 14/51 at the middle dose and 31/55 at the high dose (United States National Toxicology Program, 1993).

3.1.2 Rat

Groups of 60 male and 60 female Fischer 344/N rats, six weeks of age, were administered 1,2,3-trichloropropane (purity, > 99%) in corn oil by gavage at doses of 0 (vehicle control), 3, 10 or 30 mg/kg bw on five days per week for up to 104 weeks. Eight to 10 rats per group were removed for histopathological evaluation at 15 months. Survival rates of rats that received 10 or 30 mg/kg were significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were 34 control males, 32 at the low dose and 14 at the middle dose; and 31 control females, 30 at the low dose and 8 at the middle dose; none of the animals at the high dose survived. Histopathological evaluation revealed increased incidences (life-table test or logistic regression analysis) of neoplasms of the oral mucosa and forestomach in males and females, neoplasms of the pancreas, preputial gland and kidney in males, and neoplasms of the clitoral gland and mammary gland in females (Table 4). The incidence of focal hyperplasia of the forestomach epithelium was increased in treated rats, occurring in 3/50 control males, 28/50 at the low dose, 13/49 at the middle dose and 6/52 at the high dose; and in 1/50 female controls, 25/49 at the low dose, 11/51 at the middle dose and 15/52 at the high dose. The incidence of focal hyperplasia of the renal tubular epithelium was increased in male rats receiving 10 or 30 mg/kg bw, being seen in 0/50 controls, 1/50 at the low dose, 21/49 at the middle dose and 29/52 at the high dose (United States National Toxicology Program, 1993).

3.2 Carcinogenicity of metabolites

Mouse: 1,3-Dichloroacetone, a metabolite of 1,2,3-trichloropropane, was tested for initiation in a two-stage mouse skin tumour model. 1,3-Dichloroacetone (purity, > 99%) was applied topically in 0.2 ml ethanol to groups of 40 female SENCAR mice [age unspecified] at a dose of 0, 50, 75 or 100 mg/kg bw, three times a week for two weeks. Two weeks after the final application, 1.0 μg of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in 0.2 ml acetone was applied three times a week for 20 weeks. The numbers of animals with skin tumours at one year were: 23/199 vehicle controls, 12/25 at the low dose ($p < 0.02$; log rank test), 18/40 at the middle dose ($p < 0.02$) and 12/38 at the high dose ($p < 0.02$). In a second experiment, 1,3-dichloroacetone was given as a single application to groups of 30 female SENCAR mice at a dose of 0, 37.5, 75, 150 or 300 mg/kg bw, and TPA was applied as in the multiple-dose study. After 24 weeks, the numbers of animals with skin tumours were: 23/199 vehicle controls, 14/30 at 37.5 mg/kg bw ($p < 0.02$), 14/30 at 75 mg/kg bw ($p < 0.02$), 19/30 at 150 mg/kg bw ($p < 0.02$) and 4/20 at 300 mg/kg bw (Robinson *et al.*, 1989).

Table 4. Incidences of neoplastic lesions in Fischer 344/N rats during gavage with 1,2,3-trichloropropane for two years

