1,1,1-TRICHLOROETHANE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

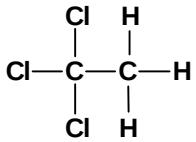
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 71-55-6
Chem. Abstr. Name: 1,1,1-Trichloroethane
IUPAC Systematic Name: 1,1,1-Trichloroethane
Synonyms: Chloroethene; methyl chloroform

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_2H_3Cl_3$ Relative molecular mass: 133.40

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Lewis, 1993)
(*b*) *Boiling-point*: 74°C (Lide, 1995)
(*c*) *Melting-point*: –30.4°C (Lide, 1995)
(*d*) *Solubility*: Slightly soluble in water (0.07 g/100 mL at 20°C (Verschueren, 1996)); soluble in acetone, benzene, carbon tetrachloride, methanol, ethanol and diethyl ether (American Conference of Governmental Industrial Hygienists, 1992; Lewis, 1993; Budavari, 1996)
(*e*) *Vapour pressure*: 13.3 kPa at 20°C; relative vapour density (air = 1), 4.6 (Verschueren, 1996)
(*f*) *Explosive limits*: Upper, 16%; lower, 7% by volume (American Conference of Governmental Industrial Hygienists, 1992)
(*g*) *Conversion factor*: $mg/m^3 = 5.46 \times ppm$

1.2 Production and use

Total world demand for 1,1,1-trichloroethane in 1987 was 578 thousand tonnes; demand in the United States in 1990 was 280 thousand tonnes. In 1989, production capacity in the United States was estimated to be 470 thousand tonnes and production capacity outside the United States was estimated to be approximately 454 thousand tonnes. All non-essential emissive uses of 1,1,1-trichloroethane will be phased out by the year 2000 (Snedecor, 1993). Production in the United States in 1993 was reported to be 205 246 tonnes (United States International Trade Commission, 1994).

1,1,1-Trichloroethane is used as a solvent for adhesives, in metal degreasing and in the manufacture of vinylidene chloride. Other applications include its use in pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks and stain repellents (American Conference of Governmental Industrial Hygienists, 1992; WHO, 1992; Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

No national estimates of exposure were available to the Working Group.

1.3.2 *Environmental occurrence*

1,1,1-Trichloroethane is likely to enter the environment from air emissions or in wastewater from its production and use in vapour degreasing, metal cleaning and other applications. It can also enter the environment in leachates and volatile emissions from landfills. It has been detected at low levels in wastewater, groundwater, drinking-water, ambient water, ambient air, and urban air samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 1910 mg/m^3 as the threshold limit value for occupational exposures to 1,1,1-trichloroethane in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established a provisional international drinking water guideline for 1,1,1-trichloroethane of 2000 µg/L (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Cohort study

In Finland, a cohort of 2050 male and 1924 female workers biologically monitored for occupational exposure to trichloroethylene (see IARC, 1995a), tetrachloroethylene (see IARC, 1995b) and 1,1,1-trichloroethane was followed up for cancer incidence during 1967–92. The Finnish population was used for estimating expected numbers of cases. In

the whole cohort, observed/expected numbers of incident cases (all sites) were 112/98 in male and 125/130 in women. Among workers exposed to 1,1,1-trichloroethane, seventeen incident cancers were seen (standardized incidence ratio (SIR), 1.6; 95% confidence interval (CI), 0.9–2.5). Ratios for which the 95% confidence interval included unity were related to cancer of the central nervous system (3 cases; SIR, 6.1) and multiple myeloma (2 cases; SIR, 16) (Anttila *et al*., 1995).

2.2 Case–control studies

A population-based case–control study on brain cancer was carried out in some areas in the United States with petroleum refining and chemical manufacturing industries (i.e., activities suspected of being associated with brain cancer) and is described in detail in the monograph on dichloromethane (see this volume). Probability, intensity, duration and calendar time of life-long individual exposures to each of six chlorinated aliphatic hydrocarbons, including 1,1,1-trichloroethane, were assessed through an ad-hoc job–exposure matrix. Whereas risk excesses of some consistency were associated with exposure to other chlorinated aliphatic hydrocarbons, exposure to 1,1,1-trichloroethane showed little indication of an association with brain cancer (Heineman *et al*., 1994).

