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WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER

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Environmental Affairs

With the compliments

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SL 034681

TRICHLOROETHYLENE

This compound was previously evaluated by an IARC Working Group in February, 1976 (IARC, 1976a). Since that time new data have become available and are included in this monograph.

Two reviews are available (Lyman, 1978; Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

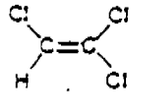
Chem. Abstr. Services Reg. No.: 79-01-6

Chem. Abstr. Name: Trichloroethane

Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethinyl trichloride; ethylene trichloride; TRE; Tri; trichloroethylene; 1,1,2-trichloroethylene

Algylen; Anamenth; Benzinol; Blacosolv; Blancosolv; Cecolene; Chlorilen; Chlorylen; Chlorylea; Chlorylen; Circosolv; Crawhaspol; Densinfluat; Dow-Tri; Dukeron; Fleck-Flip; Flock Flip; Fluate; Gemalgene; Germalgene; Lanadin; Lethurin; Narcogen; Narkogen; Narkosoid; Nialk; Perma-A-Chlor; Perm-A-Clor; Petzinol; Philex; Threthylen; Threthylene; Trethylene; Triad; Trial; Triasol; Trichloran; Trichloren; Triclene; Tri-Clene; Trielene; Trielin; Trilen; Trilene; Triklone; Triline; Trimar; Triol; TRI-plus; TRI-plus M; Vestrol; Vitran; Westrosol

1.2 Structural and molecular formula and molecular weight



C_2HCl_3 Mol. wt: 131.4

1.3 Chemical and physical properties of the pure substance

From Weast, (1976), unless otherwise noted.

(a) Description: Colourless liquid (Irish, 1963)

(b) Boiling point: 87°C

(c) Melting point: -73°C

(d) Freezing point: -86.8°C (Irish, 1963)

(e) Density: d_4^{20} 1.4642

(f) Refractive index: n_D^{20} 1.4773

(g) Spectroscopy data: λ vapour ε 200 nm; infrared, Raman, nuclear magnetic resonance, and mass spectral data have also been tabulated (Grasselli & Ritchey, 1975)

(h) Solubility: Miscible (0.1% w/v at 20°C) with water (Irish, 1963); miscible with acetone, ethanol, diethyl ether, chloroform and oils (Lloyd *et al.*, 1975)

(i) Volatility: Vapour pressure is 77 mm Hg at 25°C (Irish, 1963)

(j) Vapour density: 4.54 (air = 1) (Irish, 1963)

(k) Stability: Nonflammable; when pure and containing a stabilizer, it is stable in presence of air, moisture, light, and in contact with metals up to 130°C ~~(Hardie, 1964)~~. When heated with ozone, it decomposes rapidly into products such as hydrogen chloride, phosgene, carbon monoxide and chlorine peroxide. At 700°C and above, the vapour decomposes to give a mixture of dichloroethylene, tetrachloroethylene, carbon tetrachloride, chloroform, and methyl chloride (Hardie, 1964). Upon contact with certain metals, open flames or ultra-violet, it decomposes almost instantly to phosgene and/or hydrogen chloride, chlorine and dichloroacetyl chloride ~~(US Occupational Safety and Health Administration, 1975)~~. In the presence of alkali, trichloroethylene decomposes to highly toxic dichloroacetylene (US Occupational Safety and Health Administration).

(l) The most important reaction of trichloroethylene is its oxidative breakdown of atmospheric oxygen, greatly accelerated by elevation of temperature, exposure to light, especially ultra-violet; not hydrolyzed by water under normal conditions; reacts with alkali under pressure at 150°C to produce glycolic acid and with sulphuric acid to give monochloroacetic acid (Hardie, 1964)

(m) Conversion factor: 1 ppm in air is equivalent to 5.37 mg/m^3

1.4 Technical products and impurities

Trichloroethylene is available in the US in high purity, electronic, USP, technical, metal degreasing and extraction grades (Hawley, 1971). Typical analysis of a commercial grade is: boiling range at 760 mm, 86.6-87.8°C; density, d_4^{15} 1.467-1.471; acidity (as HCl), 0.005% max.; alkalinity (as NaOH), 0.001% max; no free halogen; residue on evaporation, 0.005 max.; moisture content, not cloudy at -12°C.

Antioxidants, such as amines (0.001 to 0.01% or more) (Copelin, 1967) or combination of epoxides such as epichlorohydrin (See also IARC, 1976) and esters (0.2 to 2% total) (Starks, 1956), are added to trichloroethylene.

Specifications for trichloroethylene produced in Japan are: specific gravity (15°C/40°C), 1.4680; boiling range, 86.5-88.2°C; non-volatile matter, 0.005% max.; acid content (as HCl), 0.0002% max.

