

**TRICHLOROETHYLENE,
TETRACHLOROETHYLENE,
AND SOME OTHER
CHLORINATED AGENTS**

VOLUME 106

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, 2-9 October 2012

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**IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS**

1,1,1,2-TETRACHLOROETHANE

1,1,1,2-Tetrachloroethane was considered by previous IARC Working Groups in 1986, 1987, and 1998 ([IARC, 1986, 1987, 1999](#)). New data have since become available and these have been taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

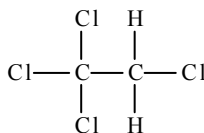
Chem. Abstr. Serv. Reg. No.: 630-20-6

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

IUPAC Systematic Name: 1,1,1,2-Tetrachloroethane

Synonym: (Chloromethyl)trichloromethane

1.1.2 Structural and molecular formulae, and relative molecular mass



Relative molecular mass: 167.85

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless heavy liquid ([HSDB, 2012](#))

Boiling-point: 130.2 °C ([Haynes, 2012](#))

Melting-point: -70.2 °C ([Haynes, 2012](#))

Density: 1.5406 g/cm³ at 20 °C ([Haynes, 2012](#))

Solubility: Slightly soluble in water (1.07 g/L at 25 °C); soluble in acetone, benzene, chloroform; miscible in diethyl ether and ethanol ([Haynes, 2012](#))

Volatility: Vapour pressure, 1 kPa at 17 °C ([Haynes, 2012](#))

Octanol/water partition coefficient (P): log P, 2.93 ([HSDB, 2012](#))

Conversion factor: mg/m³ = 6.87 × ppm, calculated from: mg/m³ = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa).

1.1.4 Technical products and impurities

1,1,1,2-Tetrachloroethane is available in research quantities at a purity of > 99% ([Sigma Aldrich, 2012](#)).

Trade names for 1,1,1,2-tetrachloroethane include: Freon 130a, F130a and HCC 130a ([Springer Materials, 2013](#)).

Table 1.1 Methods for the analysis of 1,1,1,2-tetrachloroethane

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Air collected in specially prepared canister; desorb on cold trap	GC/MS	NR	EPA (1999a)
		GC/ECD	NR	
		GC/FID	NR	
		GCPID	NR	
	Analyte collected on sorbent tube; thermally desorb to GC	GC/MS	NR	EPA (1999b)
		GC/ECD	NR	
		GC/FID	NR	
		GCPID	NR	
Water	Purge with inert gas and trap; desorb to GC	GC/PID	NR	EPA (1988)
		GC/HECD	0.01 µg/L	EPA (1995a)
	Purge with inert gas and trap; desorb to GC	GC/MS	0.05 µg/L	EPA (1988) , EPA (1995b)
Liquid and solid wastes	Purge with inert gas and trap	GC/PID	NR	EPA (1996a)
		GC/HECD	0.005 µg/L	
	Purge with inert gas and trap and various other methods	GC/MS	5 µg/kg (soil/sediment)	EPA (1996b)
			500 µg/kg (wastes)	
			5 µg/L (ground water)	

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

1.1.5 Analysis

Methods for the analysis of volatile organic compounds have been reviewed by [Delinsky et al. \(2005\)](#) and [Demeestere et al. \(2007\)](#). Selected methods for the analysis of 1,1,1,2-tetrachloroethane in various matrices are identified in [Table 1.1](#).

1.2 Production and use

1.2.1 Production process

(a) Manufacturing processes

1,1,1,2-Tetrachloroethane is a by-product in industrial chlorination reactions, mainly from the production of 1,1,1-trichloroethane from 1,1-dichloroethane, 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane from 1,2-dichloroethane. It can be prepared in a highly purified form by isomerization of 1,1,2,2-tetrachloroethane or by chlorination of 1,1-dichloroethylene at approximately 40 °C in the liquid

phase. Aluminium chloride is used in both reactions as a Lewis catalyst ([HSDB, 2012](#)).

(b) Production volume

Between 1 and 10 million pounds [454–4540 tonnes] of 1,1,1,2-tetrachloroethane were produced in or imported into the USA in 2002 ([EPA, 2008](#)).

1.2.2 Use

A major use of 1,1,1,2-tetrachloroethane was as a solvent in the manufacture of insecticides, herbicides, soil fumigants, bleaches, paints and varnishes. In the 1990s, 1,1,1,2-tetrachloroethane was used primarily as a feedstock for the production of solvents such as trichloroethylene and tetrachloroethylene ([HSDB, 2012](#)). It was used in World War II to impregnate clothing as a defence against mustard gas ([Norman et al., 1981](#)).

