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DECOS and NEG Basis for an Occupational Standard

Tetrachloroethane

Marita Luotamo
Vesa Riihimäki

Nordic Council of Ministers

ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE

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ARBETE OCH HÄLSA
Redaktör: Anders Kjellberg
Redaktionskommitté: Anders Colmsjö,
Elisabeth Lagerlöf och Ewa Wigaeus Hjelm

Arbetslivsinstitutet,
171 84 Solna, Sverige

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Preface

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DECOS) of the Dutch Health Council and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic Countries.

The document on health effects of Tetrachloroethane was written by Dr Marita Luotamo and Dr Vesa Riihimäki from the Finnish Institute of Occupational Health, Helsinki, Finland, and has been reviewed by the DECOS as well as by the NEG.

V.J. Feron
Chairman
DECOS

P. Lundberg
Chairman
NEG

Contents

Abbreviations

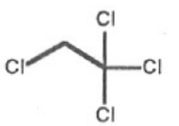
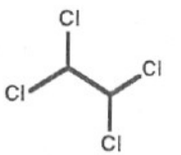
TCA	=	Tetrachloroethane
1,1,1,2-TCE	=	1,1,1,2- Tetrachloroethane
1,1,2,2-TCE	=	1,1,2,2- Tetrachloroethane
P450	=	cytochrome P450
OEL	=	occupational exposure level
MTD	=	maximum tolerated dose
GSH	=	glutathione (reduced)
ESR	=	electron spin resonance
DEN	=	diethylnitrosamine
GGT+	=	γ-glutamyl-transferase positive
ASAT	=	aspartate amino-transferase
ALAT	=	alanine aminotransferase
NOAEL	=	no-observed-effect-level

1. Introduction

Tetrachloroethanes are ethanes in which four hydrogen atoms have been replaced by chlorine. Tetrachloroethane has two isomers: 1,1,1,2- and 1,1,2,2-tetrachloroethane (in this report abbreviated 1,1,1,2-TCE and 1,1,2,2-TCE, respectively). 1,1,1,2-Tetrachloroethane has not been used on an industrial scale, whereas 1,1,2,2-TCE has been manufactured and used extensively. The latter isomer has mainly been used as a solvent for cellulose acetate, fats, waxes, greases, rubber and sulphur and as a dope in the varnish to render aeroplane wing surfaces impervious to moisture and air. It has also been used in electrical equipment and supplies, chemicals and allied products, electric, gas and sanitary services. 1,1,2,2-Tetrachloroethane has been used from the beginning of this century until its high toxicity was detected, and after the 1970s its use has nearly ended.

According to European Parliament and Council Directive (24), 1,1,1,2- and 1,1,2,2-TCE may not be used in concentrations equal to or greater than 0.1% by weight in substances and preparations placed on the market for sale to the general public.

2. Substance identity

	1,1,1,2-TCE	1,1,2,2-TCE	Ref.
CAS number	630-20-6 *	79-34-5 *	
Systematic name	Tetrachlororethane asymmetric tetra	Tetrachlororethane symmetric tetra	
Synonyms		Acetylene tetrachloride [1], 1.1-dichloro-2,2,-dichloroethane, tetra-chloroethane, symtetrachloroethane	[1] (81)
Trade name	Not commercially available	Acetosal, Bonoform, Cellon Westron, 1,1,2,2-Czterochlorethan (Polish), NCI-C03554 RCRA Waste Number U209	
Molecular formula	$ClHC\text{-}CHCl_3$	$Cl_2HC\text{-}CHCl_2$	
Structural formula			
Molecular mass	167.84	167.84	

* CAS number 25322-20-7 (tetrachloroethane, isomer not specified)

3. Physical and chemical properties ((86), if not otherwise stated)

	1,1,1,2-TCE	1,1,2,2-TCE	Reference
Melting point	-68.7°C	-42.5°C	
Boiling point	130.5°C	146.5°C	
Relative density	1.5468	1.5958	
Vapour pressure	0.66 kPa (20°C) [1]	0.680 kPa (20°C)	[1] (93)
Saturation concentration in air	0.65 % (20°C) (= 45.3 g/m^3)	0.67% (20°C) (= 46.7 g/m^3)	
Solubility in water	No data available	0.3% w/w (20°C)	(9)
Solubility	Soluble in ethanol, diethylether, acetone, benzene, chloroform	Soluble in methanol, ethanol, benzene, diethyl ether, petroleum ether, carbon tetrachloride, chloroform, carbon disulphide, dimethyl-formamide, oils [2]	[2] (111)
Refractive index	no data available	1.4918	(9)
Conversion factors	1 cm^3/m^3 = 6.87 mg/m^3 [4] 1 mg/m^3 = 0.146 cm^3/m^3 (25°C, 101.3 kPa)	1 cm^3/m^3 = 6.87 mg/m^3 [3] 1 mg/m^3 = 0.146 cm^3/m^3 (25°C, 101.3 kPa)	[3] (9) American convention
Conversion factors	1 cm^3/m^3 = 6.96 mg/m^3 1 mg/m^3 = 0.144 cm^3/m^3 (20°C, 101.3 kPa)	1 cm^3/m^3 = 6.96 mg/m^3 1 mg/m^3 = 0.144 cm^3/m^3 (20°C, 101.3 kPa)	European convention (used in this report)

1,1,1,2-Tetrachloroethane is a colourless, non-flammable, heavy liquid. In general 1,1,1,2-TCE is more stable than its symmetrically substituted isomer. Thermal decomposition at 500-600°C yields trichloroethylene and hydrogen chloride (105).

1,1,2,2-Tetrachloroethane is a colourless, non-flammable, heavy liquid with a sweetish odour. 1,1,2,2-Tetrachloroethane is sufficently stable and can be stored without adding stabilizers, if there is no exposure to moisture, air and light.

In this document all the tetrachloroethane concentrations in air are given first as mg/m^3 (= 1,000 x mg/L) and after that the units used in the original article. The conversion factor used in this report is that of the European convention (see above in this Section).

4. Production, occurrence and use

Neither 1,1,1,2-TCE nor 1,1,2,2-TCE are known to occur as natural products.

4.1. 1,1,1,2-Tetrachloroethane

1,1,1,2-Tetrachloroethane was first synthetized by A. Mouneyrat in 1898. It is a common by-product of many industrial chlorination reactions of C_2 hydrocarbons but it is not produced on an industrial scale (105).

4.2. 1,1,2,2-Tetrachloroethane

1,1,2,2-Tetrachloroethane was first synthetized in 1869, and the first industrial scale production process was developed in 1903. 1,1,2,2-Tetrachloroethane became the first chloroethane to be produced in high tonnage before World War I, and was mainly used as a solvent for cellulose acetate, fats, waxes, greases, rubber and sulphur. Due to its relatively low cost, non-flammability and good solvent capacity, tetrachloroethane was widely used in industry for many years (5). Its main use was as an additive in varnish applied to aeroplane wing surfaces to render them impervious to moisture and air (75, 105). The isomer was also used in electronic and pesticide industry and as an organic intermediate in the production of trichloroethylene from acetylene (78). Tetrachloroethane was used by the U.S. Army during World War II to impregnate clothing for protection against mustard gas (76), in fabric cleaning and clothes "spotting", artificial silk industry and in the manufacture of artificial pearls (5). Due to the toxicity of 1,1,2,2-TCE, it has largely been replaced since World War II by less toxic solvents (75): Subsequent to the replacement of trichloroethylene by 1,1,1-trichloroethane and the development of more economical processes for the production of tetrachloroethylene, 1,1,2,2-TCE has become less important for the production of chlorinated solvents (105). Currently the trend has partly been reversed by international agreements prohibiting the use of 1,1,1-trichloroethane for environmental reasons.

In the U.S.A., approximately 222 million kg were produced in 1967, but the production declined to about 17 million kg by 1974 (U.S. International trade Commission, 1977 in (93)). No data of the chemicals use in Europe and Japan are available (44). In Norway, 0.6 tonnes of 1,1,2,2-TCE was produced or imported in 1994 (Petter Kristensen, National Institute of Occupational Health, personal communication). In Denmark, no 1,1,2,2-TCE was produced, imported or used (Adolf Schaich Fries, Institute of Occupational Health, Denmark, personal communication). In Finland, 1,1,2,2-TCE was not produced, imported or used.

1,1,2,2-Tetrachloroethane is currently produced by catalytic addition of chlorine to acetylene. In most processes the substance is a non-isolated intermediate which is immediately thermally cracked for the production of trichloroethylene. However, it may also be isolated as a by-product and used as a feedstock in the production of trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene. Consequently 1,1,2,2-TCE may appear as a minor impurity in the previous end products. Due to toxicity concerns and new processes for manufacturing chlorinated

ethylenes, the manufacture of 1,1,2,2-TCE as an end product now appears to be very limited (1). It may be used as a solvent, insecticide or fumigant; however, it is not currently registered for use as a pesticide in the USA (1).

5. Occupational exposure

In 1976, NIOSH reviewed the exposure levels of 1,1,2,2-TCE in occupational settings (75). A study from that late 50s and others from the 60s are reported. In a relatively old study from 1957 the levels of tetrachloroethane (TCE) was measured in a penicillin factory in which TCE was used as an extraction liquid (48). The concentrations of TCE ranged from 10-1,700 mg/m^3 (1.5-247 ppm) measured in 170 air samples taken from different points of the process and from within the ventilation systems.

In a study conducted in India, hundreds of workers were exposed to tetrachloroethane in 23 different bangle-manufacturing plants; the measured average 1,1,2,2-TCE concentrations in air varied from 63-680 mg/m^3 (9-98 ppm) (59).

Horiguchi and coworkers reported 1,1,2,2-TCE concentrations from 520-1,570 mg/m^3 (75-224 ppm) in three Japanese artificial pearl producing factories (40). Subsequently two factories ceased using 1,1,2,2-TCE, and the remaining factory succeeded in reducing the level of 1,1,2,2-TCE to around 140 mg/m^3 (20 ppm) (40).

In an Italian study, 75 workers at two plants were exposed to tetrachloroethane during four different process events: i) tetrachloroethane production via chlorination of acetylene; ii) production of tri- and tetrachloroethylene from TCE; iii) storage and loading of TCE; and iv) quality control laboratories of the two plants (32). At the first activity the average minimum concentration was 2.5 mg/m^3 (0.37 ppm), average maximum 9.1 mg/m^3 (1.33 ppm) with a single peak at 22 mg/m^3 (3.2 ppm). During maintenance and unusual circumstances the concentrations ranged from 34-103 mg/m^3 (5-15 ppm) with occasional peaks at 278 mg/m^3 (40 ppm).

6. Sampling and analysis of substance at workplace

Few contemporary reports concerning industrial hygiene measurements of tetrachlororethanes have been found. Obviously there has not been pressing needs to method development in recent times.

NIOSH (75) has presented an analytical method for 1,1,2,2-TCE ("Analytical method for 1,1,2,2-tetrachlororethane", Appedix II). The sample is collected in a charcoal tube (in the range of 0.5-15 ppm), and tetrachlororethane is desorbed, and an aliquot analyzed by a gas chromatograph. The coefficient of variation for the total analytical and sampling method at the air concentration range of 16-70 mg/m^3 (2.3-10 ppm) was 0.057 (75).

Three different passive samplers (Abcor, duPont, 3M) were assessed for the measurement of 1,1,2,2-TCE in air, and the results were compared with infrared measurements. The passive samplers showed an average bias of +2.0%, at the level of 21 mg/m^3 (3 ppm) (25).

Four portable chromatographs using electron capture and photoionization detectors were compared under field conditions for the analysis of 1,1,2,2-TCE. The electron capture detector had a lower limit of detection compared to the photoionization detector (50).

A gas chromatographic-mass spectrometric analysis using methylene chloride extraction, DB-Wax-30N capillary column and temperature programming, detected 1,1,2,2-TCE as a leached rubber stopper component (17).

7. Toxicokinetics

Table 1 shows partition coefficients between important (biological) media for 1,1,1,2-TCE and 1,1,2,2-TCE, measured *in vitro*. Tetrachloroethanes are quite soluble in blood and tissues.