2. Production, Use, Occurrence and Analysis

2.1 Production and Use

(a) Production

Trichloroethylene was prepared by Fischer in 1864 during experiments on the reduction of hexachloroethane with hydrogen (Hardie, 1964). The first commercial method for its preparation was the dehydrochlorination of acetylene-derived 1,1,2,2-tetrachloroethane (see monograph, p.) by reaction with calcium hydroxide or by gas-phase pyrolysis. Although this method is still used today, over 90% of the trichloroethylene produced in the US is prepared by the chlorination and dehydrochlorination of 1,2-dichloroethane (see monograph, p.). This is also the process used in Japan.

Trichloroethylene has been produced commercially in Austria and the UK since 1908, in Germany since 1910, in the US since 1925 (Hardie, 1964), and in Japan since 1935. Production of trichloroethylene in the US in 1977 was 132 million kg (US International Trade Commission, 1977). Output has been decreasing since 1970, when a reported 277 million kg were produced by seven companies (US Tariff Commission, 1972). This decrease in production is due primarily to legislation restricting the use and emissions of trichloroethylene and to the closing of three acetylene-based and one ethylene-based plants.

US exports of trichloroethylene in 1976 were 16 million kg, mostly to the Federal Republic of Germany (3.8 million kg), France (3.4 million kg), Mexico (2.1 million kg) and Brazil (2 million kg) (US Department of Commerce, 1977a). US imports during that year totalled 7 million kg (US Department of Commerce, 1977b).

It is estimated that at least 9 companies produce trichloroethylene in western Europe with total production in excess of 200 million kg/year. In at least three countries (France, the Federal Republic of Germany, and the United Kingdom) annual production is estimated to exceed 50 million kg/year. These countries, and Italy engage in both imports and exports of trichloroethylene in the range of 10-50 million kg/year.

Annual production of trichloroethylene in the COMECON countries is estimated to be greater than 100 million kg.

In Japan, four companies produced 80 million kg trichloroethylene in 1976, compared to 106 million kg in 1972. In 1976, 11 million kg trichloroethylene were exported from Japan.

(b) Use

Of the trichloroethylene produced in the US in 1977, 82% was used for vapour degreasing of fabricated metal parts; 15% was exported; and the remainder (3%) was used in a variety of miscellaneous applications.

Trichloroethylene is widely used in vapour degreasing, since all of its physical and chemical properties fall within the limits required in vapour degreasing processes. One disadvantage of trichloroethylene in this use is its high photochemical reactivity, causing smog, and leading to restrictions on its use. Since trichloroethylene decomposes rapidly upon exposure to high temperature, open flame or ultraviolet light (See section 1.3 (k)) a proposed standard was issued by the US Occupational Safety and Health Administration on October 20, 1975, which requires that operations involving high temperature, open flames or ultraviolet light be outside of areas in which trichloroethylene vapours are present, unless such operations are appropriately shielded and ventilated (US Occupational Safety and Health Administration, 1975).

Miscellaneous applications of trichloroethylene include its use as a solvent in the textile industry; as a solvent for adhesives, and lubricants; and as a low temperature heat transfer fluid.

It has also b en used as a component in several consumer products (Lloyd *et al.*, 1975).

A pharmaceutical grade of trichloroethylene is used as a general anaesthetic in surgical, dental and obstetrical procedures and as an analgesic in the treatment of trigeminal neuralgia. It has been used as a disinfectant and detergent for skin, minor wounds and surgical instruments. It has also been used on a variety of animals as a volatile anaesthetic.

The use of trichloroethylene as an extraction solvent (e.g., for use in manufacture of decaffeinated coffee and extraction of spice oleoresins) has been approved by the US Food and Drug Administration (FDA) for many years. However, on September 27, 1977, the FDA proposed regulations prohibiting the use of trichloroethylene as a food additive, directly or indirectly. Specific examples and practices to be prohibited included use in hop extraction, decaffeination of coffee, the isolation of spice oleoresins, adhesive coatings and components, and in vinyl chloride-hexane-1 copolymers. Food containing any added or detectable level of trichloroethylene will be deemed to be adulterated when the final order has issued. On the same date, the FDA also proposed a regulation that any human drug containing trichloroethylene is a new drug and will be deemed to be misbranded. Under this regulation anesthetics containing trichloroethylene would be banned. Also it was proposed to declare trichloroethylene a deleterious substance, thereby causing any cosmetic product to be deemed to be adulterated under existing law. The FDA also proposed a regulation prohibiting the use of trichloroethylene as an additive to animal and pet food. ~~Such practices as the use of trichloroethylene as an additive to animal and pet food~~ Such practices as the use of trichloroethylene for the extraction of oil-seed products would be prohibited. The FDA also proposed an order prohibiting the use of trichloroethylene in animal drug products, such as its use as an inhalation anesthetic, skin disinfectant, and in detergents (US Food and Drug Administration, 1977).