Table 1.2 Concentrations of 1,1,1,2-tetrachloroethane in air

Location	Concentration		Comments	Reference
	Mean	Range		
Outdoor air				
<i>Remote</i>				
Eight sites; north and south Atlantic	NR	0.2–1.7 ppt	Background tropospheric levels	Class & Ballschmiter (1986)
Hamburg, Germany	NR	0.006–0.3 µg/m ³	12 sites	Bruckmann et al. (1988)
Phoenix, AZ, USA	8.5 ppt	NR		Singh et al. (1981)
Oakland, CA, USA	4.2 ppt	NR		Singh et al. (1981)
Los Angeles, CA, USA	3.7 ppt	NR		Singh et al. (1981)
Throughout country, USA	0.071 ppt	ND–3.1 ppt	43 sites	HSDB (2012)
Throughout country, USA	2.2 ppt	ND–63	602 sites	HSDB (2012)
Kuwait City, Kuwait	39 µg/m ³	ND–708	1994–95	Bouhamra (1997)^a
Indoor air				
Kuwait	216 µg/m ³	ND–2557 µg/m ³	1994, 1995	Bouhamra (1997)^a

^a [The Working Group noted that the median reported was higher than the mean, which raises doubt about the validity of the data]
 ND, not detected; NR, not reported; ppt, parts per trillion

1.3 Occurrence and exposure

1.3.1 Natural occurrence

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

1.3.2 Environmental occurrence

1,1,1,2-Tetrachloroethane may be formed incidentally during the manufacture of other chlorinated ethanes and released into the environment as air emissions or in wastewater. It has been detected at low levels in urban air, ambient air, drinking-water, ambient water, groundwater, wastewater and soil samples ([HSDB, 2012](#)).

(a) Air

[Table 1.2](#) presents some recent data on levels of 1,1,1,2-tetrachloroethane in air.

(b) Water

Data on the levels of 1,1,1,2-tetrachloroethane in water were available from one study in Maryland, USA, which reported a maximum

concentration of 3 µg/L in river water near a military testing area ([Burton et al., 2002](#)).

1.3.3 Exposure

No data were available on levels of 1,1,1,2-tetrachloroethane in occupational settings or in the general population.

1.4 Regulations and guidelines

There are no exposure limits for 1,1,1,2-tetrachloroethane.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See [Table 3.1](#)

Table 3.1 Studies of carcinogenicity in experimental animals given 1,1,1,2-tetrachloroethane by gavage

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F ₁ (M) 103 wk or 65 wk NTP (1983)	0, 250, 500 mg/kg bw per day, 5 days/wk, in corn oil 50/group	Hepatocellular adenoma: 6/48, 14/46, 21/50 Hepatocellular carcinoma: 12/48, 13/46, 6/50 Hepatocellular adenoma or carcinoma (combined): 18/48, 27/46, 27/50	Life-table test $P < 0.001$ (trend) $P = 0.021$ (lower dose) $P < 0.001$ (higher dose) $P = 0.012$ (trend) $P = 0.010$ (higher dose) $P < 0.001$ (trend) $P = 0.035$ (lower dose) $P < 0.001$ (higher dose)	Purity, > 99.4% Toxicity made it necessary to kill mice at higher dose at 65 wk, which reduced the sensitivity of the study.
Mouse, B6C3F ₁ (F) 103 wk or 65 wk NTP (1983)	0, 250, 500 mg/kg bw per day, 5 days/wk, in corn oil 50/group	Hepatocellular adenoma: 4/49, 8/46, 24/48 Hepatocellular carcinoma: 1/49, 5/46, 6/48 Hepatocellular adenoma or carcinoma (combined): 5/49, 13/46, 30/48	Life-table test $P < 0.001$ (trend) $P < 0.001$ (higher dose) $P < 0.001$ (trend) $P = 0.008$ (higher dose) $P < 0.001$ (trend) $P = 0.011$ (lower dose) $P < 0.001$ (higher dose)	Purity, > 99.4% Toxicity made it necessary to kill mice at higher dose at 65 wk, which reduced the sensitivity of the study.
Rat, F344/N (M) 103 wk NTP (1983)	0, 125, 250 mg/kg bw per day, 5 days/wk, in corn oil 50/group	Liver neoplastic nodules or hepatocellular carcinoma (combined): 0/49, 1/49, 3/48 Mammary gland fibroadenoma: 6/49, 15/49, 7/46	$P = 0.058$ (trend)	Purity, > 99.4% Reduced survival in the group at the higher dose reduced the sensitivity of study.
Rat, F344/N (F) 103 wk NTP (1983)	0, 125, 250 mg/kg bw per day, 5 days/wk, in corn oil 50/group		$P \leq 0.024$ (lower dose)	Purity, > 99.4%