7.1. Uptake

Inhalation uptake in humans has been measured indirectly as exhaled TCE. A volunteer inhaled 2.5 mg of uniformly ^{38}Cl-labelled 1,1,2,2-TCE vapour from a 150 mL bulb, held their breath for 20 seconds, and exhaled through an activated-charcoal trap (two exhalations). Ninety-seven per cent of the inhaled tetrachloroethane was retained; and only 3.3% of the inhaled tetrachloroethane vapour was exhaled during the following hour (67).

Information on dermal absorption in humans has not been located. However, the human skin permeability coefficient for 1,1,2,2-TCE was calculated as 0.009 cm/h (106); the corresponding steady state flux of 1,1,2,2-TCE from a saturated water solution (3 mg/ml) is therefore 27 µg per cm^2 and h. These relatively low values imply that the skin penetration potential of the compound is limited. However, compared to the inhalation uptake at the occupational exposure limit (OEL) of 1 ppm = 7 mg/m^3, extensive skin contact may lead to significant absorption. As an example, if the palms of both hands (about 400 cm^2) are in contact with 1,1,2,2-TCE, skin uptake would amount to approximately 10.8 mg per hour.

7.2 Distribution

When adult C57B1 mice were injected ^{14}C-1,1,2,2-TCE *i.v.* (3 mg/kg; 9 µCi in 20 µL DMSO), highest concentrations of irreversibly bound metabolites were found between 1 and 240 min in the respiratory and gastrointestinal systems (olfactory and tracheobronchial mucosa, mucosa of the oral cavity, tongue, nasopharynx, esophagus and cardiac region of the forestomach), in the liver, in the contents of the gallbladder, as well as in the inner zone of the adrenal cortex and in the interstitium of the testis (23).

Table 1. Partition coefficients for 1,1,1,2-TCE and 1,1,2,2-TCE *in vitro* (at 37°C)

Partition coefficient	1,1,1,2-TCE	1,1,2,2-TCE	Reference
Octanol / water (log_{10}-value)	2.6 1)	2.4 7)	1) ICIS in (45) 7) (1)
Oil / water		370 3)	3) (84)
Oil / air		6358 4)	7) (31)
Blood / air	41.7 2)	142 5)	2) (31)
		72.6 6)	5) (28) 6) (67)
Serum / air		78.2 6)	6) (67)
Liver / blood	2.12 2)	1.38 2)	2) (31)
Muscle / blood	0.95 2)	0.71 2)	2) (31)
Fat / blood	51.5 2)	26.5 2)	2) (31)

The oil/blood partition coefficient calculated on the basis of blood/air and oil/air coefficients is 45.

7.3. Biotransformation

One dose of ^{14}C-1,1,2,2-tetrachloroethane was injected *i.p.* into female albino mice (dose 0.21-0.32 g/kg) and the elimination of radioactivity was followed for 3 days. Half of the dose (45-61%) was expired as carbon dioxide and 28% (range 23-34%) of the activity was excreted with the urine. Around 16% of the dose retained in the animal and less than 4% was expired unchanged (113). Metabolites identified in the urine collected for 24 h (mean activity %) were dichloroacetic acid (27%), trichloroacetic acid (4%), trichloroethanol (10%), oxalic acid (7%) and glyoxylic acid (0.9%). From these data, the authors proposed the following metabolic scheme for 1,1,2,2-TCE which has been supplemented with some more recent data (36, 78) (Fig. 1). The biotransformation seems to involve a stepwise hydrolytic cleavage of carbon chlorine bonds via dichloroacetic acid (and through subsequent intermediates) to glyoxylic acid (a, b, c, Fig. 1). More recent evidence show that the hydroxylation of 1,1,2,2-TCE yielding 1,1-dichloroacetyl chloride (route k) is the predominant metabolic pathway to dichloroacetic acid (36). Glyoxylic acid is further metabolized (m, n). Some of the tetrachloroethane undergoes (enzymatic and non-enzymatic) dehydrochlorination to trichloroethylene (d), which gives rise to trichloroethanol and trichloroacetic acid (e, f, g), and some is oxidized to tetrachloroethylene (h), which contributes to the formation of trichloroacetic acid and oxalic acid (i, j). There is also evidence for a reductive dechlorination pathway (l) to form a carbon centered radical (78).

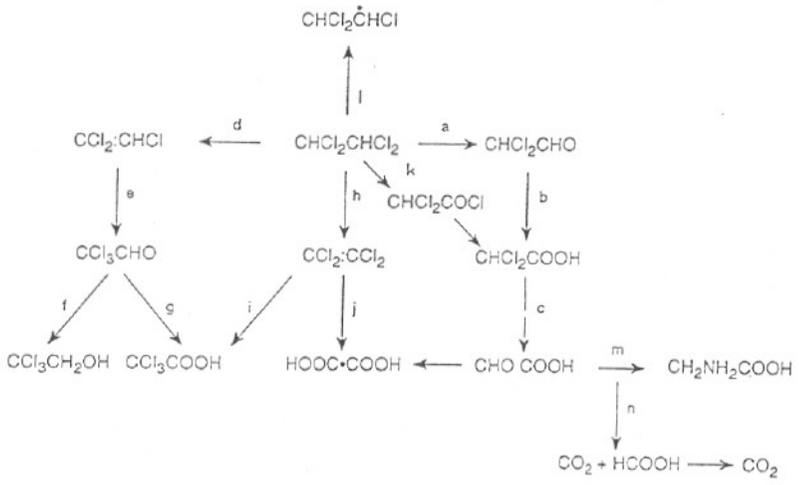


Figure 1. Suggested metabolic pathways of 1,1,2,2-TCE (1)

Wistar rats (about 70 g, 6-8 animals per group) of both sexes were given 1,1,1,2-TCE and 1,1,2,2-TCE (2.78 mmol/kg = 467 mg/kg) *i.p.*, or were exposed to the vapour of the compounds (1,374 mg/m^3 = 200 ppm) for 8 h and urine was collected for 48 h. Total trichlorocompounds, trichloroacetic acid and trichloroethanol were determined colorimetrically by the Fujiwara reaction under conditions described by Tanaka and Ikeda (95). The authors point out, that these estimates using the Fujiwara reaction also include other metabolites than trichloroacetic acid and trichloroethanol. After inhalation exposure, the urinary excretion of total trichlorocompounds in rats was 199 mg/kg bw from 1,1,1,2-TCE and 8.2 mg/kg bw from 1,1,2,2-TCE. 1,1,1,2-Tetrachloroethane gave rise to large amounts of trichloroacetic acid (39.4 mg/kg bw) and trichloroethanol (159.6 mg/kg bw) excretion, whereas 1,1,2,2-TCE yielded less than one-twentieth of these amounts (1.7 and 6.5 mg/kg bw, respectively). After a single *i.p.* injection of 1,1,1,2-TCE, the total 48-h urinary excretion of trichlorocompounds was 114.2 mg/kg bw, trichloroacetic acid excretion was 16.9 mg/kg bw and trichloroethanol excretion was 97.3. mg/kg bw. After an *i.p.* injection of 1,1,2,2-TCE, the amounts of these metabolites were 2.1, 1.3, and 0.8 mg/kg bw, respectively (42).

Male Osborne-Mendel rats and male B6C3F1 mice were given 1,1,1,2-TCE and 1,1,2,2-TCE at two dose levels, the maximum tolerated dose (MTD) and 1/4 MTD orally as unlabelled compounds 5 days per week for 4 weeks, followed by a single

dose of the corresponding radiolabelled compound in corn oil. The doses of 1,1,1,2-TCE were 200 mg/kg and 50 mg/kg to rats and 400 mg/kg and 100 mg/kg to mice. The doses of 1,1,2,2-TCE were 100 mg/kg and 25 mg/kg to rats, and 200 mg/kg and 50 mg/kg to mice (66). A similar proportion of the dose of 1,1,2,2-TCE was exhaled unchanged in experiments with rats (7.03%) and mice (9.69%), while rats exhaled much more 1,1,1,2-TCE unchanged (34.14%) than mice (5.89%), At least three fourths of the dose was found as CO_2, in excreta, or in carcass, and 78.7% and 67.8% of 1,1,2,2-TCE, and 64.8 and 84.3% of 1,1,1,2-TCE in rats and mice, respectively, were considered to be metabolized. Apart from CO_2 trichloroethanol and trichloroacetic acid were major metabolites from both 1,1,1,2- and 1,1,2,2-TCE (66).

Studies with rodents suggest that the main metabolic pathway for 1,1,1,2-TCE gives rise to trichloroethanol and trichloroacetic acid while the corresponding pathway for 1,1,2,2-TCE yields dichloroacetic acid. Although not depicted in Fig. 1, further detailed studies on the metabolism of dichloroacetate and trichloroacetate in mice and rats have demonstrated a potential for the formation of toxic metabolites (acid chloride intermediate from dichloroacetate and dichloroacetyl free radical from trichloroacetate) (54).

Metabolism of 1,1,1,2-TCE involves both oxidative and reductive pathways; both processes are dependent on phenobarbital-inducible forms of cytochrome P450 (abbreviated P450)(10). The former leads to trichloroethanol as the major metabolite (60). Under unaerobic conditions 1,1,1,2-TCE was metabolized extensively in rat liver microsomes to 1,1-dichloroethylene (the main metabolite) and 1,1,2-trichloroethylene. The ratio of the two was about 25:1 (99). Oxygen strongly inhibited the reduction of 1,1,1,2-TCE *in vitro*. 1,1,1,2-TCE was metabolized to 1,1-dichloroethylene (75-220 higher concentrations) and 1,1,2-trichloroethylene also *in vivo*, (99). The reductive pathways involve one- or two-electron reductions. The former leads to a free radical formation, and this reactive product can either interact with membrane components and induce lipid per-oxidation, producing 1,1,2-trichloroethane, or bind covalently with nucleic acids and proteins. The latter reaction, which is the preferred pathway, yields 1,1-di-chloroethylene (10).

Metabolism of 1,1,2,2-TCE *in vitro* (rat liver microsomes) was shown to be P450 dependent (11, 13, 47). In another study, 1,1,2,2-tetrachloroethane was oxidized to dichloroacetic acid by rat liver microsomes and purified P450b (35). 1,1,2,2- Tetrachloroethane was metabolized by rat liver microsomes *in vitro* only through an oxidative route, no reductive metabolism was observed (70, 99, 100, 102). However, an *in vivo* CD1 mouse study with 1,1,2,2-TCE indicated the formation of a carbon centered radical, presumably $CHCl_2\dot{C}HCl$, and subsequent lipid peroxidation in the liver (78), suggesting that in addition to the oxidative biotransformation, some reductive metabolism of 1,1,2,2-TCE occurs. Microsomal and cytosolic GSH-transferases have also been shown to contribute to the metabolism of both 1,1,2,2- and 1,1,1,2-TCE (10, 11).

A reconstituted monooxygenase system from phenobarbital treated rats, which lacked aldehyde dehydrogenase, effectively metabolized 1,1,2,2-TCE to dichloro-

acetic acid (36). This finding suggests that dichloroacetaldehyde is not an obligatory intermediate in dichloroacetic acid formation and gives support to the involvement of an acyl chloride intermediate. A partially purified antibody against the major phenobarbital-induced form of P450 (CYP2B subfamily), which was capable of inhibiting 46% of 7-ethylcoumarin deethylase activity, inhibited almost to the same extent the formation of dichloroacetic acid from 1,1,2,2-TCE in phenobarbital treated intact rat liver microsomes (36).

Metabolic activation of 1,1,2,2-TCE in male BALB/c mouse liver microsomes, and binding to calf thymus DNA, was enhanced by phenobarbital pretreatment and inhibited by addition of SKF 525A or diethylmaleate. The latter suggested that even glutathione conjugation (microsomal and cytosolic GSH-transferases) have an important role in the metabolic activation of 1,1,2,2-TCE in the mouse (11). In contrast, another study showed that addition of glutathione to incubates containing microsomal and cytosolic fractions of the C57B1 mouse olfactory mucosa and liver decreased the binding of 1,1,2,2-TCE to macromolecules, indicating that glutathione-mediated activation does not play a major role in binding (23).

