TRICHLOROACETIC ACID

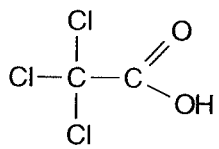
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 76-03-9
Chem. Abstr. Name: Trichloroacetic acid
IUPAC Systematic Name: Trichloroacetic acid
Synonyms: TCA; TCAA; TCA (acid); trichloracetic acid; trichloroethanoic acid; trichloromethanecarboxylic acid

1.1.2 Structural and molecular formulae and relative molecular mass



$C_2HCl_3O_2$ Relative molecular mass: 163.39

1.1.3 Chemical and physical properties of the pure substance

From Lide (1993), unless otherwise specified

(*a*) *Description*: Colourless to slightly yellowish, deliquescent crystals with a slight characteristic odour (Budavari, 1989; Hoechst Chemicals, 1990)

(*b*) *Boiling-point*: 197.5 °C

(*c*) *Melting-point*: 58 °C (α-form); 49.6 °C (β-form)

(*d*) *Density*: 1.62 at 25 °C/4 °C

(*e*) *Spectroscopy data*: Infrared (prism [36, 11 346]]; grating [29 681]), ultraviolet [1–6], nuclear magnetic resonance (proton [6]; C-13 [10]) and mass [1026] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Soluble in water, acetone, methanol, ethanol and diethyl ether; slightly soluble in hydrocarbons and chlorinated hydrocarbons (Hoechst Chemicals, 1990; Lide, 1993). In aqueous solution, trichloroacetic acid and trichloroacetate exist as an equilibrium mixture, the proportions of each depending principally on the pH. The pK_a of trichloroacetic acid is 0.70.

(*g*) *Volatility*: Vapour pressure, 1 mm Hg [0.133 kPa] at 51 °C (Verschueren, 1983)

(*h*) *Stability*: Aqueous solutions undergo gradual hydrolysis, depending on the temperature, especially in the presence of alkali and alkaline earth ions; hydrolysed to chloroform, carbon dioxide and carbonate (Budavari, 1989; Hoechst Chemicals, 1990)

(*i*) *Reactivity*: Highly reactive with most metals (Hoechst Chemicals, 1990)

(*j*) *Octanol/water partition coefficient (P)*: log P, 1.33 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 6.68 \times ppm$[1]

1.1.4 Technical products and impurities

Trichloroacetic acid is available commercially in three grades: crude (purity 96%), technical (purity, 98%) and a 90% aqueous solution with the following specifications: dichloroacetic acid (see monograph, this volume), 1.2–2.5% max.; sulfuric acid, 0.3–0.5% max. and iron, 0.001–0.002% max. (Hoechst Chemicals, 1990). Trichloroacetic acid is also available in a reagent grade at a purity of 98–100%, containing maxima of 0.001% chloride, 0.002% heavy metals (as lead), 0.001% iron, 0.002% nitrate, 0.0005% phosphate and 0.02% sulfate (Sigma Chemical Co., 1992; Mallinckrodt Chemical, Inc., 1993; Aldrich Chemical Co., 1994a,b). Trade names for trichloroacetic acid include Aceto-Caustin and Amchem Grass Killer.

1.1.5 Analysis

Two ion chromatography methods have been described for the determination of haloacetic acids, including trichloroacetic acid. The first is based on anion-exchange separation with suppressed electrolytic conductivity detection; the second is based on anion-exclusion separation with ultraviolet detection. The detection limits for trichloroacetic acid are 80 µg/L for the first method and 5.1 µg/L for the second (Nair *et al.*, 1994).

A high-performance liquid chromatography method is available for the separation and quantitative determination of trichloroacetic acid in effluents. The samples were chromatographed with aqueous ammonium sulfate as the mobile phase and quantified by ultraviolet absorption at 210 nm. The detection limit for trichloroacetic acid is 10 µg/L (Husain *et al.*, 1992, 1993).

A method has been described for the determination of organic acids, including trichloroacetic acid, in ambient air. Ion-exchange resin was used as the adsorbent for sampling and subsequently as the catalyst for methylation of the adsorbed acids by methyl formate. The methyl esters were analysed by capillary GC–mass spectrometry. The limit of detection was 0.8 ng/L with and 56.4 ng/L without preconcentration (Sollinger *et al.*, 1992).

In a method for the microdetermination of chloroacetic acids in water, trichloroacetic acid was converted into the difluoroanilide derivative by reaction with difluoroaniline and dicyclohexylcarbodiimide. The derivative was extracted into ethyl acetate and determined by GC with

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

electron capture detection. The detection limit for trichloroacetic acid was about 0.6 μg/L (Ozawa & Tsukioka, 1990; Ozawa, 1993).

A method for the determination of trichloroacetic acid using flow injection and chemiluminescence detection is based on generation of bromine from the bromate–bromide–acid reaction *in situ*; the bromine is then reacted with hydrogen peroxide to liberate oxygen for the oxidation of luminol. The minimal detectable concentration of trichloroacetic acid was 15 mmol [2.5 g] (Shakir & Faizullah, 1990).