No data on use patterns in Europe were available.

The estimated 1977 Japanese consumption pattern for trichloroethylene is: metal cleaning, 63%; solvent and other uses, 23%; and exports, 14%.

It was reported in May 1978 that trichloroethylene has been accepted by the US Environmental Protection Agency as a candidate for issuance of a notice of a rebuttable presumption against renewal (RPAR) of registration

(see 'General Remarks on Substances Considered', p.) on the basis of possible oncogenicity (Anon., 1978).

The US Occupational Safety and Health Administrations health standards for exposure to air contaminants require that an employee's exposure to trichloroethylene does not exceed an eight-hour time-weighted average of 535 mg/m^3 (100 ppm) in the working atmosphere in any eight-hour work shift of a forty-hour work week (US Occupational Safety and Health Administration, 1975). The corresponding standard in the Federal Republic of Germany is 260 mg/m^3, in the German Democratic Republic, 250 mg/m^3, in Sweden, 160 mg/m^3, and in Czechoslovakia, 250 mg/m^3 (Winell, 1975).

The US Occupational Safety and Health Administration proposed on October 20, 1975, that the maximum allowable concentration be reduce from (200 ppm) to (150 ppm) (US Occupational Safety and Health Administration, 1975). The maximum acceptable ceiling concentration in the USSR is 10 mg/m^3 (Winell, 1975).

The US National Institute for Occupational Safety and Health has recently recommended that occupational exposure to halogenated anesthetic agents, including trichloroethylene, be controlled so that no worker is exposed at concentrations greater than (2 ppm) (NIOSH, 1977b).

2.2 Occurrence

Trichloroethylene is not known to occur as a natural product. The occurrence of trichloroethylene in air, water, soil and sediments, food, marine organisms, and man have been reviewed (Battelle Columbus Laboratories, 1977).

(a) Air

The US Environmental Protection Agency has estimated that approximately 60% of the total annual world production of trichloroethylene is released to the environment, with annual emissions of about 540 million kg to the atmosphere and 9.1 million kg to the ocean (Fuller, 1976). The dispersive uses of trichloroethylene (metal cleaning and solvent applications) have been estimated to result in annual emissions of 192 million kg in the US (Fuller, 1976) and 100 million kg in Japan (Ohta *et al.*, 1976).

The background ambient air concentration of trichloroethylene has been reported for several world-wide locations including: (1) Western Ireland, at levels of 80 ng/m^3 (15 ppt) (Lovelock, 1974); (2) over the

North Atlantic, at less than 27 ng/m^3 (5 ppt) (Lovelock, 1974); (3) rural area 27 ng/m^3 (5 ppt) and (4) the northern hemisphere, at a level of about 80 ng/m^3 (15 ppt), and the southern hemisphere, at a level of about 8 ng/m^3 (1.5 ppt) (Cox *et al.*, 1976).

Trichloroethylene has also been detected in ambient air in: (1) the North eastern US, at typical levels of 1 µg/m^3 (0.18 ppb) in urban areas and less than 0.1 µg/m^3 (0.02 ppb) in rural areas (Lillian *et al.*, 1975); (2) Michigan, at levels of 150-500 ng/m^3 (30-90 ppt) (Russell & Shadoff, 1977); (3) at 4 California sites at levels of 83-1670 ng/m^3 (15.6-310.8 ppt) (Singh, 1976); (4) at five US land stations ranging from 2 to 28 ng/m^3 (0.4-5.2 ppt) and eleven sea stations ranging from 1 to 22 ng/m^3 (0.2-4 ppt) (Murray & Riley, 1973); (5) Tokyo, Japan, at twenty-six sites, at average levels of 6.4 µg/m^3 (1.2 ppb) (Ohta *et al.*, 1976) and (6) Manchester, England, at levels of 5.35-342 µg/m^3 (1-64 ppb) (Pearson & McConnell, 1975).

(b) Water

A summary of reported occurrences of trichloroethylene found in raw water samples, lake water sample, finished drinking water samples, raw sewage sample, rivers and in samples of effluent from chemical plants and sewage treatment plants is available (Shackelford & Keith, 1976). In samples of surface waters collected from 204 sites near heavily industrialized areas trichloroethylene was detected at 88 sites, at levels greater than 1 µg/l (Ewing *et al.*, 1977).

Trichloroethylene has been detected in: (1) tap water (Dowty *et al.*, 1975); (2) tap, lake, spring, and subterranean water at levels of 105, 38, 5, and 80 ng/l, respectively (Grob & Grob, 1974); and (3) effluent water from a chemical production plant at levels of 0.2 mg/l (Eurocop-Cost, 1976).