The hepatic rate of 1,1,1,2-TCE metabolism in fed male and female Wistar rats measured *in vitro* ranged from 6.9-8.1 nmol/g liver tissue and minute. The corresponding values for 1,1,2,2-TCE were 13.3-15.7 nmol/g liver tissue and minute (69). These rates of metabolism were increased 2-4 fold by fasting (69), and 4-5 fold by chronic ethanol consumption (85). While these treatments did not increase the total microsomal P450 content, they suggested that ethanol inducible P450 isoform, CYP2E1, is involved in TCE metabolism. However, male Wistar rats given methanol, isopropanol or ethanol as one large dose by gavage 18 h prior to challenge, or the same alcohols in drinking water for 5-6 weeks and then challenged by an *i.p.* injection of 140 or 240 mg/kg 1,1,2,2-TCE, showed no or very small serum ALAT elevations compared to control animals that had not received alcohols (51). In contrast, alcohol pretreatments which are known to induce CYP2E1 mediated metabolism enhanced hepatotoxicity of chloroform and carbon tetrachloride in the same study. Therefore it appears unlikely that CYP2E1 is involved in the metabolic activation of 1,1,2,2-TCE.

Metabolic kinetic constants of 1,1,1,2-TCE and 1,1,2,2-TCE were determined *in vivo* by a gas phase method. Male Fischer 344 rats (200-300 g) were exposed by inhalation to a constant concentration for 6 hours 2,450 mg/m^3 (352 ppm) of 1,1,1,2-TCE and 2,440 mg/m^3 (350 ppm) of 1,1,2,2-TCE and then placed in 2.5-liter exhaled breath chambers with fresh air flow. The chamber effluent was serially analyzed for test chemical. Optimized maximum metabolic rates (V_{max}) were 6.39 mg/kg/h (= 38.7 µmol/h) for 1,1,1,2-TCE and 12.9 mg/kg/h (= 71.5 µmol/h) for 1,1,2,2-TCE (31).

1,1,1,2-Tetrachloroethane was transformed to 1,1-dichloroethylene with an apparent K_m of 19.50 mM, V_{max} of 59.0 nmol/min/mg in the presence of oxygen by microsomes from phenobarbital-treated male Holzman rats (102). In hepatic microsomes from Aroclor 1254 treated rats, the apparent V_{max} for 1,1,2,2-TCE dechlorination was 18.2 nmol/min/mg protein and the Km 0.55 mM (83).

7.4. Elimination

About half of an *i.p.* administration of ^{14}C-1,1,2,2-TCE given to female albino mice was excreted over 3 days, for further details, (see Section 7.3 "Biotransformation") (8, 113).

According to basic toxicokinetic principles the temporal characteristics of distribution of the free compound to tissues are a function of the compound's solubility, tissue volumes and tissue blood flows. These factors determine the attainment of equilibrium, often expressed by tissue time constants: the time for the tissue to reach 63% of the equilibrium concentration (21). Elimination by washout is a reverse phenomenon to distribution. Concerning fatsoluble substances that are rapidly metabolized, mobilization from adipose tissue may be rate-limiting for elimination. A calculation of the tissue time constant for TCE in human fat (based on perfusion rate 0.32 L/min, tissue volume 14.5 L and oil/blood partitioning of 45) would yield a time constant of 34 hours. Thus it may be predicted that the unbound compound would not have a long residence time in the human body.

8. Methods of biological monitoring

Due to its limited industrial exposure, there are no reports concerning biological monitoring methods for the assessment of exposure to TCE. It can be envisaged that TCE could be measured in blood for biological monitoring purposes like other chlorinated aliphatic hydrocarbons. Similarly, analysis of metabolites such as trichloroacetic acid and trichloroethanol could be used for biomonitoring purposes, but the drawback is that they are not specific to TCE.

However, because there are no data on the relationship between TCE concentrations in ambient air and tissues (blood) among occupationally exposed workers, and because the essential toxicokinetic data on metabolism and excretion in humans are lacking, meaningful application of biological monitoring for TCE is not possible.

9. Mechanisms of toxicity

In tissue binding studies adult male Wistar rats and male BALB/c mice were injected *i.p.* with ^{14}C-labelled-1,1,2,2-TCE (11) and 1,1,1,2-TCE (10) (127 µCi/kg bw). Some of the animals were daily pretreated with 100 mg/kg bw *i.p.* phenobarbitone injections for 2 days before sacrifice. Fasted animals were killed 22 h later, their organs (liver, kidney, lung, stomach) were removed, pooled and processed in order to obtain DNA, RNA and proteins (10, 11). 1,1,2,2-Tetrachloroethane was bound covalently to DNA and RNA, and to proteins of the microsomal and cytosolic fractions in liver, lung, kidney and stomach. With the exception of the lung, specific activity in the DNA from mouse organs was higher

than that from rat organs. On the contrary, the binding to RNA and proteins was higher in rat organs than in mouse organs. Cytosolic fractions from all assayed organs of the mouse and from rat liver and, to a lesser extent from rat lung, enhanced binding of 1,1,2,2-TCE to macromolecules *in vitro*. The interaction of 1,1,2,2-TCE with synthetic polyribonucleotides was clearly higher in the presence than in the absence of NADPH and GSH. The highest specific activity was observed in poly(G) (11).

After *i.p.* injection of 1,1,1,2-TCE, binding to DNA was highest in mouse lung. With the exception of stomach, DNA and RNA from mouse organs were labelled more than DNA from rat organs. Labelling of proteins and especially RNA from organs of both species was higher than labelling of DNA. Microsomes isolated from the liver of both species were efficient in bioactivating 1,1,1,2-TCE, and gave similar binding values. Binding to DNA was also mediated by microsomes isolated from the mouse lung and to a smaller extent by microsomes isolated from the mouse kidney. Microsomal fractions from lung and kidney of the rat and from stomach of both species were ineffective (10).

When both tetrachloroethanes were given to rats and mice orally (66) (for experimental details, see Section 6.3 of that Ref.), 1,1,2,2-TCE was extensively covalently bound to hepatic proteins both in rats and mice; covalent binding was much lower for 1,1,1,2-TCE. Since both tetrachloroethane isomers have caused hepatic tumours (adenomas and/or carcinomas) in mice, and since especially 1,1,2,2-TCE showed genotoxicity in some short term assays *in vitro*, it is of interest to note the reactivity of the compounds to DNA. The magnitude of binding to the mouse and rat liver DNA (covalent binding index) was higher for 1,1,2,2-TCE than for 1,1,1,2-TCE; the interaction with DNA was found comparable to recognized weak-to-moderate carcinogens (61). Concerning metabolism in the liver, studies suggest that tetrachloroethane isomers may be metabolically activated to acylchlorides or free radicals; toxicity may ensue from protein binding and lipid peroxidation. Metabolism of 1,1,2,2-TCE in the mouse was associated with reduced hepatic levels of a wide variety of microsomal P450 enzymes and haeme, indicating damage to the liver endoplasmic reticulum (78). With electron spin resonance (ESR) spectroscopy spin-trapping *in vivo* techniques the authors found evidence in support of the occurrence of a free radical species, presumably $CHCl_2\dot{C}HCl$ free radical. There was evidence of concomitant peroxidation of polyunsaturated fatty acids based on characteristic conjugated diene signals in lipids extracted from liver microsomes of 1,1,2,2-TCE treated mice (78).

10. Effects in animals and *in vitro* studies

10.1. Irritation and sensitisation

Liquid 1,1,2,2-TCE is a strong irritant of the skin and mucosal membranes (93). No reports were located concerning sensitisation. No data were found in 1,1,1,2-TCE.

10.2. Acute toxicity

Acute toxicity data on 1,1,1,2-TCE and 1,1,2,2-TCE are given in Tables 2 and 3, respectively.

The anaesthetic potency of TCE has been demonstrated in different studies: cats exposed to 5,700 mg/m^3 (830 ppm) developed narcosis in 4 h and deep narcosis in 5 h, while the cats exposed to 57,000 mg/m^3 (8,300 ppm) reached light narcosis in 25 min and deep narcosis in 40 min (56).

In different inhalation exposures to TCE lasting a few hours (55, 77) mice assumed a lateral position at 7,460-10,000 mg/m^3 (1,091-1,455 ppm), lost their reflexes at 9,996-14,990 mg/m^3 (1,450-2,180 ppm) and died at 40,000 mg/m^3 (5,820 ppm).

Table 2. Acute toxicity data for 1,1,1,2-TCE source: RTECS(R) (80) (extracted from RTECs)

Species	Acute toxicity	Route	Dose
rat	LD_{50}	oral	670 mg/kg
rat	LC_{50}	inhalation	14,600 mg/m^3 (2,100 ppm) / 4h
mouse	LD_{50}	oral	1,500 mg/kg
mouse	LD_{50}	intraperitoneal	1,275 mg/kg
rabbit	LC_{50}	inhalation	19,500 mg/m^3 (2,800 ppm) / 4h
rabbit	LD_{50}	skin	20,000 mg/kg

Table 3. Acute toxicity data for 1,1,2,2-TCE source: RTECS(R) (80) (extracted from RTECs)

Species	Acute toxicity	Route	Dose
human	TDLo	oral	30 mg/kg
human	TCLo	inhalation	1,000 mg/m^3 /30 min
rat	LCLo	inhalation	7,000 mg/m^3 (1,000 ppm)/4h
rabbit	LDLo	subcutaneous	500 mg/kg
guinea pig	LDLo	intraperitoneal	500 mg/kg
dog	LDLo	oral	300 mg/kg
dog	LDLo	intravenous	50 mg/kg
cat	LCLo	inhalation	19,000 mg/m^3/45 min
rat	LD_{50}	oral	250 mg/kg
mouse	LC_{50}	inhalation	4,500 mg/m^3/2h
mouse	LD_{50}	intraperitoneal	821 mg/kg
mouse	LD_{50}	subcutaneous	1,108 mg/kg

TDLo/TCLo = lowest published toxic dose/concentration

LDLo/LCLo = lowest published lethal dose/concentration

10.3. Short-term exposure

Most studies available are relatively old (between 1911 and 1962) and are conducted by the inhalation and injection routes. The isomer of TCE was usually not specified, but it is likely that it was 1,1,2,2-TCE. Two relatively recent studies from 1972 conducted with rats administered 1,1,2,2-TCE by the inhalation and oral routes are also available.

Inhalation exposure of cats to TCE, ranging from 4,880 mg/m^3 (710 ppm) to 41,900 mg/m^3 (6,100 ppm), resulted in prostration to deep narcosis dose-dependently (57). In another study, two cats and two rabbits were exposed to 1,1,2,2-TCE at concentrations of 800-1,100 mg/m^3 (116-160 ppm) for 8-9 h/day, 6 days/week, for 4 weeks: all animals showed initial stage of prostration, but no remarkable changes in body weight, behaviour, body temperature or blood studies (56). When mice were exposed to high concentrations of TCE 41,060 mg/m^3 (5,900 ppm) for 3 h daily 3/10 mice died within one week; at 45,900 mg/m^3 (6,600 ppm) for 3 h 4/10 mice died within one week; at 48,700 mg/m^3

(7,000 ppm) for one 2-hour period per week, 5 mice died after first exposure, three more after the third and the remaining mouse died after the fifth exposure (41). Six rats were exposed to 62,600 mg/m³ (9,000 ppm) of TCE for 2 h/day, 2 days/week, one rat died after the second exposure, two after the fourth, and the remaining three rats died after the 11th exposure. Among these last three rats two had decreased red blood cell counts and haemoglobin levels, but no significant change was found in the white blood cell counts. The mice and rats showed congestion in tissues and fatty degeneration of the liver (41).