A multi-channel, microwave-induced plasma atomic spectroscopic GC detector has been used to characterize the profiles of chlorinated humic acid on capillary columns and the contents of carbon, chlorine and bromine in drinking-water. This technique makes it possible to estimate the empirical formulae of separated compounds with sufficient accuracy for useful peak identification. Trichloroacetic acid was among the compounds characterized by this method (Italia & Uden, 1988).

Trichloroacetic acid can be determined in water and urine by differential pulse polarography (Pergola *et al.*, 1988). The authors also discuss the advantages and disadvantages of the other methods commonly used for the determination of trichloroacetic acid in urine (spectrophotometry and chromatography) and in water (fluorimetric and mass spectroscopy).

A method has been described for the determination of trichloroethylene metabolites, including trichloroacetic acid, in rat liver homogenate, blood and urine. The method is based on selective thermal conversion of trichloroacetic acid into chloroform, which is determined by head-space GC with electron capture detection (Christensen *et al.*, 1988; Køppen *et al.*, 1988). A similar procedure was reported for human plasma (Ziglio *et al.*, 1984).

A spectophotometric method for the determination of trichloroacetic acid at the level of parts per million in air, serum and urine involves a modification of the Fujiwara reaction and measurement of a red colour developed by the reaction between a polyhalogenated compound and pyridine in the presence of alkali. The addition of acetic acid and sulfanilic–formic acid reagent produced a yellow–orange chromophore with an absorption maximum at 505 nm (Bhattacharjee *et al.*, 1991).

The United States Environmental Protection Agency (1990) reported a method for the determination of haloacetic acids, including trichloroacetic acid, in drinking-water, groundwater, raw water and water in any intermediate treatment stage. The method involves adjusting the pH to 11.5 and extraction with methyl-*tert*-butyl ether to remove neutral and basic organic compounds. The aqueous sample is then acidified to a pH of 0.5, and the acids are extracted into methyl-*tert*-butyl ether. The acids are then converted to their methyl esters with diazomethane. The methyl esters are determined by capillary GC with electron capture detection. The detection limit for this method is 0.085 μg/L.

1.2 Production and use

1.2.1 Production

Trichloroacetic acid is produced on an industrial scale by exhaustive chlorination of acetic or chloroacetic acid. Heavy metal salts have been used as chlorination catalysts (Koenig *et al.*,

1986). Trichloroacetic acid has also been manufactured by nitric acid oxidation of chloral (see monograph, this volume) and hydrolytic oxidation of tetrachloroethylene (see monograph, this volume) (Freiter, 1978).

Information on the global production and use of trichloroacetic acid are not available; however, most is converted to its sodium salt, and about 21 000–23 000 tonnes of this product are used annually as a selective herbicide (Koenig *et al.*, 1986). Production in the Member States of the European Union was estimated to have been 750 tonnes in 1979 (Environmental Chemicals Data and Toxicology of Chemicals, 1993).

Trichloroacetic acid is produced by four companies in Japan, by three companies each in Germany and India, and by one company each in Brazil, China, Italy, Romania, the Russian Federation, Spain and the United Kingdom (Chemical Information Services, Inc., 1994).

1.2.2 Use

The main use for trichloroacetic acid is in the production of its sodium salt, which is used as a selective herbicide. The sodium salt is also used in formulations with 2,4-D and 2,4,5-T (see IARC, 1987a) as a broad-spectrum herbicide. Trichloroacetic acid has been used as an etching agent for surface treatment of metals, as a swelling agent and solvent in plastics and as an auxiliary in textile finishing (Koenig *et al.*, 1986). It has been used as a decalcifier, a fixative in microscopy and to precipitate proteins (Budavari, 1989). It is used as a colour reagent in thin-layer and paper chromatography. The esters of trichloroacetic acid are important starting materials in organic synthesis (Neumüller, 1988). Because it is strongly corrosive, trichloroacetic acid has been used in medicine to remove genital warts, to treat extensive actinic keratosis of the face and scalp (Brodland & Roenigk, 1988; Boothby *et al.*, 1990; Kling, 1992; Wang *et al.*, 1992) and as an astringent and antiseptic (Heithersay & Wilson, 1988). In dentistry, trichloroacetic acid is recommended for treatment of external cervical root resorption (Heithersay & Wilson, 1988; Lewinstein & Rotstein, 1992).

1.3 Occurrence

1.3.1 Natural occurrence

Trichloroacetic acid is not known to occur as a natural product.

1.3.2 Occupational exposures

The National Occupational Exposure Survey conducted between 1981 and 1983 indicated that 35 124 employees in the United States of America were potentially exposed occupationally to trichloroacetic acid in seven industries and 1562 plants (United States National Institute for Occupational Safety and Health, 1994a).

Because trichloroacetic acid is the major end metabolite of trichloroethylene and tetrachloroethylene in humans (see pp. 112 and 186), it has been used as a biological marker of exposure to those compounds for many years. It is also a metabolite of 1,1,1-trichloroethane (see IARC, 1987b) and 1,1,2,2-tetrachloroethane (see IARC, 1987c); and chloral hydrate (see monograph this volume) is rapidly oxidized to trichloroacetic acid in humans. The levels of

trichloroacetic acid reported in human blood and urine after occupational exposure to trichloroethylene, tetrachloroethylene or 1,1,1-trichloroethane are summarized in Table 1.