In the Montreal case–control study carried out by Siemiatycki (1991) (for details, see the monograph on dichloromethane in this volume), the investigators estimated the associations between 293 workplace substances and several types of cancer. 1,1,1-Trichloroethane was one of the substances evaluated. About 1% of the study subjects had ever been exposed to 1,1,1-trichloroethane. Among the main occupations to which 1,1,1-trichloroethane exposure was attributed in this population were electricians, industrial equipment mechanics and rail transport equipment mechanics. For most types of cancer examined (oesophagus, stomach, colon, rectum, pancreas, prostate, bladder, skin melanoma, lymphoma), there was no indication of an excess risk due to 1,1,1-trichloroethane. For lung cancer in the French Canadians (the major ethnic group in this region) based on seven cases exposed at any level, the odds ratio was 3.5 (90% CI, 1.0–12.0). For kidney cancer among the whole population, based on four cases exposed at any level, the odds ratio was 2.4 (90% CI, 1.0–6.0). [The interpretation of the positive results has to take into account the multiple testing context. Workers had multiple exposures.]

3. Studies of Cancer in Experimental Animals

1,1,1-Trichloroethane was tested for carcinogenicity in one experiment in mice and in one in rats by oral administration and in one experiment by inhalation exposure in rats. Although a few liver tumours were observed in male mice, these experiments were considered to be inadequate for evaluation (IARC, 1979).

3.1 Oral administration

Rat: A group of 40 male and 40 female Sprague-Dawley rats, seven weeks of age, was given 500 mg/kg bw technical-grade 1,1,1-trichloroethane (maximum levels of stabilizers and impurities: 1,4-dioxane, 3.8%; 1,2-epoxybutane, 0.47%; nitromethane, 0.27%; *N*-methylpyrrole, < 1 ppm; chloroform, 100 ppm; carbon tetrachloride, 250 ppm; 1,1-dichloroethane, 426 ppm; 1,2-dichloroethane, 2300 ppm; 1,2,3-trichloroethane, 41.8 ppm; 1,1-dichloroethylene, 398 ppm; *trans*-1,2-dichloroethylene, 50 ppm; trichloroethylene, 200 ppm; tetrachloroethylene, 475 ppm) dissolved in olive oil by gavage once a day on four to five days per week for 104 weeks. A group of 50 males and 50 females treated with olive oil alone served as controls. After the end of the treatment period, animals were held until spontaneous death. The experiment lasted for 141 weeks. A complete autopsy was carried out on each animal and histopathological examinations were performed on almost all organs and any other organ with pathological lesions. An increased incidence of leukaemia/lymphoma was found in treated males and females [no statistical analysis given]. The incidences of leukaemia/lymphoma were 3/50 control males, 9/40 treated males, 1/50 control females and 4/40 treated females (Maltoni *et al*., 1986). [The Working Group noted that survival and body weight are indicated only in graphs; survival at 112 weeks of age was about 30% and 50% for control and treated males and about 35% and 55% for control and treated females, respectively; no noteworthy difference in body weight was observed between control and treated animals.]