Fiessinger and co-workers (26) reported toxic effects of TCE to mice after repeated inhalation exposure (groups of four mice in 17 L chamber with Petri dish containing 10-20 mL of TCE, for 1-1.5 hours, the evaporation did not exceed 1.5 mL for each exposure). Some of the mice were comatose by the end of the exposure period, exhibited convulsive movements and staggering of the limbs. After the eighth exposure or a total of 10 hours, the mice had bristly hair, had lost weight and were anorectic. Between 8th and 28th exposures hepatic lesions developed, the liver became yellowish, and signs of centrilobular degeneration with some fatty infiltration were seen.

Müller (68) reported several studies of the effects of TCE on mice, guinea pigs and one rabbit. Mice were exposed to TCE via inhalation (inhalation chamber TCE concentration was 80,000 mg/m³ (11,400 ppm), at the beginning of the exposure). After six hours deeply anaesthetized mice were removed to fresh air. After repeating the exposure the next day with the same mice, the animals had convulsions and died within a few hours. At autopsy fatty degeneration of the liver particularly in the peripheral of lobes was shown and also focal fatty degeneration of the renal tubular cells.

Müller (68) injected (*i.v., i.p., s.c.*) TCE into an unspecified number of guinea pigs and mice. The animals died in convulsions shortly after an injection dose of 0.2 mL (no other test doses were reported), and autopsies revealed no morphologic changes. Injecting mixtures of TCE in olive oil, glycerin or paraffin subcutaneously into an unspecified number of guinea pigs produced similar effects: the guinea pigs died within a few hours in convulsions (no morphologic changes were apparent at autopsy). In paraffin the lethal dose of TCE was 0.7 mL. When administered in five injections over 14 days (cumulative dose 0.7 mL, details on the schedule of individual injections were not given), no clinical signs were seen preceding death, other than body weight losses, but autopsies revealed liver and kidney damage (68).

One rabbit was given an *i.v.* dose of 0.2 g TCE and the animal went into immediate narcosis, apparently recovered after about 15 min, but died after 30 hours. The autopsy indicated liver enlargement with pasty, fine yellow fields, and the microscopic examination showed severe coarse- and fine-droplet fatty degeneration of the parenchymal cells, especially in the periphery of the lobes (68).

One adult male monkey (*Macaca cynomolga Linné,* 4.5 kg) was injected subcutaneously with TCE (50% v/v) 5 mL on day 1, 2 mL on day 4, 1 mL on day 19, 2 mL on day 20, 4 mL on day 29. The animal showed periods of

unconsciousness and became comatose and died two days after the last injection (its body weight decreased from 4.5 to 3.3 kg at death). There were no remarkable changes in the total white blood cell count, but the differential count showed lymphopenia and neutrophilocytosis (41).

Two short term rat studies of 1,1,2,2-TCE with more modern designs and objectives were located.

The subacute inhalation toxicity of 1,1,2,2-TCE was investigated with rats as part of a large study involving also the chronic toxicity design and an in-built reproductive toxicity study (87, 33). Groups of 7 male rats (strain not defined) exposed to 13.3 mg/m³ of 1,1,2,2-TCE for 2, 4 or 8 days (within 10 days), other groups of 7 rats that received 4 g of ethanol by gavage at the end of the first, third and the seventh exposure, and appropriate controls, were studied with haematological and biochemical methods, and histological and histochemical investigations were performed on the liver, kidney, lung, brain (cerebrum and cerebellum), adrenal, testis and the thyroid gland. There were no changes in the body weight and organ weights, and some inconsistent changes were noted in serum proteins over the course of the experiment. The liver and renal lipid concentrations were unchanged. Histopathological examination of the liver showed slight inflammatory changes with periportal round-cell infiltration and even small necrotic foci; there was moderate accumulation of lipid in liver cells throughout the course of the study. The authors report that one rat in the tetrachloroethane *plus* ethanol group at the termination on day 2 and five rats in the TCE group at the termination on day 4 showed testis atrophy. Apparently there was no atrophy among the rats terminated on day 10. Therefore the findings were not consistent for an effect by tetrachloroethane and moreover, it is doubtful if such a histopathological change could have developed within a few days of exposure. There were no remarkable findings in other organs (changes found in the thyroid cannot be evaluated).

In an oral study, 1,1,2,2-TCE was given to groups of 10 male rats (of undefined strain) in doses of 3.2, 8, 20 or 50 mg/kg by gavage for up to 7 days (during up to 10 days) with and without exposure to elevated temperature (35°C), and the liver, kidney, thyroid, adrenal, testis, spleen and trachea/oesophagus were examined with histological, enzyme histochemical and histoautoradiographic techniques (34). In the same paper the authors report on their subchronic toxicity investigations which lasted for 60 or 150 days. However, distinction between results from the short and long term administration is not made. It is stated that the histological changes (in the liver, kidneys, testis and the thyroid gland) were dose dependent, whereas the histochemical and autoradiographic findings were more dependent on the duration of the experiment (for further details, see Section 10.4).

10.4. Long term exposure

Dogs were given 150 times 1 mL doses of tetrachloroethane over a 1-year period (the route of exposure and the specifics of the experiment were not given): early symptoms consisted of gastrointestinal upset, diarrhoea, intestinal haemorrhage,

followed by jaundice and marked ascites with continued administration, the liver was hypertrophic after 1 year and returned to normal size within 3 months after the exposure stopped (2).

Adult male cynomolgus monkey (weigth 7 kg), was exposed to tetrachloroethane during 9 months for a total of 190 exposures (2 h/day, 6 days/week concentrations ranged 13,900-27,800 mg/m^3 (2,000-4,000 ppm) during the first 20 exposures, 6,960-13,900 mg/m^3 (1,000-2,000 ppm) for the next 140 exposures and 20,900-27,800 mg/m^3 (3,000-4,000 ppm) for the rest of the experiment). The monkey developed diarrhoea and anorexia after the 12th exposure, and at and after the 15th exposure it became nearly unconscious 20-60 min after the beginning of each exposure. Red blood cell counts and haemoglobin levels decreased reversibly during the 3-4 months. Histologically no definitive changes in heart, lungs, kidneys, pancreas and testes were seen, but the central zone of liver had marked vacuolization of the cytoplasm (41).

Schmidt et al. (87) conducted a subchronic study with male rats involving inhalation of 13.3 mg/m^3 of 1,1,2,2-TCE for 9 months. After 110 days 7 exposed rats and 7 sham-exposed controls were killed for examinations, and at the end of the inhalation period (265 days) corresponding groups of 7 rats were killed and examined. The remaining animals were allowed to recover until day 325 when again groups of 7 animals were terminated for examinations. The rest of the animals (apparently about 150 rats) were kept until their natural death. Daily exposures lasted 4 h/day but it is not specified how many days per week. Histochemical investigations were performed on the liver but the results are inadequately reported in a companion paper (33). The longevity of the rats was not affected by exposure. The authors report that apart from one special examination, all the slight deviations found occurred only at one point in time (exposed group: somewhat lower body weight at 4 months, increased liver lipids at 7 months). The special examination was a biological test of the ACTH activity of the hypophysis of the study animals (an increase, viz. a decreased concentration of ascorbic acid in the adrenal after injecting a pituitary extract, was found which was greatest at 4 months and lessened towards the end of the experiment). Therefore one has to conclude that the effects by 1,1,2,2-TCE found in the study were very slight. No further conclusions can be drawn because only a very limited number of end points were examined and because only one exposure level was used.

In the previously mentioned oral study with male rats, 1,1,2,2-TCE was given by gavage to groups of 10 rats at dose levels of 8 or 20 mg/kg during 60 days and at 3.2 or 8 mg/kg during 150 days (34). The authors report that the most remarkable findings concerned the liver but some effects were noted also in the kidney, testis and the thyroid. The lowest dose of 3.2 mg/kg was given as a threshold for chronic effects. However, the study is impossible to evaluate because no quantitative data on the dose-effect and dose-response relationships were given.

Another subchronic inhalation study of 1,1,2,2-TCE with female Sprague Dawley rats involved exposure to a single level of 560 ml/m^3 (= ppm), which

would correspond to 3,900 mg/m^3, for 5 or 6 hours per day, 5 days/week, for 15 weeks (103). Routine haematology and the histopathology of the liver, kidneys, lungs, ovaries, uterus and adrenal glands were examined. A slight decrease of the haematocrit level, increased relative liver weight, signs of hepatic hyperplasia (increased number of binucleated cells and transient increase of DNA synthesis), granulation and vacuolization of the liver were found. There were no effects in the kidneys, lungs, reproductive organs and adrenals.

It is also worth noting that the oral (gavage) carcinogenicity studies of 1,1,1,2-TCE (72) with Fischer 344/N rats and B6C3F1 mice, and 1,1,2,2-TCE (71) with Osborne-Mendel rats and B6C3F1 mice (for further details, see Section 10.6) involved the gross and microscopic examination of major tissues and organs: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice) and bile duct, pancreas, oesophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, brain, uterus, mammary gland, and ovary. For rats, the non-neoplastic, inflammatory, degenerative and proliferative lesions that were seen in the 1,1,2,2-TCE dosed and control animals were similar in number and kind to those lesions occurring naturally in aged rats. For mice, a large number in the high dose level group died at weeks 69 and 70; histopathological examination revealed acute toxic tubular nephrosis as the apparent cause of death. In addition, hepatocellular carcinomas were found in most of these mice (71). In the carcinogenicity studies with 1,1,1,2-TCE (72) mice of each sex developed behavioural signs of central nervous system (CNS) toxicity (weakness, inactivity, loss of coordination) from week 51 at the high dose level (500 mg/kg) while among rats, CNS involvement was observed from week 44 at the high dose (250 mg/kg).

10.5. Mutagenicity and genotoxicity

Genotoxicity studies with 1,1,1,2-TCE are given in detail in Table 4, and corresponding studies with 1,1,2,2-TCE are shown in Table 5.

Testing in *Salmonella* with a variety of strains (forward and reverse mutations) have given mostly negative results for 1,1,1,2-TCE. In *in vitro* mammalian test systems the substance gave positive responses for sister chromatid exchange in Chinese hamster ovary cells without metabolic activation (30) and in the mouse lymphoma forward mutation assay with metabolic activation (96, 97). There was no induction of DNA repair in rat hepatocytes (64, 110). Only one *in vivo* study with 1,1,1,2-TCE was located. It concerned mitotic recombination in *Drosophila* and gave a negative result (107).

There is a wealth of mutagenicity and genotoxicity information on 1,1,2,2-TCE from *in vitro* studies, but limited data concerning *in vivo* studies. Most tests with a variety of *Salmonella* tester strains have given negative results (five out of eight studies available), while three have shown some positive findings, one of them with metabolic activation (63). 1,1,2,2-TCE induced prophage lambda in *Escherichia coli* in a test system which contained metabolic activation (but not its absence) (19).

1,1,2,2-Tetrachloroethane caused gene conversions and mitotic recombinations in *Saccharomyces cerevisiae* at high concentrations (7). *In vitro* studies with mammalian cells have shown positive sister chromatid exchange responses in Chinese hamster ovary cells and BALB/c-3T3 cells (30, 12). DNA repair tests with mouse and rat hepatocytes have yielded negative results (64, 110). Both positive and negative results were obtained in cell transformation assays with BALB/c-3T3 cells (64, 12, 13).

Assesment of unscheduled DNA synthesis and S-phase synthesis in mouse primary hepatocytes derived from animals that had been gavaged with one dose of 1,1,2,2-TCE gave negative results (65). Two *in vivo* studies with *Drosophila* detecting either sex-linked lethal mutations (112) or mitotic recombination (107) were negative.

Overall, while the genotoxicity studies of 1,1,2,2-TCE do not give a consistent picture, the substance appears to have some potential for genotoxicity. This may relate to the observed covalent binding of 1,1,2,2-TCE to the DNA in liver and other tissues (10, 11, 23) and consequent DNA damage.