Table 1. Concentrations of trichloroacetic acid in human blood and urine

Job description (country)	Exposure	Concentration of trichloroacetic acid	Reference
Metal degreasing (Switzerland)	Trichloroethylene, 10–300 ppm [54–1611 mg/m^3]	57–980 mg/L (urine)	Boillat (1970)
Metal degreasing (USA)	Trichloroethylene, 170–420 mg/m^3	3–116 mg/g creatinine (urine)	Lowry *et al.* (1974)
Workshop (Japan)	Trichloroethylene, 3–175 ppm [16.1–940 mg/m^3]	9–297 mg/L (urine)	Ikeda *et al.* (1972)
	Tetrachloroethylene, 50–400 ppm [339–2712 mg/m^3]	Mean, 50 mg/L (urine)	
Printing factory (Japan)	1,1,1-Trichloroethane, 4.3–53.5 ppm [23–289 mg/m^3]	0.5–5.5 mg/L	Seki *et al.* (1975)
Workshop (Japan)	Trichloroethylene	Range of means, 108–133 mg/L (urine) (trichloroacetate)	Itoh (1989)
Automobile workshop (Japan)	Trichloroethylene, 1–50 ppm [5–269 mg/m^3]	Average, 136 mg/g creatinine (urine)	Ogata *et al.* (1987)
Dry cleaning, degreasing (former Yugoslavia)	Trichloroethylene	0.43–154.92 µmol/L (blood) [0.07–25.3 mg/L] 0.58–42.44 mmol/mol creatinine (urine) [0.84–61 mg/g]	Skender *et al.* (1988)
Solvent exposure (Republic of Korea)	Tetrachloroethylene, 0–61 ppm [0–414 mg/m^3]	0.6–3.5 mg/L (urine)	Jang *et al.* (1993)
Degreasing (Sweden)	Trichloroethylene, 3–114 mg/m^3	2–260 µmol/L (urine) [0.3–42.5 mg/L]	Ulander *et al.* (1992)
Dry cleaning (former Yugoslavia)	Trichloroethylene, 25–40 ppm [134–215 mg/m^3]	13.47–393.56 µmol/L (blood) [2.2–64 mg/L] 1.92–77.35 mmol/mol creatinine (urine) [2.8–112 mg/g]	Skender *et al.* (1991)
	Tetrachloroethylene, 33–53 ppm [224–359 mg/m^3]	1.71–20.93 µmol/L (blood) [0.3–3.4 mg/L] 0.81–15.76 mmol/mol creatinine (urine) [1.2–23 mg/g]	
Printing workshop (Japan)	1,1,1-Trichloroethane, 5–65 ppm [27–351]	2–5 mg/L (urine)	Kawai *et al.* (1991)
Printing and ceramics workshop (Germany)	Trichloroethylene, 5–70 ppm [26.9–376 mg/m^3]	2.0–201.0 mg/g creatinine (urine)	Triebig *et al.* (1982)

Table 1 (contd)

Job description (country)	Exposure	Concentration of trichloroacetic acid	Reference
Environmental levels (Japan)	Trichloroethylene: air: 1.7–26.9 μg/m^3 water: 12–123 μg/L Tetrachloroethylene: air: 2.9–40 μg/m^3 water: 2–68 μg/L	8.1–60.0 μg/L (plasma) 6.2–72.0 μg/g creatinine (urine)	Ziglio *et al.* (1985)

The average concentration of trichloroacetic acid in 177 urinary measurements made in 1986–88 at the Finnish Institute of Occupational Health was 77.1 μmol/L [12.6 mg/L], with a range of < 50–860 μmol/L [< 8.2–140.5 mg/L]. Seven samples exceeded the Finnish biological action level of 360 μmol/L [59 mg/L] (Rantala *et al.*, 1992).

1.3.3 Air

No data were available to the Working Group.

1.3.4 Water

Trichloroacetic acid is produced as a by-product during aqueous chlorination of humic substances (Christman *et al.*, 1983; Miller & Uden, 1983; Legube *et al.*, 1985; Reckhow *et al.*, 1990). Consequently, it may occur in drinking-water after chlorine disinfection of raw waters containing natural organic substances (Hargesheimer & Satchwill, 1989; see IARC, 1991). The concentrations of trichloroacetic acid measured in various water sources are summarized in Table 2. It has been identified as a major chlorinated by-product of the photocatalytic degradation of tetrachloroethylene in water but a minor by-product of the degradation of trichloroethylene (Glaze *et al.*, 1993).

1.3.5 Food

Residues of trichloroacetic acid have been found in the seed of wheat, barley and oats after treatment with trichloroacetic acid as a postemergence herbicide (Kadis *et al.*, 1972). Trace concentrations (0.01–0.19 ppm [mg/kg]) of trichloroacetic acid have been detected in vegetables and fruits irrigated with water containing trichloroacetic acid; slightly higher levels (0.13–0.43 mg/kg) were detected in field bean pods and seeds (Demint *et al.*, 1975).