bw, body weight; F, female; M, male; wk, week

3.1 Mouse

Oral administration

Groups of 50 male and 50 female B6C3F₁ mice were given 1,1,1,2-tetrachloroethane at a dose of 0, 250, or 500 mg/kg bw per day by gavage in a corn oil vehicle, 5 days per week, for a scheduled duration of 103 weeks (NTP, 1983). Owing to toxicity in the central nervous system, male and female mice in the group receiving the higher dose were killed after 65 weeks of exposure. Mice in the group receiving the lower dose and in the control group were killed after 103 weeks. In males, there was a statistically significant treatment-related increase in the incidence of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined). There was a positive trend in the incidence of hepatocellular carcinoma, with the incidence in male mice at the higher dose being statistically significantly increased [based on life-table analysis that adjusted for early mortality.] In females, statistically significant increases in the incidence of hepatocellular adenoma and of hepatocellular carcinoma were observed in mice at the higher dose. A positive trend with daily dose was still evident for both tumour types, despite female mice in the group at the higher dose being killed at 65 weeks. [The Working Group noted that termination at 65 weeks reduced the ability of the study to detect late developing tumours.]

3.2 Rat

Oral administration

Groups of 50 male and 50 female F344/N rats were given 1,1,1,2-tetrachloroethane at a dose of 0, 125, and 250 mg/kg bw per day by gavage in a corn oil vehicle, 5 days per week, for 103 weeks (NTP, 1983). Survival of male rats was significantly reduced relative to controls at the end of the experiment: control group, 29 out of 50; lower dose, 25 out of 50; and higher dose, 21 out of 50.

Survival was not significantly reduced in female rats.

A marginal positive trend ($P = 0.058$) in the combined incidence of liver neoplastic nodules or hepatocellular carcinoma was observed in male rats (0 out of 49, 1 out of 49, 3 out of 48). The one hepatocellular carcinoma observed in this study was in the group at the higher dose.

A statistically significant increase ($P \leq 0.024$) in the incidence of fibroadenoma of the mammary gland in female rats was observed in the group receiving the lower dose relative to controls (6 out of 49, 15 out of 49, 7 out of 46). The incidences of other neoplasms in treated rats were not statistically different from controls. However, a rare renal tubular cell adenoma and a rare transitional cell papilloma of the bladder were observed in the group of male rats at the higher dose, a rare renal tubular cell adenoma was observed in the group of female rats at the higher dose, and six uncommon mesotheliomas of the tunica vaginalis or the peritoneum were observed in male rats at the lower dose (3 out of 50) and higher dose (3 out of 48). No such tumours were observed in controls. [The Working Group noted that the high mortality among male rats given the high dose reduced the sensitivity of this study.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Absorption

(a) Humans

No direct data on the absorption of 1,1,1,2-tetrachloroethane in humans exposed by inhalation, or by oral or dermal administration, were available. Estimates of the human

blood:air partition coefficient *in vitro* for this compound averaged about 30 ([Meulenberg & Vijverberg, 2000](#)), indicating respiratory uptake of 1,1,1,2-tetrachloroethane from inhaled air under equilibrium conditions.

(b) *Experimental systems*

[Gargas & Andersen \(1989\)](#) conducted experiments in rats exposed by closed-chamber, whole-body inhalation. Chamber concentrations declined with time, which was consistent with an equilibrium alveolar gas-exchange model, in which uptake by inhalation is largely determined by the partition coefficient. Estimates of the rat blood:air partition coefficient *in vitro* for this compound averaged about 42 ([Meulenberg & Vijverberg, 2000](#)), indicating considerable respiratory uptake of 1,1,1,2-tetrachloroethane from inhaled air under equilibrium conditions.

In a study by [Mitoma *et al.* \(1985\)](#), groups of male Osborne-Mendel rats were exposed to 1,1,1,2-tetrachloroethane at a dose of 25 or 200 mg/kg bw and groups of B6C3F₁ mice were exposed to 1,1,1,2-tetrachloroethane at 100 or 400 mg/kg bw, 5 days per week, for 4 weeks. The animals were then given a single dose of radiolabeled compound; 65% of the administered dose in rats and 84% in mice was recovered as metabolites in exhaled breath and urine over 48 hours.