10.6. Carcinogenicity

10.6.1. 1,1,1,2-TCE

Groups of 50 male and 50 female B6C3F1 mice, were administered 0, 250 or 500 mg/kg bw of 1,1,1,2.TCE (>99% pure with traces of chloroethane and ethylene derivatives) in corn oil by gavage on five days a week for 103 weeks (low dose) or 65 weeks (high dose). All high dose animals died or were killed when moribund after 65 weeks. Thirtyeight control males, 34 low dose males, 41 control females and 31 low dose females survived till the end of the study, i.e., 103 weeks. In spite of low survival there was a statistically significant dose-related increase in the incidence of hepatocellular adenomas in males: 6/48, 14/46 and 21/50 in control, low dose and high-dose animals, respectively, as well as in females: 4/49, 8/46 and 24/48. There was also a dose-related increase in the incidence of hepatocellular carcinomas in females: 1/49, 5/46 and 6/48 (45, 72).

Groups of 50 male and 50 female Fischer 344/N rats, were similarly administered 0, 125 or 250 mg/kg/b.w. of 1,1,1,2-TCE (>99% pure with traces of chloroethane and ethylene derivatives) for 103 weeks, and the animals were killed at 104 weeks. 29, 25 and 21 control, low dose and high-dose males, and 29, 27 and 24 females survived until the end of the study. A statistically significant increase in the incidence of fibroadenomas of the mammary gland was observed in low dose females: controls 6/49; low dose 15/49 and high-dose 7/46 (45, 72).

Table 4. Genotoxicity studies with 1,1,1,2-TCE

Species	Strain/cells	Measured endpoint	Test conditions	Results		Reference
				without activation	with activation	
Bacterial systems						
S. typhimurium	TA1535 TA1537 TA98 TA100	Reverse mutations	Dose levels ranging 0.01 - 1 mg/plate	- - - -	- - - -	(37)
S. typhimurium	TA98 TA100 TA97 TA104	Reverse mutations	Dose levels ranging 0.01 - 1 mg/plate	+ + + +	- - - -	(93)
S. typhimurium	TA1535 TA1537 TA98 TA100	Reverse mutations	S-9 mix from Osborne Mendel rats or B6C3F1 mice; closed system	- - - -	- - - -	(64)
S. typhimurium	TA100	Reverse mutations	Tedlar® vapourization desiccator	-	-	(108)
S. typhimurium	TA97 TA98 TA100 TA102	Reverse mutations	Three methods used for each strain: classical Ames-test, spot test, preincubation	- - - -	- - - -	(63)
S. typhimurium	BA13/BAL13	Forward mutations	Dose levels ranging 0.06 - 2979 nmol	-	-	(82)
Yeasts						
Saccharomyces cerevisiae	D61.M	Chromosome loss cold-interruption standard incubation	Dose at maximum 0.97 - 1.15 mg/ml 0.77 - 1.34 mg/ml	- -		(109)

Table 4. Cont.

Species	Strain/cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Fungi						
Aspergillus nidulans	Diploid P1	Chromosome missegregation	0.0125 - 0.05 % (v/v)	+		(14)
In vitro mammalian systems						
CHO cells		SCE	15.8 - 400 µg/ml (- S-9) 248 - 348 µg/ml (+ S-9)	+ -		(30)
CHO cells		Chromosome aberrations	455 - 506 µg/ml (-S-9) 348 - 443 µg/ml (+S-9)	- -		(30)
Mouse	Lymphoma cell line L5178Y/TK	Forward mutations	Lowest positive dose 200 µg/ml	-	+	(96, 97)
Rat hepatocytes	Osborne Mendel	DNA repair		-		(64)
Rat hepatocytes	Osborne Mendel	DNA repair	9.5 x 10-4 M	-		(110)
BALB/C-3T3 cells		Cell transformation	Closed system	-		(64)
In vivo						
Drosophila melanogaster		Mitotic recombination	1,000 or 2,000 ppm feeding	-		(107)

Table 5. Genotoxicity studies with 1,1,2,2-tetrachloroethane

Species	Strain/cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Bacterial systems						
S. typhimurium	TA1530	Reverse mutations	10 µmol/plate	+		(3)
	TA1535			+		
	TA1538			-		
S. typhimurium	TA1535	Reverse mutations	Up to 4 mg/plate	-	-	(57)
	TA108			-	-	
	TA1537			-	-	
	TA1538			-	-	
	TA98			-	-	
S. typhimurium	TA1535	Reverse mutations	Dose levels ranging 0.01 - 1 mg/plate	-	-	(37)
	TA1537			-	-	
	TA98			-	-	
	TA100			-	-	
S. typhimurium	TA98	Reverse mutations	Dose levels ranging 0.01 - 1 mg/plate	+	-	(93)
	TA100			+	-	
	TA97			+	-	
	TA104			+	-	
S. typhimurium	TA1535	Reverse mutations	S-9 mix from Osborne Mendel rats or B6C3F1 mice; closed system	-	-	(64)
	TA1537			-	-	
	TA98			-	-	
	TA100			-	-	
S. typhimurium	TA100	Reverse mutations	Tedlar® vapourization desiccator	-	-	(108)

Table 5. Cont.

Species	Strain/cells	Measured endpoint	Test conditions	Results		Reference
				without activation	with activation	
S. typhimurium	TA97	Reverse mutations	Three methods used for each strain:	-	+(A)	(63)
	TA98		classical Ames-test (A),	-	+(A)	
	TA100		spot test (S),	+(S)	-	
	TA102		preincubation	-	-	
S. typhimurium	BA13/BAL13	Forward mutations	Dose levels ranging 0.06-2,979 nmol	-	-	(82)
E.coli	polymerase deficient pol A+/pol A1-	DNA damage		+		(3)
Escherichia coli		Induction of prophage lambda	7.4 - 473 µM	-	+	(19)
Yeasts						
Saccharomyces cerevisae	D7	Gene conversion mitotic recombination	3.1, 5.2 or 7.3 mM	+		(7)
				+		
Saccharomyces cerevisae	D7	Gene conversion		-		(73)
	XV185-14C	reversion		-		
Fungi						
Aspergillus nidulans	diploid P1	Chromosome missegregation	0.01 - 0.04 % (v/v)	+		(14)
In vitro mammalian systems						
CHO cells		SCE	16.8 - 168 µg/ml (-S-9)	+		(30)
			451 - 558 µg/ml (+S-9)		+	

Table 5. Cont.

Species	Strain/cells	Measured endpoint	Test conditions	Results		Reference
				without activation	with activation	
CHO cells		Chromosome aberrations	455 - 506 µg/ml (-S-9)	-		(30)
			348 - 443 µg/ml (+S-9)		-	
BALB/c-3T3 cells		SCE	1,000 µg/ml (-S-9)	+		(12)
			500 µg/ml (+S-9)		+	
Mouse hepatocytes	B6C3F1	DNA repair		-		(64)
Rat hepatocytes	Osborne Mendel	DNA repair		-		(64)
Rat hepatocytes	Osborne Mendel	DNA repair	9.5 - 10-5 M	-		(110)
BALB/c-3T3 cells		Cell transformation	Closed system	-		(64)
BALB/c-3T3 cells		Cell transformation	125 - 1,000 µg/ml	+	+	(13)
BALB/c-3T3 cells		Cell transformation	31 - 500 µg/ml with or without promoting treatment with TPA		+	(12)
In vivo - in vitro						
Mouse primary hepatocytes	B6C3F1	UDS	50 - 1,000 mg/kg by gavage; hepatocyte isolation 2 or 12 h later	-		(65)
Mouse primary hepatocytes	B6C3F1	S-phase synthesis	200 - 700 mg/kg by gavage; hepatocyte isolation 24 or 48 h later	- (male mouse) equivocal (female mouse)		(65)
In vivo						
Drosophila melanogaster		Sex-linked recessive lethal mutations	800 ppm by injection	-		(112)
			1,500 ppm feeding	-		
Drosophila melanogaster		Mitotic recombination	500 or 1,000 ppm feeding	-		(107)

10.6.2. 1,1,2,2-TCE

Groups of 50 male and 50 female B6C3F1 mice were administered technical-grade 1,1,2,2-TCE in corn oil by gavage on 5 days per week. Initially, high-dose animals received 200 mg/kg bw/day, and low dose animals received 100 mg/kg bw/day; after 18 weeks the doses were increased to 300 and 150 mg/kg bw/day. Test animals were maintained at these levels for 3 weeks, followed by 5 weeks at 400 and 200 mg/kg bw/day and 52 weeks at 300 and 150 mg/kg bw/day (total treatment time 78 weeks). The measured, time-weighted average doses were 142 (low dose) and 284 (high dose) mg/kg bw/day. Animals were killed and necropsied 12 weeks after the last dose. Groups of 20 male and 20 female mice were given corn oil for 78 weeks and killed after 91 weeks; another control group of 20 male and 20 female mice were fed the standard diet for 90 weeks. By 90 weeks, only 1 male that received the high dose was still alive, whereas 34% of females lived to that time. In males, hepatocellular carcinomas occurred in 2/19 untreated controls, in 1/18 vehicle-treated controls, in 13/50 low dose animals and in 44/49 high-dose animals; in females, the respective incidences were 0/19, 0/20, 30/48 and 43/47, respectively (44, 71).

Groups of 50 male and 50 female Osborne-Mendel rats were administered technical-grade 1,1,2,2-TCE in corn oil by gavage on 5 days per week. High-dose animals received 100 mg/kg bw/day; in males, this was increased after 14 weeks to 130 mg/kg bw/day for 18 weeks followed by 9 cycles of 4 weeks at this dose and 1 week treatment-free (total 78 weeks); in females, the dose was reduced after 25 weeks to 80 mg/kg bw/day for 7 weeks followed by the cyclic treatment as above at this dose level for 45 weeks. Low dose males received 50 mg/kg bw/day for 14 weeks and 65 mg/kg bw/day for 64 weeks; females received 50 mg/kg bw/day for 25 weeks and 40 mg/kg bw/day for 53 weeks. All groups were maintained for a further 32 weeks on a standard diet without treatment. Time-weighted average doses were 62 mg/kg bw/day and 108 mg/kg bw/day in males and 43 and 76 mg/kg bw/day in females. Groups of 20 animals of each sex were administered corn oil alone; further groups of 20 males and 20 females served as untreated controls. Weight gain was consistently lower in high-dose groups than in low dose and control groups. Fifty per cent of the high-dose males, 40% of the high-dose females, 50% of the low dose males and 58% of the low dose females lived more than 105 weeks. The incidences of tumours in treated and control rats were not significantly different for any tumour type; however, 2 of 49 males treated with the high-dose developed hepatocellular carcinomas and an additional rat had a neoplastic nodule of the liver, compared with 0/20 vehicle controls (44, 71).

In the initiation protocol of an initiation-promotion study, 10 male Osborne-Mendel rats per group were subjected to partial hepatectomy, and were dosed with either 1,1,1,2-TCE (1.2 mmol/kg bw in corn oil) or 1,1,2,2-TCE (0.59 mmol/kg bw in corn oil) 24 h later followed by six days 0.05% phenobarbital in the ground chow diet for seven weeks. In the treatment with promotion protocol, 24 h after 2/3 partial hepatectomies the rats were administered diethylnitrosamine (DEN)

i.p., and five days later the rats received 1,1,1,2- or 1,1,2,2-TCE in corn oil. When administered in the promotion protocol after initiation with DEN, 1,1,2,2-TCE induced significant increases in γ-glutamyl-transferase positive (GGT+) foci above control levels. 1,1,2,2-TCE also induced significant increases in GGT+ foci when administered in the promotion protocol without DEN initiation (92, 64). Thus the study suggested that 1,1,2,2-TCE may be a complete carcinogen with a weak initiating activity and a stronger promoting activity.

Pulmonary adenoma response of a sensitive strain (A/St) of male mice was investigated in a 24 week study in which 80, 200 or 400 mg/kg 1,1,2,2-TCE was injected *i.p.* 3 times a week into groups of 20 animals for a total of 24 injections (98). The highest dose produced an elevated lung tumour response which was close to statistical significance; however, only 5 rats survived to the end of study in the high dose group.