Site and tumour type	Males				Females			
	Vehicle control	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw	Vehicle control	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw
Oral cavity								
Squamous-cell papilloma	0/50	4/50	9/49 $p < 0.001$	19/52 $p < 0.001$	1/50	5/49	10/52 $p = 0.003$	18/52 $p < 0.001$
Squamous-cell carcinoma	1/50	0/50	11/49 $p < 0.001$	25/52 $p < 0.001$	0/50	1/49	21/52 $p < 0.001$	21/52 $p < 0.001$
Papilloma or carcinoma	1/50	4/50	18/49 $p < 0.001$	40/52 $p < 0.001$	1/50	6/49	28/52 $p < 0.001$	32/52 $p < 0.001$
Forestomach								
Squamous-cell papilloma	0/50	29/50 $p < 0.001$	33/49 $p < 0.001$	38/52 $p < 0.001$	0/50	13/49 $p < 0.001$	32/51 $p < 0.001$	17/52 $p < 0.001$
Squamous-cell carcinoma	0/50	9/50 $p = 0.003$	27/49 $p < 0.001$	13/52 $p < 0.001$	0/50	3/49 $p < 0.001$	9/51 $p < 0.001$	4/52 $p = 0.001$
Papilloma or carcinoma	0/50	33/50 $p < 0.001$	42/49 $p < 0.001$	43/52 $p < 0.001$	0/50	16/49 $p < 0.001$	37/51 $p < 0.001$	19/52 $p < 0.001$
Preputial gland/clitoral gland								
Adenoma	5/49	3/47	5/49	11/50 $p = 0.023$	5/46	10/46 $p < 0.001$	13/50 $p = 0.001$	10/51 $p = 0.030$
Carcinoma	0/49	3/47	3/49	5/50	0/46	0/46	4/50	6/51
Adenoma or carcinoma	5/49	6/47	8/49	16/50 $p = 0.007$	5/46	10/46	17/50 $p < 0.001$	15/51 $p = 0.013$
Pancreas								
Acinar adenoma	5/50	21/50 $p < 0.001$	36/49 $p < 0.001$	29/52 $p < 0.001$				
Adenocarcinoma	0/50	0/50	2/49	1/52				
Adenoma or adenocarcinoma	5/50	21/50 $p < 0.001$	36/49 $p = 0.001$	29/52 $p < 0.001$				
Kidney, renal tubular adenoma	0/50	2/50	20/49 $p < 0.001$	21/52 $p < 0.001$				
Mammary gland, adeno-carcinoma					1/50	6/49	12/52 $p < 0.001$	21/52 $p < 0.001$

From United States National Toxicology Program (1993)

p values are given for incidences that are significantly greater than those of controls on the basis of life-table tests or logistic regression analysis (adjusted for survival)

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

[2-^{14}C]1,2,3-Trichloropropane (specific activity, 57 mCi/mmol; radiochemical purity, > 93%; about 5% assumed to be [2-^{14}C]2,3-dichloropropene) was administered by gavage to male and female Fischer 344 rats at a single dose of 30 mg/kg bw in corn oil. The compound was rapidly absorbed, metabolized and excreted. Six hours after treatment, the highest concentration of radiolabel was found in the tissue of the forestomach, followed by the glandular stomach, intestine, fat, liver and kidney. Tissue concentrations declined thereafter. After 60 h, most of the radiolabel derived from 1,2,3-trichloropropane was concentrated in the liver, kidney and forestomach. Extraction with organic solvents removed 17% (from liver) to 50% (from the forestomach) of the radiolabel. By 60 h, ≥ 90% of the compound had been cleared, with 50% (in females) to 57% (in males) of the dose excreted in urine. Exhalation of ^{14}C-carbon dioxide and excretion in the faeces each accounted for about 20% of the dose, with no marked difference between males and females; < 2% of the dose was exhaled as unchanged compound. More than half of the dose was excreted within 24 h. *N*-Acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine was identified as the major urinary metabolite in male rats (representing 40% of the radiolabel in urine after 6 h); smaller amounts were detected in the urine of female rats. Another urinary metabolite was identified as *S*-(3-chloro-2-hydroxypropyl)-L-cysteine (Mahmood *et al.*, 1991).

[1,3-^{14}C]1,2,3-Trichloropropane (specific activity, 8.8 mCi/mmol [radiochemical purity not given]) was injected intravenously into male Fischer 344 rats at a single dose of 3.6 mg/kg bw in Emulphor EL-620:ethanol:water (1:1:3 by volume). 1,2,3-Trichloropropane was distributed and eliminated rapidly: the initial half-life of unchanged compound in the blood was 0.29 h and the terminal half-life was 23 h. Adipose tissue accumulated 37% of the dose within 15 min. After 4 h, the liver contained the largest fraction of the dose, primarily as metabolites. Excretion was nearly complete (90% of the dose) within 24 h and occurred predominantly via the urine (47% of the dose); 25% of the dose was exhaled as carbon dioxide and 5% as unchanged 1,2,3-trichloropropane. None of the numerous other urinary and biliary metabolites accounted for more than 10% of the dose (Volp *et al.*, 1984). [The Working Group noted that these metabolites were not identified.]