Trichloroethylene has also been detected in: (1) a river, at levels of 25 µg/l (Rook *et al.*, 1975); (2) the ground water near waste deposites at levels of 100 µg/l (Kotzias *et al.*, 1975); (3) the drinking water of five cities at levels of 0-0.5 µg/l (Coleman *et al.*, 1976); and (4) influent and effluent water from a sewage treatment plant, at levels of 8.6-40.4 µg/l (Bellar *et al.*, 1974).

(c) Soil and Sediment

Concentrations of trichloroethylene in soil and sediment near production and user sites in the US ranged from 0- over 100 µg/kg (Battelle Columbus Laboratories, 1977c).

(d) Food

Trichloroethylene has been detected in the following foodstuffs in England: dairy products, meats, oils and fats, beverages, and fruits and vegetables at levels of 0.3-10, 12-22, 0-10, 0-60, and 0-5 µg/kg, respectively (McConnell *et al.*, 1975). Traces of trichloroethylene have also been found in edible oils after extraction (Gracian & Martel, 1972).

(e) Marine organisms

Trichloroethylene has been detected in three species of mollusks, at levels of 0-025 ng/g, and five species of fish, at levels of 0-479 ng/g (dry weight) (Dickson & Riley, 1976).

(f) Human

Trichloroethylene has been detected in post-mortem human tissue samples, at levels of less than 1-32 µg/kg (wet tissue) (McConnell *et al.*, 1975) and in human expired air, at levels of 0-3.9 µg/hr/subject (Conkle *et al.*, 1975)..

It has been estimated that about 60,000 people are annually exposed to trichloroethylene as an anesthetic (Fuller, 1976).

(g) Occupational Exposure

The occupational exposure to trichloroethylene has been reviewed (National Institute for Occupational Safety and Health, 1973).

Trichloroethylene has been detected in the atmosphere of dry cleaning plants (Banenko, 1974). Levels of 1076-43,000 mg/m^3 (200-8000 ppm) were also found in a small factory (Kleinfeld & Tabershaw, 1954).

Concentrations of vapour in a dial assembly workshop in a factory ranged from below 135 mg/m^3 (25 ppm) to over 538 mg/m^3 (100 ppm) and in the degreasing room, were between 800 and 1350 mg/m^3 (150-250 ppm) (Takamatsu, 1962).

The concentration to which surgeons and nurses were exposed in operating-rooms varied from 1.6-554 mg/m^3 (0.3-103 ppm) (Corbett, 1973). About 5000 medical, dental and hospital personnel are routinely exposed to trichloroethylene.

The 1974 National Occupational Hazard Survey by the US National Institute for Occupational Safety and Health (NIOSH), has estimated that

workers primarily in the aircraft manufacturing industry, in blast furnaces, and in steel mills are exposed to trichloroethylene (NIOSH, 1977a).

(h) Other

Trichloroethylene has been detected as a trace impurity in US helium (Schehl, 1973).

2.3 Analysis

A review of the analysis of trichloroethylene in waste-treatment plant sludge was made by Camisa (1975). The analytical methods to determine trichloroethylene in air, oleoresins, blood, and urine have also been reviewed (Kouner, 1975; Walter *et al.*, 1976).

Some methods used to determine trichloroethylene in environmental samples are tabulated in Table 1.

Gas chromatography with electron capture detection has been studied collaboratively by eight European laboratories to detect trichloroethylene residues in grain. The limit of detection ranged from 0.005-0.2 mg/kg (Panel on Fumigant Residues in Grain, 1974).

A system to determine trichloroethylene in water is described (Ellison & Wallbank, 1973).

Use of gas chromatography has also been made by Kuchinskii (1977) and Lillian *et al.*, (1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) Oral administration

Mouse:

Groups of 50 male and 50 female B6C3F1 mice, 5 weeks-old, were administered trichloroethylene (99% pure; 0.19% 1,2-epoxybutane and 0.09% epichlorohydrin) (See also IARC monograph on epichlorohydrin (IARC, 1976b)) in corn oil by oral gavage. High dose males recieved

[1]The Working Group was aware of ongoing studies to assess the carcinogenecity of trichloroethylene in mice by skin, subcutaneous and oral administration (IARC, 1978a) and of an inhalation study in rats and mice carried out under contract to the Manufacturing Chemist's Association Toxicology Information Program. (Preliminary results of the inhalation study indicate findings similar to the NCI Study(Page & Arthur, 1978)