1.3.6 Other

Trichloroacetic acid concentrations were determined in the urine of people living in the vicinity of dry cleaning shops where tetrachloroethylene was used in Germany. The mean

Table 2. Concentrations of trichloroacetic acid in water

Water type (location)	Concentration range (μg/L)	Reference
Chlorinated tap-water (USA) (drinking-water)	33.6–161	Uden & Miller (1983)
Chlorinated drinking-water (USA)	4.23–53.8	Norwood *et al.* (1986)
Raw water (USA)	95–2120	
Chlorinated surface, reservoir, lake and groundwaters (USA)	4.0–6.0	Krasner *et al.* (1989)
Chlorinated surface water (USA)	7.4–22	Jacangelo *et al.* (1989)
Chlorinated drinking-water (USA)	15–64	Reckhow & Singer (1990)
Raw water (USA)	60–1630	
Chlorinated treated water (Australia)	Max 200	Nicholson *et al.* (1984)
Surface, ground- and drinking-waters	< 0.1–1.0	Artho *et al.* (1991)
Chlorinated water (Switzerland)	3.0	
Chlorinated tap-water (Germany)	Not detected–3	Lahl *et al.* (1984)
Chlorinated drinking-water (Japan)	7.5	Ozawa (1993)
Rainwater (Germany)	0.9	Clemens & Schöler (1992a)
Groundwater (Germany)	0.05	
Rainwater (Germany)	0.1–20	Plümacher & Renner (1993)
Swimming pool (Germany)	Indoor: 3.3–9.1 Open-air: 46.5–100.6[a]	Clemens & Schöler (1992b)
Irrigation water (USA)[b]	0–297	Comes *et al.* (1975)
Biologically treated kraft pulp mill effluent (Malaysia)	838–994	Mohamed *et al.* (1989)
Surface water (downstream from a paper mill) (Austria)	< 3–558	Geist *et al.* (1991)
Trichloroacetic acid process effluents (India)	0.41–4.5%	Husain *et al.* (1992)

[a]The higher levels found in open-air swimming pools may be due to input of organic material by swimmers.
[b]Trichloroacetic acid was added to the water from its use as a herbicide.

values were 105 μg/L for 29 neighbours and 682 μg/L for 12 workers (maximum, 1720 μg/L) (Popp *et al.*, 1992). In Zagreb, Croatia, the levels of trichloroacetic acid in the urine of 39 people with no known exposure to solvents were 14–160 μg/L in plasma and 2–292 μg/24 h in urine (Skender *et al.*, 1993). In 66 students in Japan, the corresponding levels ranged from not detected to 930 μg/g creatinine (urine) (Ikeda & Ohtsuji, 1969); those in 94 unexposed subjects in Germany were 5–221 μg/L in serum and 0.6–261 μg/24 h in urine (Hajimiragha *et al.*, 1986).

Trichloroacetic acid was detected at levels of 10–150 μg/kg in spruce needles from the Black Forest in Germany and the Montafon region in Austria, both considered to be relatively

non-polluted areas (Frank *et al.*, 1989; Frank, 1991). The concentrations of trichloroacetic acid in pine needles from an urban area in Germany were 0.7–175 μg/kg fresh weight (Plümacher & Renner, 1993); those in conifer needles in Finland were 3–126 μg/kg fresh weight (Frank *et al.*, 1992). In the vicinity of a pulp mill in Finland, concentrations of 2–135 μg/kg were found (Juuti *et al.*, 1993). Trichloroacetic acid was also detected in earthworms (at 150–400 μg/kg wet weight) from a contaminated forest site (Back & Süsser, 1992).

1.4 Regulations and guidelines

Occupational exposure limits for trichloroacetic acid have been recommended in many countries, either as a time-weighted average or as a short-term exposure limit. The following time-weighted averages have been set: Australia, 7 mg/m^3; Belgium, 6.7 mg/m^3; Denmark, 1 mg/m^3; France, 5 mg/m^3 (ILO, 1991); Switzerland, 7 mg/m^3 (Schweizerische Unfallversicherungsanstalt, 1994); United Kingdom, 5 mg/m^3 (United Kingdom Health and Safety Executive, 1993); and the United States, 6.7 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1994) and 7 mg/m^3 (United States National Institute for Occupational Safety and Health, 1994b). In the Russian Federation, a short-term exposure limit of 5 mg/m^3 is recommended (ILO, 1991).

In the United States and Switzerland, levels of trichloroacetic acid in urine have been recommended as biological indices of exposure, at 7 mg/L at the end of the work week for exposure to tetrachloroethylene and 100 mg/g creatinine at the end of the work week for trichloroethylene. The American Conference of Governmental Industrial Hygienists (1994) noted that trichloroacetic acid in urine is a nonspecific determinant of exposure to trichloroethylene. In other countries where urinary trichloroacetic acid is the recommended biological marker for assessing exposure to trichloroethylene, there is an action level of 360 μmol/L (59 mg/L) in Finland (Aitio *et al.*, 1995); a biological tolerance value of 100 mg/L in Germany (Deutsche Forschungsgemeinschaft, 1993); and a biological tolerance value of 100 mg/g creatinine in Switzerland (Schweizerische Unfallversicherungsanstalt, 1994).