In summary, both tetrachloroethane isomers caused hepatocellular adenomas and/or carcinomas in both sexes of the mouse. 1,1,2,2-TCE also acted as a weak initiator and a strong promotor when initiated with diethylnitrosamine in an initiation/promotion bioassay with rats. The mechanism of tetrachloroethane induced liver carcinogenesis is unclear. It is noteworthy that tetrachloroethane metabolites trichloroethylene, tetrachloroethylene, dichloroacetic acid and trichloroacetic acid have been shown to be carcinogenic in rodents (for review, see IARC, (43)) and more specifically, that the two chlorinated acids have induced hepatic tumours in B6C3F1 mice (6). While some of the proposed mechanisms of tumorigenesis such as peroxisome proliferation may be of lesser relevance to humans, other mechanisms that lead to DNA and protein binding, lipid peroxidation and hepatocellular damage mediated by free radicals and acyl chlorides may also be operative.

10.7 Reproductive and developmental toxicity

Reproductive toxicity has been reviewed by IARC (44, 45) and European Union (94).

No reproductive disturbances were observed in rats exposed orally or by inhalation to 1,1,1,2-TCE, although neonates born to exposed females died within two days of birth (104). (The IARC working group noted that the report did not specify whether or not the newborn animals had themselves been exposed to 1,1,1,2-TCE, and control animals were not described (45).)

Treatment of AB-Jena and DBA mice with daily intraperiteonal injections of 300-400 mg/kg bw/day tetrachloroethane in olive oil during organogenesis gave some indication of an embryotoxic effect (at most doubling of postimplantation loss) in AB-Jena mice but not in DBA mice (88).

When male rats (strain not defined), exposed to 14 mg/m^3 (2 ppm) of tetrachloroethane for 9 months, were mated with untreated females, there were no effects in the reproductive outcome (no change in litter size, average foetal weight, male-to female sex ratio, growth rate, or neonatal mortality) (87).

10.8 Other studies

Male Wistar rats (6 rats at each concentration and 20 rats as controls) were exposed to 1,1,2,2-TCE at 68.7, 687, 6,870 mg/m³ (10, 100 and 1,000 ppm) by inhalation for 6 hours. At 24 hours after the single inhalation exposures at 68.7 and 687 mg/m³ (10 and 100 ppm), the average serum aspartate aminotransferase (ASAT = SGOT) values were 144 and 206 units, respectively, while the control rats showed an average value of 110 units. The corresponding average serum alanine aminotransferase (ALAT = SPGT) values were 51 and 53 units, respectively, for the exposed groups and 41 units for the control group. Four of the six rats exposed at 6,870 mg/m³ (1,000 ppm) for 6 hours died within 24 hours after the start of the exposure. Histologic examinations performed at necropsy after 24 and 120 hours of recovery in the 70 , 690 and 6,900 mg/m³ (10, 100 and 1,000 ppm) groups showed no definite changes in the liver, heart, kidney, spleen, brain or bone marrow (18).

Groups of 10 male Wistar rats were exposed to 1,1,2,2-TCE at 410-4,200 mg/m³ (60-600 ppm) for 4 h in an exposure chamber. The threshold concentrations for effects on the liver (alterations in several liver enzymes) were between 400-700 mg/m³. 1,1,2,2-Tetrachloroethane also transiently increased the ascorbic acid content of the liver (89).

Female Cb mice were exposed to 1,1,2,2-TCE at 4,180 mg/m³ (600 ppm) for 3 hours in a constant flow exposure chamber. Groups of 6 mice were killed at 0, 4 and 8 hours after termination of exposure; eight female mice were used as controls. Total liver lipids increased to 115, 155 and 216% at 0, 4 and 8 hours, respectively; the triglyceride content increased to 163, 288 and 518%, respectively, while the hepatic ATP content decreased to 75, 59 and 46% of the control values, respectively (101).

Paolini and coworkers (78) studied the biochemical hepatotoxicity of 1,1,2,2-TCE *in vivo* in mice. Groups of 6 male and female Swiss albino mice (CDI strain) were treated *i.p.* with a single 1,1,2,2-TCE dose of 300 or 600 mg/kg bw (corresponding to 20% or 40% of the LD_{50} = 1,476 mg/kg). No significant alteration of microsomal protein content was observed. Hepatic microsomal P450 concentration and activities of several monooxygenases, NADPH-cytochrome *c*-reductase, epoxide hydrolase, UDP-glucuronosyl transferase and glutathione S-transferase were decreased. Microsomal haeme was decreased, accompanied by a decrease in δ-aminolaevulinic acid synthetase and a significant increase in the hepatic heme oxygenase (78).

Swiss albino mice (CD1 strain) were given a single *i.p.* injection of 1,1,1,2-TCE at two dose levels (35 or 70% of the LD50: 376.6 mg/kg bw or 753.2 mg/kg bw). After 24 h, P450 levels were significantly ($p<0.01$) decreased at both doses. Ethoxyresorufin deethylase and pentoxyresorufin O-dealkylase activities were also decreased (4).

1,1,2,2-Tetrachloroethane was applied to the clipped back skin of guinea pigs (1 mL of pure solvent in a glass chamber with 3.1 cm² area). Biopsies were taken at different times of exposure for histopathological studies. A moderate karyopyknosis was found at 16 hours and pseudoeosinophilic cellular infiltration occurred at the same point in time but only in the deep and middle parts of dermis (53).

With a view to studying potential for causing immunological glomerulopathy, Brown Norway and Wistar rats were exposed to 516 ppm of 1,1,2,2-TCE, 5 h/day, 5 days/week for 13 weeks (16). Paradoxically, the exposed rats had consistently lower proteinuria than control rats. No histological lesions were found in the kidneys with light microscopy and immunofluorescence. Electron microscopy showed slight deposits within the glomerular basal membrane of the exposed rats.

Groups of 4-5 rabbits were exposed to 2, 10 or 100 mg/m³ of 1,1,2,2-TCE, 3 h/day, 6 days/week for 8 months and then immunized with typhoid; 50 unexposed rabbits served as controls. In the middle and high dose groups the summary titre of typhoid antibodies was decreased compared to controls. There was also a concomitant increase in the electrophoretic mobility of antibodies toward β- and α-globulin fractions and a decrease in the level of "normal" haemolysis to the Forsman's antigen of sheep erythrocytes (91).

In a study of acute neurochemical effects of 28 different substances, 5 14-week old male Sprague-Dawley rats were given 50 mg/kg 1,1,2,2-TCE in one dose by gavage and two hours later various neurotransmitters and their metabolites were determined in the midbrain, hypothalamus and medulla (49). While there was no change in the acetylcholine concentration of the hippocampus, some monoamine neurotransmitters or their metabolites increased in the midbrain, hypothalamus and medulla. The authors could not find any consistent compound structure-related effects among the study results.

1,1,2,2- Tetrachloroethane induced release of alanine aminotransferase from a rat hepatocyte suspension incubated for 30 to 180 minutes at concentrations of 7.5 and 10 mM (15).

1,1,2,2- Tetrachloroethane was a potent inhibitor of acetylcholinesterase activity in the human blood erythrocyte membrane *in vitro*. The enzyme inhibition was concentration dependent (52).

11. Observations in man

11.1. Acute effects by contact and systemic distribution

In the context of accidental inhalation or ingestion by humans pronounced to extremely severe toxic alterations of the liver and toxic fatty degeneration of the renal tubules were observed (40, 89, 93).

There are also reports concerning non-occupational poisonings due to ingested tetrachloroethane with suicidal intent in some cases (22, 29, 39, 58, 62). The signs and symptoms included early loss of consciousness, progressive CNS depression and death within 9 h.

Eight adult Africans (two females and six males) were mistakenly given 3 ml of tetrachloroethane orally (about 60-70 mg/kg) for eradication of hookworms (90).

Within two hours the patients lost consciousness and three became comatose with absent reflexes and enlarged, fixed pupils. The pulse was barely perceptible and respirations were shallow and rapid. After about half an hour the patients regained consciousness but were slightly confused and complained of slight headache. The recovery was uneventful.

Two male volunteers were exposed to 1,1,2,2-TCE at concentrations ranging from 20 to 2,300 mg/m^3 (2.9-335 ppm), during periods up to 30 min. During 10 min periods of exposure at 20, 30, 90 mg/m^3 (2.9, 4.4 and 13 ppm) the men did not complain of any effects. The odor was detected at 90 mg/m^3 (13 ppm). At 1,000 mg/m^3 (144 ppm) the subjects experienced dizziness after 10 min, mucosal irritation at 12 min and fatigue after 20 min. At 1,800 (262 ppm) a 10 min exposure resulted in dizziness and mucosal irritation of the mouth, eyes, and nose. The highest concentration produced a strong odor which was no more discernible after 3 min. At this concentration 1,1,2,2-TCE produced dizziness in 3 minutes and mucosal irritation in 10 minutes (57).

11.2. Effects of repeated exposure

Already at the beginning of World War I, the adverse health effects of tetrachloroethane (1,1,2,2-TCE) were known due to numerous poisonings of workers in the aircraft industries of Germany, France, England and Holland. In England alone there were 70 reported cases with 12 deaths (5). The deaths were attributed to severe toxic hepatitis with jaundice but there was no development of acute yellow atrophy of the liver. Among German aircraft factory workers 12 out of 15 workers who regularly used varnishes containing 30-50% of 1,1,2,2-TCE became ill. The patients were classified into two groups according to the symptoms: one group showed mainly gastrointestinal disturbances, jaundice and enlarged livers, the second group had neurologic disturbances (tremors, impaired hearing, paresthesias in the extremities, reduced patellar reflexes, headache, anorexia and nausea) (38). In some case reports changes in the blood picture: occurrence of a large number of mononuclear cells, a slight increase of the total white cell count and progressive anaemia were observed (5).

In a penicillin plant where 1,1,2,2-TCE concentrations ranging from 10 to 1,700 mg/m^3 (1.5 to 247 ppm) were measured in different processes, about one half of the workers exhibited adverse symptoms, particularly digestive organ complaints (loss of appetite, bad taste in the mouth, epigastric pain, sensations of pressure in the liver area), headaches, general debility, lack of stamina, loss of body weight, and occasionally painful prurigo. Among the symptomatic workers many had enlarged liver and abnormal liver function tests. All these symptoms were reduced with improvements in the working conditions which lowered the tetrachloroethane concentrations (48). Most workers became symptom-free after improvements in the working conditions which lowered the maximum 1,1,2,2-TCE levels down to 36 ppm (48).

Lobo-Mendonca (59) has reported on a thorough survey of the use of 1,1,2,2-TCE as a solvent for cellulose acetate in the manufacture of bangles in Bombay,

India. The survey involved 23 factories (so-called cottage industries), and 380 workers, representing 80% of the population employed, were examined. The raw material for bangles was cellulose acetate safety film. To dissolve the material a mixture of acetone and 1,1,2,2-TCE in equal proportions was used and during the monsoon some diacetone alcohol was added to prevent haziness. It was estimated that about 900 kg (2,000 pounds) of tetrachloroethane was used every month. The process involved both inhalation exposure and direct dermal contact with liquid 1,1,2,2-TCE. About one half of the workforce was in direct contact with the substance. Air samples were collected in different locations from the breathing zone and analyzed by titration against 0.01N silver nitrate for chloride. Tetrachloroethane concentrations ranged in 14 measurements from 9 to 98 ppm (63-680 mg/m^3).

Among workers with the most severly exposing jobs nervous symptoms and signs were the most frequent: headache and vertigo were complained by more than a third of the workforce and roughly every other person exhibited a fine tremor in the fingers (59). Almost a quarter of these workers also complained of loss of appetite and many had felt nausea, abdominal pain, and had vomited; however liver enlargement was not found. The author reported that the symptom complex of tetrachloroethane poisoning appeared after about 3 months of exposure, and a more consistent series of symptoms was evident after 6 months. There seemed to be a dose response for hand tremor: at 9-17 ppm of 1,1,2,2-TCE (factory G) 14% of workers handling the substance showed tremors, at 40-74 ppm (factory A) the corresponding frequency was 33%, at 50-61 ppm (factory T) 41%, and at 65-98 ppm (factory L) 50%. The author pointed out that the survey was unable to reveal the full impact of exposure on chronic illness and debility because of high labour turnover.