4.1.2 Distribution

(a) *Humans*

No direct data on the tissue distribution of 1,1,1,2-tetrachloroethane in humans were available to the Working Group. However, [Meulenberg & Vijverberg \(2000\)](#) used empirical regression models to predict tissue:air partition coefficients based on measured saline:air and oil:air partition coefficients. Based on their predictions, tissue:blood partition coefficients in humans were estimated to range from 1.4 (kidney) to 56 (fat), depending on the lipid content of the tissues. These values suggest

that 1,1,1,2-tetrachloroethane would be widely distributed to tissues after systemic delivery.

(b) *Experimental systems*

No direct data on the tissue distribution of 1,1,1,2-tetrachloroethane were available to Working Group. However, [Gargas & Andersen \(1989\)](#) reported tissue:blood partition coefficients in the range of 0.7 (muscle) to 26.5 (fat), suggesting that 1,1,1,2-tetrachloroethane would be widely distributed to tissues after systemic delivery.

4.1.3 Metabolism

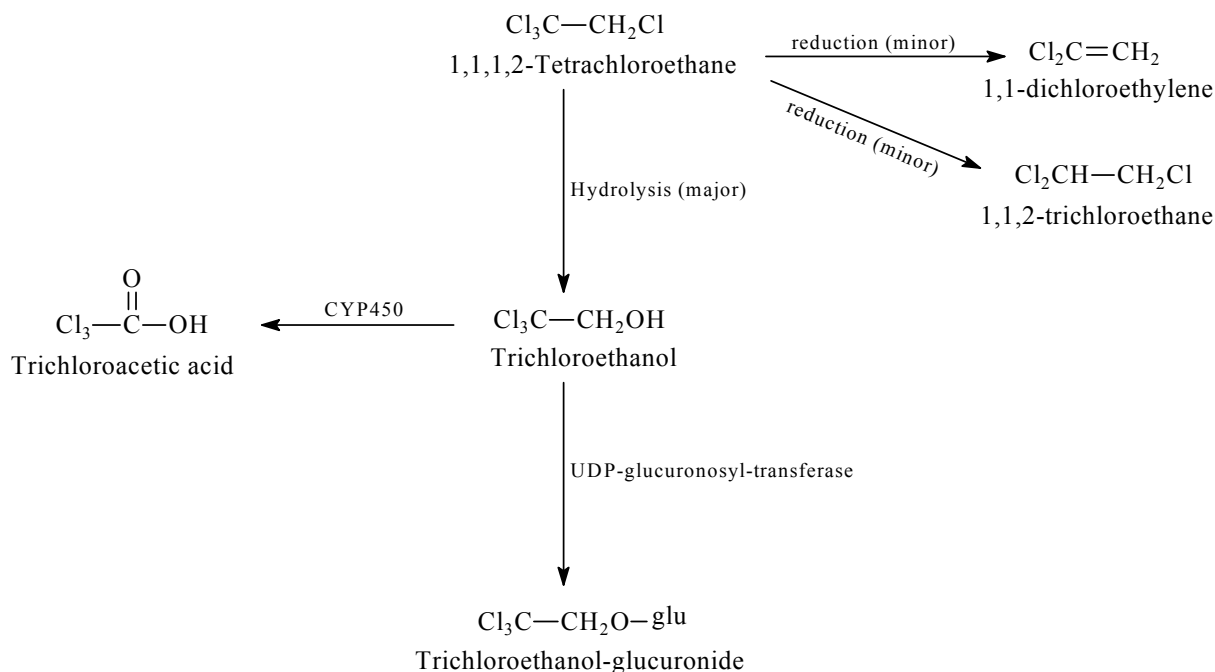
(a) *Humans*

No data were available to the Working Group.

(b) *Experimental systems*

The metabolism of 1,1,1,2-tetrachloroethane is extensive in rodents. [Yllner \(1971\)](#) reported that between 19% and 56% of the administered dose was recovered as urinary metabolites in mice injected subcutaneously with ¹⁴C-labelled tetrachloroethane. [Mitoma *et al.* \(1985\)](#) characterized the overall metabolic disposition of several chlorinated hydrocarbons, including 1,1,1,2-tetrachloroethane, in Osborne-Mendel rats and B6C3F₁ mice given either 25% or 100% of the maximum tolerated dose. [Mitoma *et al.* \(1985\)](#) reported that a small fraction was expired as carbon dioxide (1% in rats and 2% in mice), and a larger fraction was excreted in exhaled air and urine as metabolites (60% in rats and 77% in mice), after repeated oral dosing for 4 weeks.