[2-^{14}C]1,2,3-Trichloropropane (specific activity, 57 mCi/mmol; radiochemical purity, > 93%; about 5% assumed to be [2-^{14}C]2,3-dichloropropene) was administered by gavage to male B6C3F1 mice at a single dose of 30 or 60 mg/kg bw in corn oil. The compound was extensively absorbed and rapidly metabolized and excreted. By 60 h after treatment, the highest

concentrations of radiolabel were found in liver, kidney and forestomach, and in most tissues the concentrations were proportional to the dose. By 60 h, 65% of the dose had been excreted in the urine, 20% was exhaled as carbon dioxide and less than 1% as volatile compounds, whereas 16% was excreted in the faeces. Male mice exhaled ^{14}C-carbon dioxide significantly more rapidly than male rats, and the amounts and patterns of urinary metabolites in male mice were different from those in male rats. *N*-Acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine accounted for about 3% of the urinary radiolabel; no other metabolites were identified (Mahmood *et al.*, 1991).

[2-^{14}C]1,2,3-Trichloropropane (specific activity, 5.7 mCi/mmol; radiochemical purity, > 96%) was injected intraperitoneally into male Fischer 344 rats at doses of 30 mg/kg bw daily for one to three days in soya bean oil. 1,2,3-Trichloropropane bound covalently to hepatic protein, DNA and RNA, with binding levels of radioequivalents 4 h after administration of 418, 244 and 432 pmol/mg, respectively. Binding to hepatic DNA did not change significantly over 1–48 h, whereas binding to hepatic protein was maximal after 4 h. The binding to hepatic DNA and protein was cumulative when two and three doses were given 24 h apart. Covalent binding to hepatic DNA and protein was increased in animals treated with SKF 525-A; binding was decreased after treatment with phenobarbital; whereas binding was unaffected by treatment with β-naphthoflavone. Pretreatment of rats with L-buthionine (*R,S*)-sulfoximine increased binding to protein by 342% and decreased binding to DNA by 56%. Intraperitoneal administration of 1,2,3-trichloropropane depleted hepatic glutathione by 41% 2 h after a dose of 30 mg/kg bw and by 61% after a dose of 100 mg/kg bw (Weber & Sipes, 1990a).

The metabolism of [2-^{14}C]1,2,3-trichloropropane (specific activity, 5.7 mCi/mmol; radiochemical purity, > 99.5%) was studied *in vitro* in subfractions of liver from male Fischer 344 rats and human organ donors. 1,3-Dichloroacetone was identified as a microsomal metabolite of 1,2,3-trichloropropane in the presence of NADPH; it was formed at a rate of 0.27 nmol/min per mg protein with microsomes from rat liver and at 0.03 nmol/min per mg protein with microsomes from one sample of human liver. Formation of 1,3-dichloroacetone was increased after treatment with phenobarbital and dexamethasone but was decreased by treatment with β-naphthoflavone or after addition of SKF 525-A or 1-aminobenzotriazol. Addition of alcohol dehydrogenase and NADH to the microsomal incubations resulted in the formation of 1,3-dichloro-2-propanol and 2,3-dichloropropanol by reduction of 1,3-dichloroacetone and 2,3-dichloropropanol, respectively. 1,2,3-Trichloropropane was found to bind covalently to rat liver microsomal protein. The rate of binding was increased eightfold by treatment with phenobarbital, while addition of glutathione and *N*-acetylcysteine completely inhibited binding. In the presence of *N*-acetylcysteine, 1,3-(2-propanone)bis-*S,N*-acetylcysteine was the only conjugate detected. No binding occurred in the presence of rat liver cytosol and glutathione, but water-soluble metabolites were formed (Weber & Sipes, 1992).