In Italy, 75 persons were exposed to tetrachloroethane in tri- and tetrachloroethylene production, and in laboratory work at two plants. Tetrachloroethane in air varied from the low mean of 2.6 mg/m^3 (0.37 ppm) to the high mean of 9.3 mg/m^3 (1.33 ppm) with a single maximum of 278 mg/m^3 (40 ppm). Clinical examinations of the workers indicated that the pulse rate, circulatory response to postural changes, and the ECG's were not significantly different from "normal" (32).

In a retrospective cohort study, 1,099 white men who had been exposed to 1,1,2,2-TCE while using machinery that impregnated clothing (plus some exposure to dry cleaning solvents) in seven companies, and 1,319 men who served in the same companies but were not involved in the impregnation process, were investigated for mortality experience from 1946 through 1976 (76). There was an additional comparison cohort of 3,166 white men who had been engaged in water solvent processes for cleaning in other companies at the same time period. Expected numbers of deaths were calculated on the basis of the US mortality statistics. There was no increased mortality in any of the cohorts in all diseases, all malignancies, cardiovascular disease, or cirrhosis of the liver. The TCE cohort exhibited the lowest standardized mortality ratio for cirrhosis of the liver (0.48) which may be attributable to exclusion of moderate to heavy drinkers because of

liver toxicity hazard during exposure. The overall cancer mortality in the TCE exposed cohort was somewhat (26%), but not significantly, higher than in the cohort not involved in the impregnation process, and some cancer types occurred more frequently (not significantly different) in the TCE cohort: cancers of the genital organs 3 cases versus 1.65 expected, leukemia and aleukemia 4 cases versus 1.81 expected. The workers had been exposed to TCE for limited periods of time ranging from five weeks to one year, with an average of about five months.

12. Dose-effect and dose-response relationships

There are limited and uncertain data concerning dose-effect and dose-response relationships for tetrachloroethanes (1,1,2,2-TCE) in humans, other than acute effects. Acute human effects by 1,1,2,2-TCE are shown in Table 6. The following evaluation is therefore essentially based on animal data.

12.1 Short term exposure

Studies concerning short term effects of 1,1,2,2-TCE in animals are compiled in Table 7.

Table 6. Acute effects of 1,1,2,2-TCE in humans

Route of exposure	Dose or exposure conc. and duration	Effects	Reference
Ingestion	Unknown	Coma, no corneal reflex, death after 17 h, lung and liver congestion	(39)
Ingestion	Unknown	Unconsciousness, cyanosis, death 12 h later	(22)
Ingestion	Unknown	Coma shortly after ingestion, death after 9 h	(58)
Ingestion	3 ml	Unconsciousness, coma in 2 h after half an hour consciousness was regained, followed by uneventful recovery	(90)
Inhalation	2,330 mg/m^3 (335 ppm) 3-10 min	Dizziness, mucosal irritation	(57)
	1,000 mg/m^3 (144 ppm) 10-20 min	Dizziness, fatigue, mucosal irritation	
	20-90 mg/m^3 (2.9-13 ppm) 30 min	No effect	

Table 7. Short term effects of 1,1,2,2-TCE in animals via inhalation

Species	N	Exposure conc. and duration or dose	Effects	Ref.
Mouse		11,400 ppm for 6 h, exposure repeated next day	Mice: after 6 h, deep anaesthesia, convulsions, death within a few hours on the second day, fatty degeneration of the liver, focal fatty degeneration of the renal tubular cells	(68)
Mouse	10 10 10	5,900 ppm, 3 h 6,600 ppm, 3 h 7,000 ppm, 2 h period per week	3/10 mice died 4/10 mice died 5/10 died after the first exposure and the last animal died after the 11th exposure	(41)
Rat	6	9,000 ppm, 2 h/day, 2 days/week	One died after first and one after the second exposure 3/6 survived up until the 11th exposure 2/3 surviving rats showed decreased red blood cell counts and haemoglobin levels	
Mouse	4	Exposure in a closed vessel for 1-1.5 h; theoretical max concentration about 7,000 ppm	Coma, convulsive movements and staggering of the limbs; after 8 exposures, bristly hair, weight loss, anorexia; between the 8th and 28th exposures hepatic lesions	(26)
Cat	2 2	710 ppm 6,100 ppm time not given	Prostration Deep narcosis	(57)
Cat	7	830 ppm 8,300 ppm	Light narcosis in 4 h deep narcosis in 5h Light narcosis in 25 min deep narcosis in 40 min	(56)
Cat Rabbit	2 2	116-160 ppm 8-9 h/day, 6 days/week for 4 weeks	Prostration	(56)
Rat, male	7	13.3 mg/m^3 (1.9 ppm) for 2,4 or 8 days within 10 days	No effects on body weights, and organ (liver, kidney, lung, brain, adrenal, testis, thyroid) weights; liver and renal lipid concentrations unchanged, histopathology: slight periportal round-cell infiltration & small necrotic foci, moderate accumulation of lipid in the liver	(87, 33)

Table 8. Long-term studies with 1,1,1,2-TCE in animals

Route of exposure	Species	N	Exposure conc. and duration, or dose	Effects	Ref.
Gavage	Mouse B6C3F1	50 male 50 female	0 and 250 mg/kg bw for 103 weeks 500 mg/kg bw for 65 weeks	CNS toxicity at week 51 of each sex (500 mg/kg), all died or were killed moribund after 65 weeks (high dose) hepatocellular adenomas in males 6/48, 14/46 and 21/50 ($p<0.001$) in females 4/49, 8/46 and 24/48 ($p<0.001$) dose related increase of hepatocellular carcinomas: 1/49, 5/49 and 6/48 in treated females ($p<0.05$)	(72), in (45)
Gavage	Rat Fischer 344	50 male 50 female	0, 125 or 250 mg/kg bw, five days a week for 103 weeks, termination 104th week	CNS involvement from week 44 fibroadenomas of the mammary gland: 6/49, control females 15/49, low dose females 7/46, high-dose females	(72), in (45)

12.2 Long-term exposure

Long-term studies with 1,1,1,2-TCE in animals are compiled in Table 8, and the corresponding studies of 1,1,2,2-TCE are compiled in Table 9.

Table 9. Long-term studies with 1,1,2,2-TCE in animals

Route of exposure	Species	N	Exposure conc. and duration	Effects	Ref.
Inhalation	Monkey cynomolgus	1	1,000-4,000 ppm 190 exposures over 9 months (2 h/day, 6 days/week)	Diarrhoea, anorexia reduction of red blood cells and hemoglobin, vacuolation in liver cells	(41)
Inhalation	Rat Sprague-Dawley	165 rats divided in three groups	560 mL/m^3, 5-6 h/day, 5 days/week, for 15 weeks	Slight decrease of haematocrit, increased relative liver weight, signs of hepatic hyperplasia, foci of granulation & vacuolization in liver	(103)
Inhalation	Rat male	group size 7 rats	13.3 mg/m^3 (1.9 ppm) for 9 months	Lower body weight at 4 months, increased liver lipids at 7 months, consistently decreased ACTH activity of the pituitary, longevity of rats not affected	(87)

Table 9. Cont.

Route of exposure	Species	N	Exposure conc. and duration	Effects	Ref.
Gavage	Mouse B6C3F1	50 male 50 female Sham treated controls: 20 male 20 female Untreated 20 males 20 females	Low dose: 100-200 mg/kg bw/day (mean 142 mg/kg bw/day) for 78 weeks high-dose 200-400 mg/kg bw/day (mean 284 mg/kg bw/day) for 78 weeks	Large number of high-dose mice died at weeks 69 and 70 of acute toxic tubular nephrosis hepatocellular carcinomas in males: 2/19 untreated controls 1/18 sham-treated controls 13/50 low dose 44/49 high-dose in females: 0/19 sham-treated controls 0/20 untreated controls 30/48 low dose 43/47 high-dose	(71)
Gavage	Rat Osborne Mendel	50 male 50 female sham-treated controls: 20 male 20 female untreated controls: 20 male 20 female	Low dose: males: 50-65 mg/kg bw/day for 64 weeks (mean dose: 62 mg/kg bw/day) females: 40-50 mg/kg bw/day (mean dose: 43 mg/kg bw/day) high-dose males: 100-130 mg/kg bw/day (mean dose: 108 mg/kg bw/day) females: 80-130 mg/kg bw/day (mean dose: 76 mg/kg bw/day) for 78 weeks	Occurrence of tumours in treated and control rats was not significantly different for any tumour type, however, 2/49 males at the high-dose developed hepatocellular carcinomas and an additional rat had a neoplastic nodule compared to 0/20 in sham-treated controls	(71)
Gavage	Rat male	10 rats per group	8 or 20 mg/kg during 60 days; 3.2 or 8 mg/kg during 150 days	Most effects in the liver, some effects in kidney, testis and thyroid; 3.3 mg/kg given as threshold for chronic effects (dose-effect or dose-response data were not provided)	(34)

13. Previous evaluations by (inter)national bodies

International Agency for Research on Cancer concluded that there is inadequate evidence in humans of the carcinogenicity of 1,1,2,2-TCE. No epidemiological data on cancer in humans were available for 1,1,1,2-TCE. There is *limited evidence* in experimental animals for the carcinogenicity of 1,1,2,2-and 1,1,1,2-TCE. Thus, 1,1,2,2- or 1,1,1,2-TCE are not classifible as to their carcinogenicity to humans (Group 3) (46).

In the German MAK-value list 1,1,2,2-TCE is included in group IIC (substances shown to be hazardous during pregnancy without further categorization). Additionally, 1,1,2,2-TCE is classified into group IIIB (justifiably suspected of having carcinogenic potential) (20).

In the late 1970s, the National Institute for Occupational Health (NIOSH) of the United States recommeded that it would be prudent to handle 1,1,2,2-TCE in the workplace as if it were a human carcinogen and that the exposure be minimized (75, 79).

14. Evaluation of human health risks

14.1. Groups at extra risk

There is no firm evidence, mechanistic or otherwise, to indicate particular factors of individual susceptibility to tetrachloroethane toxicity.

14.2. Assessment of health risks

Tetrachloroethanes are recognized hepatotoxins and liver carcinogens in mice (44, 45, 71, 72, 78). In the liver, tetrachloroethanes are metabolically activated to acyl chlorides (1,1,2,2-TCE to dichloroacetyl chloride) or free radicals which may bind to proteins or initiate lipid peroxidation causing toxicity (78). Both compounds, 1,1,2,2-TCE more extensively than 1,1,1,2-TCE, were shown to bind covalently to rat liver DNA (11, 12). Although genotoxicity studies on tetrachloroethanes do not provide a consistent picture of effects, the compounds appear to have some potential for genotoxicity (30, 7, 11, 63, 96). The mechanism of tetrachloroethane induced liver carcinogenesis is unclear. Several metabolites are carcinogenic to rodents and produce in biotransformation reactive intermediates mentioned above. Although some of the proposed mechanisms for tumorigenesis such as peroxisome proliferation may have lesser relevance for humans, other mechanisms that lead to DNA and protein binding and consequent damage, lipid peroxidation and hepatocellular damage mediated by free radicals and acyl chlorides may be operative.

The concentration of 4,900-5,600 mg/m^3 (700-800 ppm) of 1,1,2,2-TCE caused prostration and light narcosis in cats, and some prostration was found in cats and rabbits at 840-1,100 mg/m^3 (120-160 ppm) (56, 57). At high dose levels severe CNS depression, unconsciousness, convulsions and coma, and/or hepatic lesions were noted in mice, rats, guinea pigs and rabbits. Regarding acute effects in humans, two male volunteers exposed to 1,1,2,2-TCE at concentrations ranging from 20 to 90 mg/m^3 (2.9-13 ppm) up to 30 minutes, did not complain of any effects (57). The subjects experienced dizziness after 10 minutes, mucosal irritation at 12 minutes and fatigue after 20 minutes at 1,000 mg/m^3 (146 ppm). A 30 minute exposure at 1,800 mg/m^3 (262 ppm) resulted in dizziness and mucosal irritation of the mouth, eyes and nose. Exposure to 2,330 mg/m^3 (335 ppm) caused dizziness in 3 minutes and mucosal irritation in 10 minutes. Oral ingestion of 3 ml (about 60-70 mg/kg) of 1,1,2,2-TCE by hookworm bearing patients caused lowered consciousness and among some subjects deep coma; the recovery was reported to be uneventful without specific therapy (90).