ANALYTICAL METHODS FOR TRICHLOROETHYLENE

Sample type	Extraction clean-up	Detection	Limit of detection	Reference
Formulation				
Cough syrup and encapsulated liquids	Transfer to alcohol; dilute as appropriate; transfer to separator containing 10% aqueous solution and carbon disulphide	Infra-red		Horwitz (1975)
Air				
Workplace atmospheres	Trap on charcoal; extract (carbon disulphide)	GC/FID[1]	519-7176 mg/m³	NIOSH (1977c)
Ambient	Trap in Drechsel flask fitted with rubber septum; sample with gas syringe	GC/ECD[2]	1 µg/m³	B.I.T.-S.C. (1976)
Ambient	Direct analysis	GC/ECD[2]	10 mg/m³	Kiyuaka *et al.*, (1976)
Rural	Trap on porous polymer; desorb by heating; retrap in line on GC[3] column	GC/ECD[2] GC/MS[4] confirmation	160 ng/m³ (30 ppt)	Russell & Shadoff (1977)
Atmosphere	Direct analysis	GC/MS[4]	27 ng/m³ (5 ppt)	Grimsrud & Rasmussen (1975)
Ambient	Direct analysis	Carbon dioxide laser	3.8 µg/m³ (0.7 ppb)	Kreuzer *et al.*, (1972)
Ambient	Direct analysis	Carbon dioxide laser	23 µg/m³ (4.2 ppb)	Schnell & Fischer (1975)
Water				
Sea and fresh water	Extract (n-pentane); dry	GC/ECD[2]	50 ng/l	B.I.T.-S.C. (1976)
Waste water	Extract (freon)	GC/FID[1]	0.7 ng	Austern *et al.*, (1975)

River water	Headspace analysis	GC/MS[5]		Rook *et al.*, (1975)
Drinking water	Direct injection	GC/ECD[2]	2 µg/l	Nicholson *et al.*, (1977)
Tap water	Direct injection	GC/MS[5]	0.2 µg/l	Fujii, (1977)
Biological				
Blood	Direct analysis using precolumn on GC[3] and internal standard	GC/FID[1]		Cole *et al.*, (1975 a,b)

[1]GC/FID = gas chromatography/flame ionization detector
[2]GC/ECD = gas chromatography/electron capture detector
[3]GC = gas chromatography
[5]GC/MS = gas chromatography/mass spectrometry

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MISCELLANEOUS				
OILS AND LIQUID PARAFFIN	HEADSPACE ANALYSIS	GC/FID[1]	0.2 µg	DREXLER AND ESTERKA (1977)
Spike oleoresin	dilute solvent with ethanol; add external standard	GC[3] microcoulometric	—	HOROWITZ (1975)

2000-2400 mg/kg bw/day 5 days a week for 78 weeks and females 1400-1800 mg/kg bw/day. Low dose males and females received 1000-1200 mg/kg bw/day and 700-900 mg/kg bw 5 days a week for 78 weeks. All surviving animals were observed until they were 95 weeks of age. Time-weighted average doses were 1169 and 869 in low dose males and females and 2339 and 1739 mg/kg bw/day in high dose males and females. Groups of 20 male and 20 female mice served as vehicle-treated matched controls. Survival was reduced in high dose males and control males. Hepatocellular carcinomas occurrred in 1/20 control males and 0/20 control females, in 26/50 low dose males and 4/50 low dose females, and in 31/48 high dose males and 11/47 high dose females. Metastases of the liver-cell tumours to the lung were found in 7/98 treated males and in 1 control male. The first hepatocellular carcinomas ~~were~~ was observed in a mouse treated with the high dose of trichloroethylene that died during week 27. Lung tumours occurred in both sexes in the treated groups: 5/50 (5 adenomas) and 4/50 (2 adenomas, 2 carcinomas) in males and females of the low dose group and 2/48 (1 adenoma, 1 carcinoma) and 7/47 (5 adenomas, 2 carcinomas) in males and females treated with the high dose of trichloroethylene. In the controls, only one lung adenoma was reported among the females (National Cancer Institute, 1976). [The Working Group noted that the low dose males and females received 1 and 0.7 mg/kg bw/day epic~~hl~~hydrin and the high dose males and females received 2.1 and 1.56 mg/kg bw/day epichlorohydrin.]

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, 4 weeks of age, received by gavage trichloroethylene (99% pure; 0.19% 1,2 epoxybutane and 0.09% epichlorohydrin) (See also IARC, 1976b) in corn oil 5 days a week for 78 weeks. High dose animals received varying dose schedules of 1000-1500 mg/kg bw and low dose animals received 500-750 mg/kg bw. All surviving animals were killed 110 weeks after the start of treatment. The time-weighted average doses were 549 and 1097 mg/kg bw/day. A group of 20 male and 20 female vehicle-treated rats served as controls. In males 17/20 controls, 42/50 low dose and 47/50 high dose rats died before the end of the study. In females 12/20, 35/48 (controls/low dose) and 37/50 (high dose) rats died. Median survival time was approximately 60 weeks for high dose males and 85 weeks for low dose males. In females the median survival time of high and low dose rats was approximately 70 weeks. In males, 5/20 controls, 7/50 low dose and 5/50 high dose rats developed tumours. In females, 7/20 controls, 12/48 low and 12/50 high dose rats developed tumours.