4.1.3 Comparison of humans and animals

No data were available on the toxicokinetics of 1,2,3-trichloropropane in humans. 1,3-Dichloracetone is generated in human liver microsomes at a rate one-tenth of that in rat liver microsomes.

4.2 Toxic effects

4.2.1 Humans

The limited information available indicates that brief exposure (15 min) to 100 ppm [about 600 mg/m^3] 1,2,3-trichloropropane (purity unknown) can irritate the eye and throat (Silverman *et al.*, 1946).

4.2.2 Experimental systems

The toxicology of 1,2,3-trichloropropane in experimental animals and humans has been reviewed (United States Agency for Toxic Substances and Disease Registry, 1992; Anon., 1993).

The oral LD_{50} of 1,2,3-trichloropropane in rats is reported to be 320 mg/kg bw, whereas its approximate lethal concentration after exposure by inhalation for 4 h is 1000 ppm [about 6000 mg/m^3] (Kennedy & Graepel, 1991). A similar LD_{50} was observed in rats after dermal (Anon., 1993) and oral administration, indicating that it is absorbed by these routes.

Groups of 10 male and female Sprague-Dawley rats were administered 1,2,3-trichloropropane (purity, 99.3%; 0.7% tetrachloropropane) in corn oil by gavage at doses of 0, 0.01, 0.05, 0.20 or 0.80 mmol/kg bw [0, 1.5, 7, 29 or 117 mg/kg bw] daily for 10 days, or 0, 0.01, 0.05, 0.10 or 0.40 mmol/kg bw [0, 1.5, 7, 14 or 29 mg/kg bw] daily for 90 days [the doses are given incorrectly as mmol/kg bw in Table 1 and Figure 1 of the report]. The primary histological finding was cardiopathy associated with inflammation. Myocardial necrosis and degeneration occurred in a diffuse pattern, with marked eosinophilia at the highest dose after exposure for 10 days; cardiopathy was also noted at the lower doses in the 90-day study. A mild hepatotoxic response was noted in animals receiving the high dose in each study. Bile-duct hyperplasia was observed after exposure for 90 days (Merrick *et al.*, 1991).

Groups of 20 male and female Fischer 344/N rats and B6C3F1 mice received 1,2,3-trichloropropane (purity, > 99%) in corn oil by gavage at doses of 8, 16, 32, 63, 125 or 250 mg/kg bw on five days per week for eight (interim sacrifice) or 17 weeks; groups of 30 animals of each sex served as controls. Rats receiving the highest dose that died during the first several weeks had severe multifocal, centrilobular hepatocellular necrosis. The necrosis was more extensive in female rats, and the necrosis seen in animals at 125 mg/kg bw was less extensive than that seen at 250 mg/kg bw. Rats that received the high dose and died had severe nephrotoxicity with diffuse acute tubular necrosis in the outer stripe of the outer medulla. The nephrotoxicity seen at the time of the eight-week interim sacrifice in rats given 125 mg/kg bw was characterized by regenerative hyperplasia with karyomegaly. At the end of the study, chronic renal inflammation was also seen. Rats given 250 mg/kg bw had extensive necrosis of the olfactory and respiratory epithelium in the nose; these lesions were also seen at 125 mg/kg bw later in the study. Mice at the two highest doses had focal hepatocellular necrosis; those that died early while receiving the high dose also had necrosis, regeneration and hyperplasia of the bronchiolar epithelium. Minimal pulmonary changes were noted at the end of the study in the group receiving 125 mg/kg bw. At the time of the eight-week interim evaluation and at the end of the study, a number of mice receiving 250 mg/kg bw had minimal acanthosis and hyperkeratosis of the forestomach (United States National Toxicology Program, 1993).