The United States Environmental Protection Agency (1994) proposed that the maximal level of haloacetic acids (the sum of the concentrations of mono-, di- and trichloroacetic acids and mono- and dibromoacetic acids) in drinking-water be 0.06 mg/L. WHO (1993) recommend a provisional guideline value of 100 μg/L for trichloroacetic acid in drinking-water.

2. Studies of Cancer in Humans

No studies were available on people exposed to trichloroacetic acid. In view of the fact that it is a metabolite of trichloroethylene and tetrachloroethylene, the results of studies on populations exposed to those compounds may be relevant (see pp. 95 and 176). In particular, urinary levels of trichloroacetic acid were measured in workers exposed to the parent compounds in two cohort studies (Axelson *et al.*, 1978, 1984 [abstract], 1994; Anttila *et al.*, 1995) and in one descriptive study (Vartiainen *et al.*, 1993).

3. Studies of Cancer in Experimental Animals[1]

3.1 Oral administration

Mouse: A group of 25 male B6C3F1 mice, four weeks of age, was given drinking-water containing 5 g/L trichloroacetic acid (purity, > 99%) neutralized with sodium hydroxide to a pH of 6.5–7.5. A control group of 27 mice received drinking-water containing 2 g/L sodium chloride. Both groups were kept for 61 weeks, at which time they were killed and necropsied. Two of 22 control mice and 8/22 treated mice had hepatic adenomas ($p < 0.01$, Fisher's exact test); and 0/22 controls and 7/22 treated mice had hepatocellular carcinomas ($p < 0.01$) (Herren-Freund *et al.*, 1987). [The Working Group noted that the study also included groups of mice treated with 2.5 or 10 μg/kg bw *N*-nitrosoethylurea at 15 days of age followed four weeks later by treatment with drinking-water containing 2 or 5 g/L trichloroacetic acid; no promoting effect was demonstrated. The results of this experiment are not included, since phenobarbital, used as a positive control, was inactive.]

Groups of male and female B6C3F1 mice, 37 days old, received either 1.0 or 2.0 g/L trichloroacetic acid (neutralized to pH 6.8–7.2 with 10 N sodium hydroxide) in the drinking-water for up to 52 weeks, at which time the study was terminated. A group of 11 male mice received 1 g/L trichloroacetic acid for 52 weeks; 24 male mice received 2.0 g/L trichloroacetic acid for 52 weeks and a further 11 males received 2.0 g/L trichloroacetic acid for 37 weeks and then water alone until week 52. The last group was included in order to assess the reversibility of any hepatic effects. Two groups of 35 and 11 male control mice were kept for 52 weeks. Groups of 10 female mice received either 0 or 2.0 g/L trichloroacetic acid for 52 weeks. The study also included groups of five male mice given 2.0 g/L trichloroacetic acid and sacrificed at 15, 24 or 37 weeks, and the corresponding controls given water alone. Livers and kidneys were weighed and examined for macroscopic lesions. Microscopic examination was undertaken only of lesions of the liver found in the 35 male controls, the 11 males treated with 2.0 g/L trichloroacetic acid for 37 weeks and other groups [numbers unspecified] chosen at random. The lesions were classified histologically as hyperplastic nodules, adenomas or hepatocellular carcinomas. The results in male mice at 52 weeks are summarized in Table 3. No hyperplastic nodules or neoplastic lesions were seen at week 52 in the females receiving 2.0 g/L trichloroacetic acid. Multifocal necrosis was seen in both males and females (Bull et al., 1990). [The Working Group noted the lack of detailed reporting of the results.]

3.2 Mid-term assays

Rat: The potential initiation–promotion activity of trichloroacetic acid in the liver was investigated in two sets of mid-term studies in rats, in which enzyme-altered foci were the end-point. Use of a standard initiation protocol followed by promotion with phenobarbital did not result in initiation of γ-glutamyl transpeptidase-positive foci , but promotion with trichloroacetic acid at doses of 50–5000 mg/L in drinking-water for 12 months after initiation with *N*-

[1] The Working Group was aware of studies in progress in male rats treated by gavage and in mice administered the compound in the drinking-water (IARC, 1994).

nitrosodiethylamine increased the size of the foci (Parnell *et al.*, 1988). In similar study, trichloroacetic acid did not promote the formation of glutathione *S*-transferase placental form-positive foci (Hasegawa & Ito, 1992).