No liver-cell tumours occurred. The tumours occurred in various organs in treated and vehicle control animals and were mainly reticulum-cell sarcomas, lymphosarcomas or malignant lymphomas, fibroadenomas of the mammary gland, haemangiosarcomas at various sites, follicular adenocarcinomas of the thyroid, chromophobe adenomas of the pituitary and renal hamartomas. Toxic nephropathy was observed in rats of both sexes treated with high and low doses of trichloroethylene (National Cancer Institute, 1976). [The Working Group noted the poor survival of treated rats and that the low and high dose animals received 0.5 and 1 mg/kg bw/day epichlorohydrin.]

In a preliminary report of an ongoing study, groups of 30 male and 30 female Sprague Dawley rats, 13 weeks of age, were given 50 or 250 mg/kg bw trichloroethylene (purity unspecified) in olive oil by oral gavage 4–5 times per week for 52 weeks followed by observation for life. A group of 30 male and 30 female controls received olive oil alone. Results were reported 76 weeks after the start of treatment at which time 46 controls, 39 low dose and 34 high dose males and females combined of each group were still alive. Among high dose rats that had died 1 lymphoid leukaemia and 1 plasmocytoma was observed (minimum latent period 38 weeks) and 2 plasmocytomas occurred in low dose animals that had died (minimum latent period 70 weeks). No such tumours were found in controls (Maltoni & Scarnato, 1977).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

A wide variation in impurities and manufacturing processes produces inconsistency in the evaluation of experimental trichloroethylene toxicity (Defalque, 1961). Pure trichloroethylene decomposes readily into highly toxic products. The extensive literature on toxicity of trichloroethylene has been reviewed by Aviado *et al.* (1976), Browning (1965), Defalque (1961), US Occupational Safety and Health Administration (1975), Lloyd *et al.* (1975), Von Oettingen (1964), Smith (1966), and Walter *et al.* (1976).

In rats, the oral LD_{50} was 7.2 g/kg bw (Smyth *et al.*, 1969) and in mice, 2.85 g/kg bw (Aviado *et al.*, 1976). The i.p. LD_{50} in mice was 3.2 g/kg bw (Klaassen & Plaa, 1966) or 1.83 g/kg bw (Schumacher & Grandjean, 1960); that in dogs was 2.8 g/kg bw (Klaassen & Plaa, 1967). The lowest lethal

i.v. dose for dogs 150 mg/kg bw, and in rabbits, the s.c. lethal dose was 1.8 g/kg bw (Barsoum & Saad, 1934).

The maximum concentrations of vapour which produced no toxic effects after exposure for 7 hours daily on 5 days a week for 6 months were: rats and rabbits, 1076 mg/m^3 (200 ppm); guinea-pigs, 538 mg/m^3 (100 ppm); monkeys, 2150 mg/m^3 (400 ppm) (Adams *et al.*, 1951). 30 exposures (8 h daily, 5 days/weeks, to 3825 mg/m^3 (700 ppm) or continuous exposure to 189 mg/m^3 (35 ppm) for 90 days) did not cause any visible sign of toxicity in rats, dogs, monkeys, guinea-pigs and rabbits (Prendergast *et al.*, 1967).

In 8 cats exposed to concentrations of 108 mg/m^3 of air (20 ppm) for 1-1.5 hours per day for 4-6 months, centrilobular hepatitis, nephritis, hypertrophy of lymphoid glands and splenomegaly were observed (Mosinger & Fiorentini, 1955). In mice, trichloroethylene caused less damage to the kidneys and liver than did carbon tetrachloride or chloroform (Klaassen & Plaa, 1966).

In a chronic toxicity study the maximal tolerated oral dose of industrial grade trichloroethylene in Osborne-Mendel rats was 1100 mg/kg bw for both sexes, and 2340 mg/kg (male) and 1740 mg/kg (female) in B6C3F1 hybrid mice (National Cancer Institute, 1976).

Embryotoxicity and teratogenicity

Groups of rats and mice were exposed 7 hours daily on days 6-15 of gestation to 1600 mg/m^3 (300 ppm) in air trichloroethylene inhalation without effects on the average number of implantation sites per litter, litter size, the incidence of foetal resorptions, foetal sex ratios or foetal body measurements. No treatment-related increased incidence in skeletal or visceral malformations was observed (Schwetz *et al.*, 1975).