Groups of 15 male and female CD rats were exposed by inhalation to 0, 5, 15 or 50 ppm (0, 30, 90 or 302 mg/m^3) 1,2,3-trichloropropane (purity, 98.9%) for 6 h per day, on five days per week for 13 weeks. Hepatocellular hypertrophy was observed in male rats at all doses. Dose-related focal peribronchial lymphoid hyperplasia was observed primarily in males and splenic extramedullary haematopoiesis only in females (Johannsen *et al.*, 1988).

Groups of 10 male and female Sprague-Dawley rats were administered 1,2,3-trichloropropane (stated purity, 99%), solubilized with 0.5% Emulphor, in their drinking-water at concentrations of 0, 1, 10, 100 or 1000 mg/L for 13 weeks. Animals of each sex receiving the highest concentration showed mild changes, consisting of anisokaryosis, accentuated zonation and occasional fatty vacuolation of the liver; female rats also had biliary hyperplasia. In addition, mild cellular changes were seen in the kidneys and thyroids of animals at the highest dose. The activities of hepatic aminopyrine demethylase and aniline hydroxylase were increased in animals receiving the highest concentration (Villeneuve *et al.*, 1985).

4.3 Reproductive and prenatal effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

Maternal toxicity was observed in female Sprague-Dawley rats administered 1,2,3-trichloropropane by intraperitoneal injection of 37 mg/kg bw on days 1–15 of gestation and killed on day 21, but there was no sign of fetal toxicity or malformations (Hardin *et al.*, 1981).

Groups of 10 male and 20 female CD rats were exposed to 1,2,3-trichloropropane in air at concentrations of 0, 30 or 90 mg/m^3 for 6 h per day on five days per week during a 10-week premating period; females were further exposed during a mating period of up to 40 days. Histopathological examination of the testes, epididymides and ovaries revealed no treatment-related toxic effect. Except for a marginal decrease in mating rates among animals at the highest dose, 1,2,3-trichloropropane neither altered fertility nor induced embryotoxic or teratogenic effects (Johannsen *et al.*, 1988).

1,2,3-Trichloropropane was administered by gavage at doses of 0, 30, 60 or 120 mg/kg bw to groups of 20 male and female CD-1 mice during a seven-day precohabitation and a 98-day cohabitation period. The controls and the group receiving 120 mg/kg bw were additionally used in a cross-over mating experiment, in which treated females were mated with control males and vice versa. 1,2,3-Trichloropropane induced a dose-related impairment of fertility in the absence of gross general toxicity, determined on the basis of body weight. Fewer pairs at the high dose delivered third, fourth or fifth litters, and the litters included fewer live pups. A similar impairment of survival rates was observed among pups of treated females that had been mated with untreated males. The weights of the livers of both male and female F_0 mice were increased, and the weights of the kidneys and ovaries of female mice were reduced; epididymal weight was slightly reduced in animals at the high dose, but sperm parameters were not influenced. Taken together, the data indicate impairment of the female reproductive system. Assessment of the

fertility of the last second-generation litter born from the F_0 generation also revealed a decreased number of pups, although other indications of fertility were not altered. In summary, the study indicates that 1,2,3-trichloropropane is toxic to the reproductive system of Swiss CD-1 mice (Gulati *et al.*, 1990).

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems (see also Table 5 and Appendices 1 and 2)

1,2,3-Trichloropropane was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic activation system, but it did not induce SOS repair functions in *Escherichia coli* PQ37.

It did not induce unscheduled DNA synthesis in primary rat hepatocytes. It induced gene mutation at the thymidine kinase locus in L5178Y mouse lymphoma cells, sister chromatid exchange in Chinese hamster V79 and ovary cells and chromosomal aberrations in Chinese hamster ovary cells, only in the presence of metabolic activation. As reported in an abstract, 1,2,3-trichloropropane enhanced the transformation of Syrian hamster embryo cells by simian adenovirus SA7 [dose not given].