Table 3. Lesions in the livers of male B6C3F1 mice given trichloroacetic acid in the drinking-water

Dose (g/L) × no. of weeks	No. of mice	No. with macroscopic lesions	Total no. of lesions	No. of macroscopic lesions examined histologically (no. of mice)	No. of hyperplastic nodules (no. of mice)	No. of hepatic adenomas (no. of mice)	No. of hepatocellular carcinomas (no. of mice)
Control (water alone) × 52	35	2	2	2 (2)	1 (1)	0	0
1 × 52	11	5	7	7 (5)	3 (1)	2 (2)	2 (2)
2 × 52	24	19	30	16 (11)	10 (9)	1 (1)	4 (4)
2 × 37	11	4	5	5 (4)	2 (2)	0	3 (3)

From Bull *et al.* (1990)

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

After administration of a single oral dose of 3 mg/kg bw trichloroacetic acid to healthy volunteers, the mean plasma half-life of the compound was about 50 h and the volume of distribution was about 115 ml/kg bw (Müller *et al.*, 1974). The long plasma-half life of trichloroacetic acid in human subjects is consistent with its extensive binding to plasma proteins (Sellers & Koch-Weser, 1971).

4.1.2 Experimental systems

As trichloroacetic acid is a metabolite of trichloroethylene and tetrachloroethylene in both humans and experimental animals, its toxicokinetics are also described in the monographs on those compounds.

After administration of trichloroacetic acid as single doses of 5, 20 or 100 mg/kg bw in water to male Fischer 344 rats and male B6C3F1 mice, the total amount of radiolabel excreted in the urine of animals of each species was 60–70% of the administered dose, about 60% of which appeared to be unchanged trichloroacetic acid. The plasma half-life of trichloroacetic acid in

rodents was about 6 h, and the concentration in blood over time was similar in the two species (Larson & Bull, 1992a,b). The volume of distribution was 365–485 ml/kg bw in rats and 335–555 ml/kg bw in mice.

The major urinary products in mice and rats after administration of trichloroacetic acid by gavage are trichloroacetic acid itself and oxalic and thiodiacetic acids (Larson & Bull, 1992a). Reductive dechlorination of trichloroacetic acid yields dichloroacetic acid (see monograph, this volume), which is metabolized by two main routes: ultimately to oxalate and carbon dioxide, probably via glucolate and glyoxylate as intermediate metabolites; or to monochloroacetate after reductive dechlorination, followed by glutathione conjugation of monochloroacetate to thiodiacetic acid (Crabb & Harris, 1979; Stacpoole *et al.*, 1990; Larson & Bull, 1992a).

4.1.3 Comparison of humans and animals

Biotransformation of trichloroacetic acid occurs by similar routes in humans and rodents; however, the apparent volume of distribution appears to be smaller in humans than in rats or mice, perhaps because of the extensive binding of trichloroacetic acid to human plasma proteins. This effect may also account for the slower rate of systemic clearance in humans than in rodents.

4.2 Toxic effects

4.2.1 Humans

Little is known about the toxicity of trichloroacetic acid, although it is corrosive to the skin and eyes.

4.2.2 Experimental systems

Since trichloroacetic acid undergoes reductive metabolism to free radicals, its ability to elicit a lipid peroxidative response in liver was investigated in male Fischer 344 rats and male B6C3F1 mice after administration of a single oral dose of 100–2000 mg/kg bw in water. A dose-dependent response was induced, which was more potent in mice than in rats. Significant increases in the formation of thiobarbituric acid reactive substances were observed at a dose of 300 mg/kg bw in mice but only at a dose of 1000 mg/kg bw in rats (Larson & Bull, 1992a).

More total radioactivity was associated with albumin and haemoglobin in male Fischer 344 rats than in male B6C3F1 mice 4–120 h after a single oral dose of 20 mg/kg bw ^{14}C-trichloroacetic acid. In contrast, incorporation of radiolabelled amino acids resulting from the metabolism of the chloroacetate (glycine from glyoxylic acid) was more extensive in mice; this result is consistent with the more extensive metabolism in this species (Stevens *et al.*, 1992).

Exposure of male and female Sprague-Dawley rats to trichloroacetic acid at 24 or 240 mg/kg bw per day in the drinking-water for 14 days resulted in reduced weight gain only in the group given the higher dose (Davis, 1986). Male Sprague-Dawley rats administered trichloroacetic acid in the drinking-water for 90 days, at concentrations providing daily doses of about 4, 35 or 350 mg/kg bw, had decreased body weights. Animals given the high dose also had increased ratios of liver and kidney weight to body weight and increased hepatic peroxisomal activity (Mather *et al.*, 1990). Male Sprague-Dawley rats were given trichloroacetic acid in the

drinking-water at a concentration of 45.8 mmol/L [7.48 g/L] to provide an approximate intake of 785 mg/kg bw per day. After 90 days, body weights were decreased, and minimal histopathological changes were seen in the liver and lung (Bhat *et al.*, 1991).

Trichloroacetic acid, dichloroacetic acid and chloroform are formed during the chlorination of drinking-water (see IARC, 1991). After concomitant administration of trichloroacetic acid (at 0.92 and 2.45 mmol [150 and 400 mg]/kg bw by gavage, three times over 24 h) and chloroform (one intraperitoneal injection of 0.75 mg/kg bw once after the last dose of trichloroacetic acid) to male and female Sprague-Dawley rats, the renal toxicity of chloroform was increased (Davis, 1992).