The major urinary metabolite in the rat, guinea-pig, and rabbit ([Truhaut & Nguyen-Phu-Lich, 1973](#)), and mouse ([Yllner, 1971](#)) was trichloroethanol, with smaller amounts of trichloroacetic acid. [Yllner \(1971\)](#) considered that the possibility that trichloroethylene was an intermediate in the metabolism of 1,1,1,2-tetrachloroethane was inconsistent with the very small fraction (0.02%) of the administered dose expired

Fig. 4.1 Proposed metabolism of 1,1,1,2 tetrachloroethane

Prepared by the Working Group

as trichloroethylene. Therefore, [Yllner \(1971\)](#) hypothesized that trichloroethanol is formed via hydrolytic removal of chlorine (see [Fig. 4.1](#)).

Anaerobic incubation of 1,1,1,2-tetrachloroethane with microsomes from rat liver showed extensive reductive metabolism to 1,1-dichloroethylene and 1,1,2-trichloroethane at a ratio of about 25:1 ([Thompson et al., 1984](#)). The results of these experiments *in vitro* were consistent with evidence of 1,1-dichloroethylene and 1,1,2-trichloroethane in the blood of rats treated with 1,1,1,2-tetrachloroethane *in vivo* ([Thompson et al., 1984](#)). However, these metabolites are likely to be minor, because the trace amounts of trichloroethanol and trichloroacetic acid resulting from metabolism of 1,1-dichloroethylene and 1,1,2-trichloroethane ([ATSDR 1989, 1994](#)) cannot account for the trichloroethanol and trichloroacetic acid found in the urine after administration of 1,1,1,2-tetrachloroethane.

4.1.4 Excretion

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

In experimental animals, 1,1,1,2-tetrachloroethane is eliminated primarily as metabolites in urine, with small amounts as carbon dioxide in expired air. At higher doses (g/kg bw), the parent compound is excreted in expired air ([Mitoma et al., 1985; Yllner, 1971](#)). The patterns of elimination in rats and mice are qualitatively similar ([Mitoma et al. 1985](#)). Elimination is fairly rapid, with a large fraction excreted in the first 24 hours, but significant amounts of trichloroacetic acid are present in the urine at 48–72 hours after exposure ([Yllner 1971](#)).

4.2 Genotoxicity and related effects

4.2.1 Humans

No studies on the genotoxicity of 1,1,1,2-tetrachloroethane in humans were available to the Working Group.

4.2.2 Experimental systems

Several studies examining the potential genotoxicity of 1,1,1,2-tetrachloroethane were available. These are summarized in [Table 4.1](#) and are discussed below. While the results of the various tests were not always consistent, most suggested that 1,1,1,2-tetrachloroethane is genotoxic, and that metabolic activation is generally required to elicit genotoxicity.

(a) Covalent binding to DNA

In a study by [Colacci et al. \(1989\)](#), covalent binding to DNA, RNA, and proteins of liver, lung, kidney, and stomach was assessed in organs of male Wistar rats and BALB/c mice 24 hours after administration of 1,1,1,2-tetrachloroethane by intraperitoneal injection. Binding to DNA *in vivo* was generally higher in mouse organs than in rat organs. The covalent binding index (CBI) was calculated as 82 for mouse liver DNA, and 40 for rat liver DNA, thus classifying 1,1,1,2-tetrachloroethane as a weak to moderate initiator.

[Paolini et al. \(1990\)](#) studied covalent binding of radiolabelled 1,1,1,2-tetrachloroethane to DNA and specifically assessed the influence of the presence of reduced purine nucleotides and cytochrome P450 activity on the responses. Binding of [¹⁴C]-labelled 1,1,1,2-tetrachloroethane to DNA *in vitro*, as mediated by microsomes from mouse liver, was increased 4.4-fold upon addition of both NADPH and NADH. They also observed a significant enhancement with addition of the purine nucleotides in mutagenesis experiments in the diploid D7 strain of *Saccharomyces cerevisiae*. Specifically, the frequencies of mitotic gene conversion and

reverse point mutation were both enhanced. No evidence of mutagenesis was observed without addition of NADH.