Absorption, distribution, excretion and metabolism

A review is available (Piotrowski, 1977).

Following inhalation of trichloroethylene, no trichloroethylene was detected in the blood of organs of rats (Kimmerle & Eben, 1973a).

Dogs exposed to trichloroethylene excreted trichloroacetic acid and the glucuronide of trichloroethanol in the urine (Barrett & Johnston, 1939; Butler, (1949).

When ^{36}Cl-trichloroethylene was given by gavage to rats, 10-20% of the dose was excreted in the urine as 1-5% trichloroacetic acid and 10-15% trichloroethanol, 0-0.5% was excreted as trichloroethylene in the faeces and 72-85% as trichloroethylene in the expired air (Daniel, 1963).

The demonstration of the enzymic conversion of trichloroethylene to chloral by liver microsomes from rabbits, rats and dogs supports the suggestion of Powell (1945) that the trichloroethylene oxide intermediate rearranges into chloral hydrate (Byington & Leibman, 1965; Leibman, 1965). ~~Chloral was also identified as a trichloroethylene metabolite in the isolated perfused lung of rats and guinea-pigs (Dalbey & Bingham, 1978).~~ Chloral was also isolated *in vitro* as an intramolecular rearrangement product of trichloroethylene oxide; chloral is then in part reduced to trichloroethanol or oxidized to trichloroacetic acid (Bonse & Henscher, 1976; Bonse *et al.*, 1975). Spectral evidence for the formation of trichloroethylene oxide (2,2,3-trichloro-oxirane) during incubation of trichloroethylene with metabolizing hepatic microsomes was reported by Uehleke *et al*, (1977).

In vivo and *in vitro* ~~radioactivity of~~ ^{14}C-trichloroethylene is irreversibly bound to liver endoplasmic protein (Allemand *et al.*, 1978; Bolt *et al.*, 1977; Uehleke & Poplawski-Tabarelli, 1977 ~~and~~ Van Durren & Banerjee, 1976). Binding is correlated with the activity of hepatic mixed-function oxidase (Uehleke & Poplawski-Tabarelli, 1977); thus, treatment of animals with inducers of hepatic mixed function oxidase such as phenobarbital, methylcholanthrene, Aroclor 1254, hexachlorobenzene, increased the hepatotoxicity of trichloroethylene (Carlson, 1974; Moslen *et al.*, 1977a) and depleted hepatic glutathione (Moslen *et al.*, 1977b). In another assay with *Salmonella typhimurium* TA100, the pure compound was not mutagenic either in the presence or absence of rat liver microsomes; in addition it was shown that two of the impurities found in a technical trade sample of trichloroethylene, epichlorohydrin and 1,2-epoxybutane were mutagenic in the same study in the absence of rat liver microsomes (Henschler *et al.*, 1977).

Mutagenicity and other related short-term tests

Trichloroethylene was mutagenic in *Escherichia coli* K12 and in *Salmonella typhimurium* TA100 (Greim *et al.*, 1975; Simmon *et al.*, 1977) in the presence of a microsomal activation system ~~(Henschler et al., 1977)~~.

In *Saccharomyces cerevisiae* strain XV185-14C, trichloroethylene induced reverse mutations in the presence of mouse liver microsomes and the mutation

frequencies were concentration-dependent. On the basis of their data, the authors concluded that trichloroethylene induced base-pair as well as frameshift type mutations (Shahin & Von Borstel, 1977). Positive results had also been reported in the same species for the induction of gene mutations and mitotic gene conversion (strain D7) in the presence of mammalian microsomes as well as in host(mouse)-mediated assay (strain D4) (Bronzetti *et al.*, 1978).

Mice given single i.p. injections of trichloroethylene (in doses of 50% of LD_{50} in dimethylsulphoxide) or five repeated injections of 1/6 LD_{50} (at one day invervals) showed no increase in the frequency of chromosome aberrations in their bone marrow cells (Cerná & Kypenová, 1977).

In spot tests for somatic mutations, i.p. treatment of pregnant mice with 1 mM trichloroethylene induced coat colour muations in embryos exposed in utero (Fahrig, 1977). [To what extent the positive mutagenic results reported with trichloroethylene are due to impurities in the test samples could not be determined by the Working Group].

(b) Humans

Numerous fatalities as a result of trichloroethylene anaesthesia and of industrial intoxications were combined. Sudden death, probably due to ventricular fibrillation has been reported upon exertion shortly after intense exposure (Defalque, 1961).