The main effect in male and female B6C3F1 mice of exposure to trichloroacetic acid at 1000 and 2000 mg/L in drinking-water for up to 52 weeks was marked accumulation of lipid and lipofuscin in liver cells, in the virtual absence of any significant increase in cell size or in the onset of focal necrotic areas and with only marginal induction of cell proliferation and organ hypertrophy (Bull *et al.*, 1990; Sanchez & Bull, 1990; Bull *et al.*, 1993). In another study, however, a threefold increase in hepatic DNA synthesis was seen in male and female B6C3F1 mice exposed to trichloroacetic acid at 100–1000 mg/kg bw per day in corn oil by gavage for 11 days (Dees & Travis, 1994). Similarly, administration of trichloroacetic acid at 5 g/L in drinking-water for seven days resulted in an almost fourfold increase in the labelling index in livers of male B6C3F1 mice, whereas hepatic DNA synthesis was reduced to 10% of the control values in male Fischer 344 rats. Administration of trichloroacetic acid produced similar induction of peroxisomal palmitoyl-coenzyme A oxidation in rats and mice (Watson *et al.*, 1995).

Induction of peroxisome proliferation has been repeatedly associated with the chronic toxicity and carcinogenicity of trichloroacetic acid to the liver (DeAngelo *et al.*, 1989). It can induce peroxisome proliferation in the livers of both mice and rats, as indicated by increased activities of palmitoyl-coenzyme A oxidase and carnitine acetyl transferase, the appearance of a peroxisome proliferation-associated protein and increased volume-density of peroxisomes after exposure to trichloroacetic acid for 14 days. The compound induced peroxisome proliferation in mouse but not in rat kidney (Goldsworthy & Popp, 1987), and it induced peroxisome proliferation in primary cultures of hepatocytes from rats and mice but not in those from humans (Elcombe, 1985; Herren-Freund *et al.*, 1987).

4.3 Reproductive and prenatal effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

Treatement of pregnant rats with trichloroacetic acid at 0, 330, 800, 1200 or 1800 mg/kg bw per day by gavage on gestation days 6–15 resulted in a dose-dependent increase in the frequency of resorptions per litter, a reduction in fetal weight and length and an increased frequency of

anomalies of the heart and eyes. Maternal toxicity, as evidenced by decreased weight, was observed at all doses (Smith *et al.*, 1989).

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems (see also Table 4 and Appendices 1 and 2)

Trichloroacetic acid did not induce λ prophage in *Escherichia coli* and was not mutagenic to *Salmonella typhimurium* strains in the presence or absence of metabolic activation. Trichloroacetic acid, however, reacts with dimethyl sulfoxide (a solvent used commonly in this assay) to form unstable, mutagenic substances, which have not been identified (Nestmann *et al.*, 1980).

The frequency of chlorophyll mutations was increased in *Arabidopsis* after treatment of seeds with trichloroacetic acid.

It did not induce DNA strand breaks in mammalian cells *in vitro*. Gap-junctional intercellular communication was observed in mouse hepatocytes *in vitro*. Chromosomal aberrations were not induced in human lymphocytes exposed *in vitro* to trichloroacetic acid neutralized to avoid the effects of low pH seen in cultured mammalian cells.

DNA strand breaks were reported in one laboratory in the livers of mice and rats treated 4 h previously with trichloroacetate; none were observed 24 h after repeated daily dosing with 500 mg/kg bw (Nelson & Bull, 1988; Nelson *et al.*, 1989). Peroxisome proliferation, as indicated by β-oxidation of palmitoyl-coenzyme A, was observed only after induction of DNA damage (Nelson *et al.*, 1989). DNA strand breakage was not observed in the livers of mice or rats (Chang *et al.*, 1992). [The reasons for the contrasting results obtained using similar techniques are unclear.]

In one study, trichloroacetic acid induced micronuclei and chromosomal aberrations in bone-marrow cells and abnormal sperm morphology after injection into Swiss mice *in vivo*. In another study, in which a 10-fold higher dose was injected into C57BL/JfBL/Alpk mice, no micronucleus induction was observed.

Mutation of proto-oncogenes in tumours induced by trichloroacetic acid

The expression of c-*myc* and c-H-*ras* in mRNA was studied by in-situ hybridization in the livers of male B6C3F1 mice treated with trichloroacetate at 1 or 2 g/L in the drinking-water for 52 weeks. Expression of c-*myc*, corrected for the background frequency, was increased by about three times in hepatic hyperplastic nodules and by almost six times in hepatic carcinomas in comparison with normal liver. A similar comparison of c-H-*ras* expression showed no significant increase in hyperplastic nodules but an approximately fourfold increase in hepatic carcinomas (Nelson *et al.*, 1990). [The Working Group considered that the changes in proto-oncogene expression could not be attributed conclusively to trichloroacetic acid.]