Binding to hepatic DNA, RNA and protein was observed after male Fischer 344 rats, aged 9–11 weeks, were treated intraperitoneally with single or two to three repeated injections of 30 mg/kg bw ^{14}C-1,2,3-trichloropropane. DNA binding was decreased by pretreating animals with phenobarbital or the glutathione depleting agent, L-buthionine(*R*,*S*)sulfoximine, was increased by pretreatment with SKF 525-A and was not altered by pretreatment with β-naphthoflavone (Weber & Sipes, 1990a). In rats of the same strain and sex treated intraperitoneally with 30, 100 or 300 mg/kg bw, DNA strand breaks, but not DNA–DNA or DNA–protein cross-links, were detected in the alkaline elution assay. It was reported in an abstract that 1,2,3-trichloropropane did not induce unscheduled DNA synthesis in the hepatocytes of male Fischer 344 rats treated orally [dose not given].

1,2,3-Trichoropropane did not induce dominant lethal effects in the offspring of Sprague-Dawley rats that were treated at the age of 11 weeks or more by gastric intubation once a day for five days with a dose of 80 mg/kg bw and then mated with virgin females for eight successive weeks.

4.4.3 Mutagenicity of metabolites

1,3-Dichloro-2-propanol induced SOS repair functions in *E. coli* GC 4798 and mutation in *S. typhimurium* strains in the absence of exogenous metabolic systems. The addition of aldehyde dehydrogenase did not alter the activity. The genetic activity *in* vitro may have been due to formation of epichlorohydrin in the buffer system (Hahn *et al.*, 1991). Sister chromatid exchange was induced in cultured mammalian cells.

Table 5. Genetic and related effects of 1,2,3-trichloropropane

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	-	-	0.00	von der Hude *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	5.5	Stolzenberg & Hine (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	4	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	2	Ratplan & Plaumann (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	4.0	US National Toxicology Program (1993)
SAO, *Salmonella typhimurium* TA100, reverse mutation	-	(+)	7	Låg *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	+	0.4	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	+	2	Ratplan & Plaumann (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	+	4.0	US National Toxicology Program (1993)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-		128	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	37.0	Ratplan & Plaumann (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	37.0	Ratplan & Plaumann (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	39	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	37.0	Ratplan & Plaumann (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	40.0	US National Toxicology Program (1993)
SAS, *Salmonella typhimurium* TA97, reverse mutation	-	+	4	US National Toxicology Program (1993)
URP, Unscheduled DNA synthesis, Fischer 344 rat primary hepatocytes *in vitro*	-		10.0	Williams *et al.* (1989)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	-	+	14	US National Toxicology Program (1993)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	-	+	44	von der Hude *et al.* (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	-	+	14	US National Toxicology Program (1993)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	-	+	60	US National Toxicology Program (1993)

Table 5 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	0.00	Hatch *et al.* (1983) (Abstract)
DVA, DNA strand breaks, rat hepatocytes *in vivo*	+		30.0 ip × 1	Weber & Sipes (1990b)
DVA, DNA–DNA and DNA–protein cross-links, rat hepatocytes *in vivo*	-		300.0 ip ×1	Weber & Sipes (1990b)
UPR, Unscheduled DNA synthesis, rat hepatocytes *in vivo*	-		0.00 po	Mirsalis *et al.* (1983) (Abstract)
DLR, Dominant lethal mutation, rats *in vivo*	-		80.0 po × 5	Saito-Suzuki *et al.* (1982)
BVD, Covalent DNA binding, rat hepatocytes *in vivo*	+		30.0 ip × 1	Weber & Sipes (1990a)
Metabolites of 1,2,3-trichloropropane				
1,3-Dichloro-2-propanol				
PRB, SOS chromotest, *Escherichia coli* GC4798	+	0	369.0	Hahn *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	582.0	Hahn *et al.* (1991)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	192.0	Hahn *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	+	147.4	von der Hude *et al.* (1987)
1,3-Dichloroacetone (1,3-Dichloropropanone)				
PRB, SOS chromotest, *Escherichia coli* PQ37	(+)	+	0.7	Le Curieux *et al.* (1994)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	0.6	Meier *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.8	Merrick *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation, fluctuation test	+	+	0.03	Le Curieux *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.8	Merrick *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	5.0	Meier *et al.* (1985)
***, *Pleurodeles waltl*, micronucleus induction *in vivo*	+		0.03, 12 d	Le Curieux *et al.* (1994)
SIC, sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	+	0.3	von der Hude *et al.* (1987)