Long-term animal studies on 1,1,2,2-TCE have yielded ostensibly conflicting results, but inadequate study design and reporting, or the different endpoints used, may explain the discrepancies. No appropriate long-term studies on tetrachloroethanes by inhalation were located. A subchronic inhalation study with 1,1,2,2-TCE with female Sprague-Dawley rats involved exposure to a single level of 560 mL/m^3 (ppm), for 5 or 6 hours per day, 5 days/week, for 15 weeks (103). Routine haematology and the histopathology of the liver, kidneys, lungs, ovaries, uterus and adrenal glands were examined. A slight decrease of the haematocrit level, increased relative liver weight, signs of hepatic hyperplasia (increased number of binucleated cells and transient increase of DNA synthesis), granulation and vacuolization of the liver were found. There were no effects in the kidneys, lungs, reproductive organs and adrenals. Another subchronic inhalation toxicity study with male rats involving inhalation exposure to 13.3 mg/m^3 (1.9 ppm) of 1,1,2,2-TCE for 9 months revealed some slight (mainly biochemical) changes at one time point (out of three) during the course of the experiment: somewhat lower body weight at 4 months and increased liver lipids at 7 months, whilst there was a consistent increase of the ACTH activity of the adenohypophysis (87).

By the oral route of administration, carcinogenicity studies with 1,1,1,2-TCE (72) and 1,1,2,2-TCE (71) by gavage with rats and mice examined a number of non-neoplastic endpoints, including histopathology of all major organs and tissues. 1,1,1,2-TCE was found to cause at the highest dose level (500 mg/kg for mice and 250 mg/kg for rats) behavioural signs of CNS toxicity towards the end the study. Mice that received the high dose of 1,1,2,2-TCE (282 mg/kg) developed acute toxic tubular nephrosis of the kidneys. In another gavage study, where 1,1,2,2-TCE was administered to rats at dose levels of 8 or 20 mg/kg during 60 days or at 3.2 or 8 mg/kg during 150 days the authors report to have found clear effects in the liver and some effects also in the kidney, testis and thyroid; the lowest dose was given as a threshold for chronic toxicity. However, it was not

possible to evaluate this study because quantitative data on the dose-effect or dose-response were not reported.

It would appear that the NOAELs for non-neoplastic effect endpoints in mice and rats can best be derived from the carcinogenicity bioassays (71, 72) and would correspond to the lower dose level used: i.e. regarding 1,1,1,2-TCE, 250 mg/kg bw/day for mice and 125 mg/kg bw/day for rats, regarding 1,1,2,2-TCE, 142 mg/kg bw/day for mice and 62 mg/kg bw/day for male rats and 43 mg/kg bw/day for female rats. Both substances however caused a clear hepatocarcinogenic response in mice even at the lower dose level.

There are two useful descriptive epidemiological surveys of workers exposed for some time to 1,1,2,2-TCE, one from Hungary (48) and the other from India (59). The air levels of 1,1,2,2-TCE have been measured in both studies with an outdated method but which may however show correctly the magnitude of the substance concentration. The observations reported in these two studies are by and large in agreement, and the more extensive survey in India (59) can be used to summarise the affects of 1,1,2,2-TCE exposure. In the most severely exposed jobs which involved both inhalation of the vapours and direct hand contact with liquid 1,1,2,2-TCE (50% in acetone), more than a third of the workforce complained of headache and vertigo, and roughly every other person exhibited a fine tremor of the fingers. Almost a quarter of these workers also complained of loss of appetite and many had experienced nausea, abdominal pain, and had vomited; however, liver enlargement was not found. The author reported that the symptom complex of tetrachloroethane poisoning appeared after about 3 months of exposure, and a more consistent series of symptoms was evident after 6 months. There seemed to be a dose-response for hand tremor with 1,1,2,2-TCE: at 9-17 ppm (in factory G) 14% of workers handling the substance showed tremors, at 40-74 ppm (in factory A) the corresponding frequency was 33%, at 50-61 ppm (in factory T) 41%, and at 65-98 ppm (in factory L) 50%. The observations of the survey were limited to recording symptomatology and some signs as the workers were reluctant to submit blood and urine for examinations. Moreover, the author pointed out that the study could not disclose the full picture of long-term effects by 1,1,2,2-TCE, because the high labour turnover made the employment periods relatively short, and because the study did not include the workers who had become ill and left the employment.

Human experience would therefore suggest that repeated exposures to 1,1,2,2-TCE may be accompanied by adverse symptoms from the CNS and the gastrointestinal tract at air levels in excess of 10-30 ppm (70-210 mg/m^3); however, skin exposure has also been involved. Acute symptoms of CNS depression and mucosal irritation were observed within 10-20 minutes at 1,000 mg/m^3 (146 ppm) in a volunteer study.

The previous human data concern studies that date back several decades. Currently, the manufacture and use of end products containing 1,1,2,2-TCE (the isomer that has commercial value) is very limited in the US and Europe. However, the substance occurs as a non-isolated intermediate in the closed production

process of trichloroethylene in some chemical industries. Thus, exposure to the tetrachloroethanes in the developed countries is presumably infrequent and low.

Although the database is far from complete, the assessment of health risks caused by tetrachloroethanes can be based on the previous human evidence involving 1,1,2,2-TCE exposure regarding non-genotoxic and non-neoplastic effects. However, the capacity of the compounds to cause liver carcinogenesis in the mouse, to act (1,1,2,2-TCE) as a weak initiator and a strong promoter in an initiation/promotion bioassay with rats, to cause genotoxicity and cell transformation in some *in vitro* assays, and the ability of the compounds to chemically interact with DNA, warrant certain concerns of possible carcinogenic effect in humans. Moreover, although tetrachloroethane-induced cancer was clearly demonstrated only with mice, there is not enough mechanistic data available to decide to what extent the effect is species specific. Human evidence is not helpful: there is one retrospective epidemiological study of cancer mortality in a cohort of workers exposed during World War II to 1,1,2,2-TCE. The study did not show an increased risk, but the study was limited and not sufficient to draw any certain conclusions.

14.3. Recommended basis for an occupational exposure limit

Tetrachloroethane has caused toxic effects in occupationally exposed workers at concentrations varying from 70 to 700 mg/m^3 (10-100 ppm). The target organs are the liver and the gastrointestinal tract, and the nervous system. Similar target organs have been identified in animal studies. Moreover, tetrachloroethane isomers have the capacity to bind to DNA, cause genotoxicity in certain *in vitro* assays, and they possess some carcinogenic activity. It is therefore prudent to consider potential carcinogenicity as the critical effect for tetrachloroethanes.

Several countries have attached the skin notation (indicating skin absorption hazard) to their respective OELs for 1,1,2,2-TCE. In a recent analysis of the industrial hygiene aspects of dermal absorption for 132 chemicals based on physical properties, 1,1,2,2-TCE was included in the list of substances with dermal toxicity potential (27).

15. Research Needs

If tetrachloroethane should still be used in industrial processes causing occupational exposure, it would be important to control the situation carefully with hygienic monitoring and hopefully even with biological monitoring of individual workers. To the latter end, valid methods should be devised. Moreover, it would be highly recommended to institute pertinent health surveillance programmes that may elucidate any adverse effects, including genotoxicity, among the workforce by long term low-level exposures. Further information of the carcinogenic mechanisms of tetrachloroethane is needed for a more complete risk assessment.

16. Summary

Luotamo M and Riihimäki V. Tetrachloroethane. DECOS and NEG Basis for an Occupational Standard. *Arbete och Hälsa* 1996:28.

Tetrachloroethane (TCE) has two isomers: 1,1,1,2- and 1,1,2,2-TCE. The latter has had most use in industry. 1,1,2,2-Tetrachloroethane has caused toxic effects in exposed workers. The target organs are the liver, gastrointestinal tract, and nervous system. In animals tetrachloroethanes: i) are carcinogenic in mouse liver; ii) are genotoxic and can cause cell transformation *in vitro* (1,1,2,2-TCE); iii) acts as a weak initiator and strong promoter in rats (1,1,2,2-TCE); and, iv) interacts with DNA. There is insufficient data on the carcinogenic effects in humans. The critical effect is, therefore, considered to be carcinogenicity for workers exposed to TCE.

Keywords: Tetrachloroethane, occupational exposure, metabolism, hepatotoxicity, genotoxicity, carcinogenicity, human toxicity, risk evaluation, occupational exposure limit

17. Summary in Swedish

Luotamo M and Riihimäki V. Tetrachloroethane. DECOS and NEG Basis for an Occupational Standard. *Arbete och Hälsa* 1996:28.

Tetrakloretan (TKE) består av två isomerer; 1,1,1,2- och 1,1,2,2-TKE. 1,1,2,2-Tetrakloroetan har i huvudsak använts i industrin. 1,1,2,2-Tetrakloroetan har framkallat toxiska effekter hos exponerade arbetare. Målorgan är lever, mag-tarmkanal och nervsystem. Djurförsök visar att tetrakloretaner: i) är cancer-framkallande i lever hos möss; ii) är genotoxisk samt orsakar cell-transformation i flera in vitro tester (1,1,2,2-TKE); iii) är svag initiator och starkt tumörpromotiv hos råttor (1,1,2,2-TKE); och iv) ämnet reagerar med DNA. Det finns endast begränsat med data om cancerframkallande effekter hos människa. Den kritiska effekten bedöms vara cancer hos arbetare exponerade för TKE.

Nyckelord: Tetrakloretan, yrkeshygienisk exponering, metabolism, hepato-toxicitet, genotoxicitet, carcinogenicitet, human toxicitet, riskvärdering, hygieniska gränsvärden

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Appendix 1

Permitted or recommended maximum levels of 1,1,2,2-TCE in air. For 1,1,1,2-TCE there is no OEL in the countries listed below.

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	1		Skin	1994	1
Finland	1	7	Skin	1996	2
	3	21	15 min short term		
Germany	1	7	Skin, IIIB	1996	3
Iceland	-	-		1989	4
Netherlands	1	7	Skin	1995	5
Norway	1	7	Skin	1995	6
Sweden	-	-		1996	7
USA (ACGIH)1		6.9	Skin, A4	1996	8
(NIOSH)	1	7	Skin, C	1994	9
(OSHA)	5	35	Skin	1994	9

C = Potential carcinogen

A4 = Not classifiable as a human carcinogen. (Identified by other sources as a suspected or confirmed human carcinogen)

IIIB = Suspected carcinogen

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3. Bergkvist M, Hedberg G, Rahm M. Utvärdering av test för bedömning av styrka, rörlighet och koordination. *Arbete och Hälsa* 1992;5.

b. Chapter in book

1. Birmingham DJ. Occupational dermatoses. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology Vol.1.* 3rd ed. New York: John Wiley, 1978: 203–235.

c. Book

1. Griffin MJ. *Handbook of human vibration.* London: Academic, 1990.
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d. Report

1. Landström U, Törnros J, Nilsson L, Morén B, Söderberg L. *Samband mellan vakenhetsmått och prestationsmått erhållna vid körsimulatorstudie av-seende effekter av buller och temperatur.* Arbetsmiljöinstitutet, 1988 (Undersökningsrappport 1988:27).

e. Articles written in langueges other than English, French, German or one of the Nordic languages

1. Pramatarov A, Balev L. Menstrual anomalies and the influence of motor vehicle vibrations on the conductors from the city transport. *Akushersto Ginekol* 1969;8:31-37 (in Russian, English abstract).

f. Article in conference proceedings

1. Mathiassen SE, Winkel J, Parenmark G, Malmkvist AK. Effects of rest pauses and work pace on shoulder-neck fatigue in assembly work. *Work and Health Conference.* Copenhagen 22–25 February 1993: 62–63 (Abstract).
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