(b) Mutation and cytogenetic effects

As shown in [Table 4.1](#), 1,1,1,2-tetrachloroethane has given negative results in tests for mutagenicity in several strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, TA98), with and without exogenous metabolic activation. Positive results have been reported by [Strubel & Grummt \(1987\)](#), in TA97 (with metabolic activation), and in TA98 or TA100 with and without metabolic activation; the results for TA104 were borderline positive in this study. In another published report of tests, however, 1,1,1,2-tetrachloroethane at higher exposures was reported to lack mutagenicity in the TA98 and TA100 strains ([Haworth et al. 1983](#)).

[Bronzetti et al. \(1989\)](#) found that 1,1,1,2-tetrachloroethane induced recombination but not mutation in *S. cerevisiae*.

[Whittaker et al. \(1990\)](#) assessed the mutagenic activity of 1,1,1,2-tetrachloroethane and 11 other organic solvents. Induced mitotic chromosome loss was assayed using the diploid yeast strain *S. cerevisiae* D61.M; the assay relied on uncovering expression of multiple recessive markers reflecting presumptive loss of the chromosome VII homologue carrying the corresponding wild-type alleles. In this assay, 1,1,1,2-tetrachloroethane did not induce chromosome loss, but elicited high degrees of respiratory deficiency, reflecting anti-mitochondrial activity.

[Foureman et al. \(1994\)](#) found that sex-linked recessive lethal mutations were not induced in *Drosophila melanogaster*.

[Crebelli et al. \(1988\)](#) tested a series of halogenated solvents for induction of mitotic segregation in *Aspergillus nidulans* diploid strain P1. 1,1,1,2-Tetrachloroethane significantly increased the frequency of morphologically abnormal colonies that produced euploid whole-chromosome segregants (haploids and non-disjunctional

Table 4.1 Studies of genotoxicity with 1,1,1,2-tetrachloroethane

Test system	Result ^a		Dose ^b (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
<i>Salmonella typhimurium</i> , forward mutation, arabinose resistance	-	-	150	Roldán-Arjona et al. (1991)
<i>S. typhimurium</i> TA100, reverse mutation	-	-	166	Haworth et al. (1983)
<i>S. typhimurium</i> TA100, reverse mutation	+	+	5	Strubel & Grummt (1987)
<i>S. typhimurium</i> TA104, reverse mutation	(+)	(+)	25	Strubel & Grummt (1987)
<i>S. typhimurium</i> TA1535, reverse mutation	-	-	166	Haworth et al. (1983)
<i>S. typhimurium</i> TA1537, reverse mutation	-	-	166	Haworth et al. (1983)
<i>S. typhimurium</i> TA98, reverse mutation	-	-	166	Haworth et al. (1983)
<i>S. typhimurium</i> TA98, reverse mutation	+	+	125	Strubel & Grummt (1987)
<i>S. typhimurium</i> TA97, reverse mutation	-	+	5	Strubel & Grummt (1987)
<i>Saccharomyces cerevisiae</i> strain D7, gene conversion, <i>trp</i> locus	+	-	168	Bronzetti et al. (1989)
<i>Aspergillus nidulans</i> strain PI, genetic crossing-over	+	NT	400	Crebelli et al. (1988)
<i>S. cerevisiae</i> , reverse mutation, <i>ilv</i> locus	-	-	1 679	Bronzetti et al. (1989)
<i>S. cerevisiae</i> strain D7, reverse mutation	-	+	839-1679	Paolini et al. (1990)
<i>S. cerevisiae</i> strain D61.M, aneuploidy	-	NT	1340	Whittaker et al. (1990)
<i>Aspergillus nidulans</i> strain PI, aneuploidy	+	NT	200	Crebelli et al. (1988)
<i>Drosophila melanogaster</i> , sex-linked recessive lethal mutations	-	NT	1500 µg/mL inj	Foureman et al. (1994)
Gene mutation, mouse lymphoma L5178Y cells, <i>Tk</i> ⁺ locus <i>in vitro</i>	-	+	200	McGregor et al. (1988)
Gene mutation, mouse lymphoma L5178Y cells, <i>Tk</i> ⁻ locus <i>in vitro</i>	-	?	200	Sofuni et al. (1996)
Sister chromatid exchange, Chinese hamster ovary cells <i>in vitro</i>	+	-	248	Galloway et al. (1987)
Chromosomal aberrations, Chinese hamster ovary cells <i>in vitro</i>	-	-	506	Galloway et al. (1987)
Chromosomal aberrations, Chinese hamster lung fibroblasts <i>in vitro</i>	-	-	200	Matsuoka et al. (1996)
Aneuploidy, Chinese hamster lung fibroblasts <i>in vitro</i>	+	+	100	Matsuoka et al. (1996)