Table 4. Genetic and related effects of trichloroacetic acid

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic activation		
PRB, λ Prophage induction, *Escherichia coli* WP2s	–	–	10 000	DeMarini *et al.* (1994)
BSD, *Bacillus subtilis* H17 *rec*$^+$ and M45 *rec*$^-$	–	0	20	Shirasu *et al.* (1976)
ECR, *Escherichia coli*, Br/try WP2, reverse mutation	–	0	20	Shirasu *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	225	Waskell (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	500	Rapson *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.00	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	4	DeMarini *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	0	20	Shirasu *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2000	Nestmann *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	20	Shirasu *et al.* (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Nestmann *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	0	20	Shirasu *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Nestmann *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	225	Waskell (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Nestmann *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.00	Moriya *et al.* (1983)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	0	20	Shirasu *et al.* (1976)
ASM, *Arabidopsis* species, mutation	+	0	1000	Plotnikov & Petrov (1976)
DIA, DNA strand breaks, B6C3F1 mouse hepatocytes *in vitro*	–	0	1630	Chang *et al.* (1992)
DIA, DNA strand breaks, Fischer 344 rat hepatocytes *in vitro*	–	0	1630	Chang *et al.* (1992)
DIH, DNA strand breaks, human CCRF-CEM cells *in vitro*	–	0	1630	Chang *et al.* (1992)
ICR, Inhibition of intercellular communication, B6C3F1 mouse hepatocytes *in vitro*	+	0	16.3	Klaunig *et al.* (1990)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	–[c]	5000	Mackay *et al.* (1995)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	+		1.0 po × 1	Nelson & Bull (1988)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	+		500 po × 1	Nelson *et al.* (1989)

Table 4 (contd)

Test system	Result[a]		Dose[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic activation	(LED/HID)	
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells *in vivo*	–		500 po × 10	Nelson *et al.* (1989)
DVA, DNA strand breaks, B6C3F1 mouse hepatic cells and epithelial cells from stomach and duodenum *in vivo*	–		1630 po × 1	Chang *et al.* (1992)
DVA, DNA strand breaks, Sprague-Dawley rat hepatic cells *in vivo*	+		100 po × 1	Nelson & Bull (1988)
DVA, DNA strand breaks, Fischer 344 rat hepatic cells *in vivo*	–		1630 po × 1	Chang *et al.* (1992)
MVM, Micronucleus induction, Swiss mice *in vivo*	+		125 ip × 2	Bhunya & Behera (1987)
MVM, Micronucleus induction, C57Bl//JfBl 10/Alpk female mice	–		1300 ip × 2	Mackay *et al.* (1995)
MVM, Micronucleus induction, C57Bl//JfBl 10/Alpk male mice	–		1080 ip × 2	Mackay *et al.* (1995)
CBA, Chromosomal aberrations, Swiss mouse bone-marrow cells *in vivo*	+		125 ip × 1	Bhunya & Behera (1987)
CBA, Chromosomal aberrations, Swiss mouse bone-marrow cells *in vivo*	+		100 ip × 5	Bhunya & Behera (1987)
CBA, Chromosomal aberrations, Swiss mouse bone-marrow cells *in vivo*	+		500 po × 1	Bhunya & Behera (1987)
SPM, Sperm morphology, Swiss mice *in vivo*	+		125 ip × 5	Bhunya & Behera (1987)

[a]+, considered to be positive; –, considered to be negative; 0, not tested

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

[c]Neutralized trichloroacetic acid

5. Summary and Evaluation

5.1 Exposure data

Trichloroacetic acid is produced commercially in small amounts by chlorination of acetic or chloroacetic acid. It is used principally in the form of the sodium salt, as a herbicide. Most human exposure to trichloroacetic acid occurs because of its metabolic formation from tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane and chloral hydrate. Trichloroacetic acid can also be formed during the chlorination of drinking-water.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of trichloroacetic acid to humans.

5.3 Animal carcinogenicity data

Trichloroacetic acid was tested by oral administration in the drinking-water in two studies in males of one strain of mice. In both studies, the incidence of hepatocellular adenomas and carcinomas was increased.

5.4 Other relevant data

Trichloroacetic acid has a longer plasma half-life in humans than in rodents, presumably because there is more binding to plasma proteins in humans. Much of an administered dose of trichloroacetic acid is excreted unchanged in the urine of rats and mice. Reductive dechlorination and glutathione conjugation are involved in the formation of the urinary metabolites, oxalate and thiodiacetic acid.

Little is known about the toxicity of this compound to humans. Single doses of high concentrations of trichloroacetic acid induce lipid peroxidation in the livers of rats and mice. Trichloroacetic acid causes hepatic peroxisome proliferation in both rats and mice *in vivo* and in cultured hepatocytes from mice and rats, but not from humans. Short-term, repeated administrations of trichloroacetic acid induced cell proliferation in the livers of mice but reduced cell proliferation in the livers of rats.

No data were available on the effects of trichloroacetic acid on human reproduction. In rats, fetotoxicity was observed at doses that are maternally toxic.

Trichloroacetic acid induced chromosomal aberrations and abnormal sperm in mice in one study. The results of studies on the induction of DNA strand breaks and micronuclei were inconclusive.

Trichloroacetic acid did not induce chromosomal aberrations in a single study or DNA strand breaks in cultured mammalian cells. Inhibition of intercellular communication has been reported. It was not mutagenic to bacteria.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of trichloroacetic acid.

There is *limited evidence* in experimental animals for the carcinogenicity of trichloroacetic acid.

Overall evaluation

Trichloroacetic acid *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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

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