[a]+, considered to be positive; (+), considered to be weakly positive in an inadequate study; -, considered to be negative; 0, not tested; for in-vivo tests, no entry of a result under 'with exogenous metabolic system'

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

1,3-Dichloroacetone (1,3-dichloropropanone) induced SOS repair functions in *E. coli* PQ37 and mutations in *S. typhimurium* strains in the absence of exogenous metabolic systems.

Sister chromatid exchange was induced in cultured mammalian cells and micronuclei were induced in the peripheral erythrocytes of the newt, *Pleurodeles waltl, in vivo.*

5. Summary and Evaluation

5.1 Exposure data

1,2,3-Trichloropropane, a chlorinated solvent, has been produced commercially for use as a paint and varnish remover and as a cleaning and degreasing agent. Currently, it is used primarily as a chemical intermediate. It has been detected in water, including drinking-water, and in soil as a result of its presence as an impurity in a commercial nematocide.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,2,3-Trichloropropane was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. It produced tumours of the oral mucosa and of the uterus in female mice and increased the incidences of tumours of the forestomach, liver and Harderian gland in mice of each sex. In rats, increased incidences of tumours were observed in the preputial gland, kidney and pancreas of males, in the clitoral gland and mammary gland of females and in the oral cavity and forestomach of both males and females.

The metabolite, 1,3-dichloroacetone, initiated skin tumour development in mice when applied topically.

5.4 Other relevant data

No data are available on the toxicokinetics of 1,2,3-trichloropropane in humans. It is rapidly absorbed and excreted after oral administration to rats and mice. Its metabolic products bind covalently to rat hepatic protein and DNA. The reactive and mutagenic metabolite, 1,3-dichloroacetone, was formed by hepatic metabolism in rat and human microsomes *in vitro.*

1,2,3-Trichloropropane causes tissue necrosis in a number of organs in rats and mice; the liver and kidney are the main target organs in the rat. In addition, myocardial and nasal epithelial damage is observed; in mice, hepatic and bronchiolar necrosis are seen.

There are no data on the effects of 1,2,3-trichloropropane on human reproduction. Studies performed in rats provided no evidence of alteration of fertility or of embryotoxic effects. In a two-generation study in mice, there was evidence of impairment of the female reproductive system.

In single studies, DNA binding and induction of DNA breaks, but not of dominant lethal mutations, were reported in rodents treated *in vivo*.

Gene mutation, sister chromatid exchange and chromosomal aberrations, but not DNA damage, were induced in rodent cells *in vitro* (all single studies, except for sister chromatid exchange). 1,2,3-Trichloropropane was mutagenic to bacteria.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 1,2,3-trichloropropane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2,3-trichloropropane.

Overall evaluation

1,2,3-Trichloropropane *is probably carcinogenic to humans (Group 2A).*

In making the overall evaluation, the Working Group took into account the following evidence:

(i) 1,2,3-Trichloropropane causes tumours at multiple sites and at high incidence in mice and rats.

(ii) The metabolism of 1,2,3-trichloropropane is qualitatively similar in human and rodent microsomes.

(iii) 1,2,3-Trichloropropane is mutagenic to bacteria and to cultured mammalian cells and binds to DNA of animals treated *in vivo*.

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

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