Table 4.1 (continued)

Test system	Result ^a		Dose ^b (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Cell transformation, BALB/c-3T3 mouse cells	-	NT	250	Tu et al. (1985)
Binding (covalent) to calf thymus DNA <i>in vitro</i>	NT	+	9.6	Colacci et al. (1989)
Binding (covalent) to calf thymus DNA <i>in vitro</i>	(+)	+	NR	Paolini et al. (1990)
Binding (covalent) to DNA, BALB/c mouse lung, liver, kidney and stomach <i>in vivo</i>	+	NT	1.46 i.p. × 1	Colacci et al. (1989)
Binding (covalent) to DNA, Wistar rat lung, liver, kidney and stomach <i>in vivo</i>	+	NT	1.46 i.p. × 1	Colacci et al. (1989)

^a +, positive; (+), weakly positive; -, negative; ?, inconclusive

^b Tests *in vitro*, µg/mL; tests *in vivo*, mg/kg bw per day

HID, highest ineffective dose; inj, injection; i.p., intraperitoneal; LED, lowest effective dose; NR, not reported; NT, not tested

diploids). A borderline increase in crossing-over frequency was also observed, suggesting the involvement of non-DNA targets in the induction of aneuploidy. Conclusive evidence for induction of aneuploidy as a primary genetic event was provided by experiments with haploid strain 35.

As summarized in [Table 4.1](#), 1,1,1,2-Tetrachloroethane induced gene mutations in the *Tk*^{+/-} assay in mouse lymphoma cells only in the presence of an exogenous metabolic activation system. It did not increase the frequency of chromosomal aberration in Chinese hamster lung fibroblasts or ovary cells, but did induce sister chromatid exchange in Chinese hamster ovary cells and aneuploidy in Chinese hamster lung fibroblasts in the absence of exogenous metabolic activation. 1,1,1,2-Tetrachloroethane did not induce cell transformation in BALB/c-3T3 cells.

4.3 Nongenotoxic mechanisms of carcinogenesis

4.3.1 Mechanisms related to carcinogenesis in the liver

(a) Cytotoxicity

(i) Humans

No data were available to the Working Group.

(ii) Experimental systems

The National Toxicology Program ([NTP, 1983](#)) conducted 2-year bioassays with 1,1,1,2-tetrachloroethane in male and female F344 rats and B6C3F₁ mice. Rats were given 1,1,1,2-tetrachloroethane at 0, 125, or 250 mg/kg bw per day in corn oil, 5 days per week for 103 weeks. Significant reduction in survival was observed in males at the higher dose. Hepatic clear-cell changes were observed in female rats. Mice were given 1,1,1,2-tetrachloroethane at 0, 250, or 500 mg/kg bw per day in corn oil, 5 days per week for 103 weeks (control, lower dose) or 65

weeks (higher dose). A large proportion of mice at the higher dose were found to be moribund at 65 weeks and were killed. Increased incidence of alterations in liver cellular structure, characterized by inflammation, necrosis, fatty metamorphosis, and hepatocytomegaly, were observed at the higher dose.

In a study of reproductive toxicity ([Truhaut et al., 1974](#)), rats were given 1,1,1,2-tetrachloroethane as a single dose at 300 mg/kg bw per day, 5 days per week, for 10 months. Adult rats and pups had hepatic fatty vacuolization, and adults also had centrilobular necrosis.

(b) Promotion of γ -glutamyltranspeptidase-positive foci

(i) Humans

No data on this mechanism in humans were located by the Working Group.

(ii) Experimental systems

[Story et al. \(1986\)](#) assessed the differences between a series of halogenated hydrocarbons and phenobarbital in induction of pre-neoplastic foci in rat liver. The assay for foci in rat liver was taken as evidence of initiating or promoting potential. Young adult male Osborne-Mendel rats were given partial hepatectomies 24 hours before receiving a single intraperitoneal dose of 1,1,1,2-tetrachloroethane or one of several other chemicals tested. One week later, the rats were started either on a diet containing phenobarbital at 0.05% (w/w), or on daily treatment with 1,1,1,2-tetrachloroethane in corn oil by gavage, for 7 weeks. Rats were killed 1 week after the end of treatment and livers were assayed for γ -glutamyltranspeptidase as a putative pre-neoplastic marker. 1,1,1,2-Tetrachloroethane was without significant effect during the initiation protocol at the maximum tolerated dose and was without effect in the promotion protocol.