Chronic inhalation of trichloroethylene affects the central nervous system (Grandjean *et al.*, 1955). Accidental ingestions produced inebriety, vomiting, diarrhoea, collapse and coma followed either by death (pulmonary oedema and liver and kidney necrosis at autopsy) or recovery with transient neurological sequelae (amnesia, headache, numbness, weakness of extremeities, psychosis, or hemiparesis) (Defalque, 1961). Toxic effects on the liver have been reported (Schüttmann, 1970). It has been suggested that the toxic action in humans was mainly due to contaminants (Browning, 1965; Defalque, 1961).

Psychophysiological function was depressed in volunteers exposed to 110 ppm (592 mg/m^3) trichloroethylene for two 4 hr periods (Salvini *et al.*, 1971). Experimental exposure of ten volunteers to 1070 mg/m^3 (200 ppm) trichloroethylene vapour for periods of 7 h during 5 days produced fatigue and sleepiness (Stewart *et al.*, 1970). Impairment of neurological and psychological functions after acute and longer exposure was also reported by Gamberale *et al.* (1976) and Triebig *et al.* (1977).

Cutaneous reactions to trichloroethylene have been reported (Bauer & Rabens, 1974; Schirren, 1971; Stewart *et al.*, 1974).

There is an indication of enhancement of the liver-toxic effect of trichloroethylene by concomitant exposure to ethanol or isopropyl alcohol (Traiger & Plae, 1974).

The uptake of trichloroethylene by the body as well as blood concentrations of trichloroethylene has been reported (Åstrand & Övrum, 1976).

The concentration of the metabolic trichloracetic acid in the urine is an indication of trichloroethylene exposure (Axelson *et al.*, 1978; Smith, 1978).

Humans exposed to trichloroethylene excrete trichloracetic acid and trichloroethanol in the urine (Kimmerle & Eben, 1973b; Nomiyama & Nomiyama, 1971; & Powell, 1945). Kinetic studies of formation and excretion of trichloroacetic acid and trichloroethanol have been reported (Fernandez *et al.*, 1977; Monster *et al.*, 1976 & Muller *et al.*, 1974). Chloral hydrate was identified as a trichloroethylene metabolite in the blood (Cole *et al.*, 1975; Scansetti *et al.*, 1959).

3.3 Case reports and epidemiological studies[1]

An epidemiological study of cancer mortality among 518 males occupational exposed to rather low levels of trichloroethylene as estimated by trichloroacetic acid in the urine has been reported (~~Axelson *et al.*, 1978~~). (Exposure categories with averages below and above 100 mg/l trichloroacetic acid in the urine were used; 100 mg/l roughly corresponds to an eight-hour time weighted average exposure of 160 mg/m^3 (30 ppm) trichloroethylene in air). When compared to the national population rates, 49 deaths from all causes were observed versus 62 expected. With no consideration given to latency or intensity of exposure, 11 deaths due to cancer of all sites were observed versus 14.5 expected. When analyses was restricted to the time period, ten or more years since onset of exposure, no significant excess of cancer was demonstrated, either for those exposed to high or lower levels of trichloroethylene. It was concluded that this study could not rule out a

[1]The Working Group was aware of 2 studies in progress: a cancer mortality study of workers occupationally exposed to trichloroethylene and a follow-up study of workers exposed to organochloride and alkylchloride compounds, to vinyl chloride, trichloroethylene and unsaturated compounds (IARC, 1978).

cancer risk to man, particularly for rare types of malignancies, such as liver cancer (Axelson *et al.*, 1978). [The small size of the study group and the relatively short latend period (mainly less than 20 years) underline this conclusion.]

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Trichloroethylene was tested in one experiment in mice and in one experiment in rats by oral administration. In mice, it produced hepatocellular carcinomas and lung tumours in both males and females. The experiment in rats was considered to be inadequate. Preliminary results of an ongoing study by oral administration to rats could not be evaluated.

Trichloroethylene is mutagenic in bacteria and yeast and in spot tests for somatic-mutations in mice.

4.2 Human data[1]

No case reports were available to the Working Group. The only epidemiological study available reported no statistically significant excess of cancer associated with exposure to trichloroethylene. However, owing to the small size of the group and the relatively short time since onset of exposure, an assessment of carcinogenicity could not be made.

The extensive production of trichloroethylene for over 50 years, together with its use as an industrial solvent and metal cleaning agent, as an inhalational anaesthetic and as a bacteriocide in drugs, food and consumer products, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in air, water and foods and in human tissues and expired air.

4.3 Evaluation

There is *limited evidence* that trichloroethylene is carcinogenic in mice ~~rats~~.

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[1]Subsequent to the meeting, the Secretariat became aware of a study of 330 deceased laundry and dry-cleaning workers who had been exposed to carbon tetrachloride, trichloroethylene and tetrachloroethylene. An excess of lung and cervical cancers and a slight excess of leukaemias and liver cancers were observed (Blair *et al.*, 1979).

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