4.3.2 Mechanisms related to toxicity in the kidney

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

The National Toxicology Program ([NTP, 1983](#)) conducted 2-year bioassays of 1,1,1,2-tetrachloroethane in male and female F344 rats and B6C3F₁ mice. Rats were given a dose of 0, 125, or 250 mg/kg per day in corn oil, 5 days per week for 103 weeks. A significant reduction in survival was observed in males at the higher dose. Male rats also showed a treatment-related increase in the incidence of mineralization of the kidneys.

The National Toxicology Program conducted a short-term study of renal toxicity with 1,1,1,2-tetrachloroethane in male F344 rats ([NTP, 1996](#)). In rats given two daily doses of (1.24 mmol/kg per day) for 21 days, hyaline droplet nephropathy was observed. An increased renal-cell labelling index, indicating replicative DNA synthesis, was also observed.

4.4 Susceptibility

No data were available to the Working Group.

4.5 Synthesis of mechanistic considerations

There is weak evidence to suggest that 1,1,1,2-tetrachloroethane is genotoxic. The overall database of studies of genotoxicity is limited. Most studies of mutagenesis in bacteria reported mixed, mostly negative, results. A few studies have indicated possible clastogenic effects, and one study showed DNA binding.

The target organs of adverse health outcomes associated with 1,1,1,2-tetrachloroethane are the liver, kidney, and central nervous system. The liver appears to be a major target organ

for 1,1,1,2-tetrachloroethane based on cancer bioassays and toxicity data. In the liver, suggested nongenotoxic mechanisms, exclusively from studies in rodents, include cytotoxicity (shown in rats and mice in a 2-year bioassay), hepatomegaly, and steatosis (fatty vacuolation reported in rats). One study examined the potential for 1,1,1,2-tetrachloroethane to promote γ -glutamyltranspeptidase-positive foci in rat liver and showed no effect. Overall, the evidence for mechanisms of carcinogenesis in the liver is weak.

Evidence of kidney toxicity in male rats was found in two (long- and short-term) studies by the National Toxicology Program. The changes included mineralization, hyaline droplet nephropathy and increased cell proliferation.

5. Summary of Data Reported

5.1 Exposure data

1,1,1,2-Tetrachloroethane has been used as a solvent in insecticides, herbicides, varnishes and other products. It now has no known commercial use, other than as an intermediate in the manufacture of chlorinated solvents. Very low levels have been reported in ambient and indoor air, and in surface water near contaminated areas.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,1,1,2-Tetrachloroethane was evaluated for carcinogenicity in a 2-year study in mice and rats treated by gavage in a corn oil vehicle. Toxicity resulted in termination of the male and female mice at the higher dose after only 65 weeks of exposure. The group receiving the lower dose and the control group continued on study for the

full treatment period. Based on survival-adjusted analyses, statistically significant increases in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or hepatocellular carcinoma (combined) were observed in male and female mice. Survival was also reduced in male rats at the higher dose. A slight increase in the trend in the incidence of liver neoplastic nodules or hepatocellular carcinoma (combined) was observed in male rats. In female rats, an increase in the incidence of fibroadenoma of the mammary gland was observed at the lower dose.

5.4 Mechanistic and other relevant data

Little information was available from studies in humans or experimental animals on the absorption and distribution of 1,1,1,2-tetrachloroethane; however, it is likely that it would be absorbed readily and distributed widely throughout the body. No data on metabolism or excretion in humans were available. In rodents, metabolism produces tetrachloroethanol and then its glucuronide and trichloroacetic acid, which would be excreted primarily in the urine. 1,1-dichloroethylene and 1,1,2-trichloroethylene may also be formed from 1,1,1,2-tetrachloroethane, albeit in lesser amounts. There is weak evidence to suggest that 1,1,1,2-tetrachloroethane is a genotoxic agent. Based on data on cancer and toxicity in animals, the liver appears as a major target organ for 1,1,1,2-tetrachloroethane. In the liver, the evidence for non-genotoxic mechanisms of carcinogenesis is weak.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

1,1,1,2-Tetrachloroethane is *possibly carcinogenic to humans (Group 2B)*.

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