3.2 Inhalation

3.2.1 *Mouse*

Groups of 50 male and 50 female $B6C3F_1$ mice, five to six weeks of age, were exposed to target concentrations of 0 (controls), 150, 500 or 1500 ppm [0, 820, 2700 or 8200 mg/m^3] production-grade 1,1,1-trichloroethane (94% (by volume) 1,1,1-trichloroethane, 5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol and nitromethane), 1% minor impurities) for 6 h per day on five days per week for 24 months (total of 516 exposure days). Time-weighted average measured exposure levels were: 151 ± 2, 502 ± 5 or 1505 ± 11 ppm. Complete gross examination was performed, and almost all organs and any grossly observed lesions suggestive of a tumour were examined histologically. There was no difference in survival between exposed mice and controls. [Survival was indicated only in graphs and was about 40–80% in males and 50–70% in females in all groups.] The body weights of treated male and female mice were similar to those of controls. A significant increasing trend was observed for combined incidences of benign tumours (adenoma and cystadenoma) of the lachrymal Harderian glands in females (3/50 control, 1/50 low-dose, 2/50 mid-dose and 7/50 high-dose; $p = 0.05$ linear trend by one-sided Cochran-Armitage test). The incidence of benign Harderian gland tumours in this study was within the normal variability at this institute (mean control incidence in females, 6.9%; range, 4–12%). In males, no significant change in the incidence of any tumour was observed (Quast *et al*., 1988).

3.2.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, four to six weeks of age, were exposed to target concentrations of 0 (controls), 150, 500 or 1500 ppm [0, 820, 2700 or 8200 mg/m^3] production-grade 1,1,1-trichloroethane (94% (by volume) 1,1,1-trichloroethane, 5% stabilizers (butylene oxide, *tert*-amyl alcohol, methyl butynol and nitromethane), 1% minor impurities) for 6 h per day on five days per week for 24 months (total of 516 exposure days). Time-weighted average measured exposure levels were: 151 ± 2, 502 ± 5 or 1505 ± 11 ppm. Complete gross examination was performed, and almost all organs and any grossly observed lesions suggestive of a tumour were examined histologically. There was no difference in survival between exposed rats and controls. [Survival was indicated only in graphs and was about 50–70% in males and 40–60% in females in all groups.] A significant decrease in body weight was observed in high-dose females. No significant increase was seen in the incidence of any tumour in males or females (Quast *et al*., 1988).

3.3 Multistage protocols and preneoplastic lesions

Rat: In an initiation study, a group of 10 male Osborne-Mendel rats, weighing 180–230 g, was subjected to a two-thirds partial hepatectomy and, 24 h later, was given a single dose of 3000 mg/kg bw 1,1,1-trichloroethane (purity, 97–99%) (maximum tolerated dose) in corn oil by gavage. Similar groups of animals were treated with 2 mL/kg bw corn oil alone (vehicle controls) or 30 mg/kg bw *N*-nitrosodiethylamine (NDEA; positive controls) followed by a two-thirds partial hepatectomy. Starting six days after partial hepatectomy, the rats received 500 mg phenobarbital/kg of diet (0.05% w/w) for seven weeks, then control diet for seven more days, after which time they were killed and the livers examined histologically for γ-glutamyltranspeptidase (γ-GT)-positive foci. There was no significant increase in the number of total γ-GT-positive foci (none and 0.27 ± 0.19/cm^2 in the 1,1,1-trichloroethane group and vehicle controls, respectively). NDEA increased the number of γ-GT-positive foci (4.04 ± 1.47) (Milman *et al*., 1988).

In a promotion study, groups of 10 male Osborne-Mendel rats (weighing 180–230 g) were given a single intraperitoneal injection of 30 mg/kg bw NDEA 24 h after a two-thirds partial hepatectomy. Starting six days later, the rats received daily 2000 mg/kg bw 1,1,1-trichloroethane (purity, 97–99%) (two-thirds of the maximum tolerated dose) in corn oil by gavage on five days per week for seven weeks. Control rats received corn oil alone during the promotion phase. After the promotion phase, rats were held for seven additional days, after which they were killed and the liver examined histologically for γ-GT-positive foci. There was no significant difference in the number of total γ-GT-positive foci between the 1,1,1-trichloroethane group and controls (2.16 ± 1.16 and 1.62 ± 0.33/cm^2, respectively) (Milman *et al*., 1988).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

1,1,1-Trichloroethane is rapidly taken up by humans after inhalation exposure. Experimental data collected in human subjects indicate that absorption of 1,1,1-trichloroethane is nearly complete following a single breath exposure (Morgan *et al.*, 1972), and that a steady-state lung retention of 25–30% in humans is achieved within 1–3 hours of continuous exposure (Monster, 1979; Nolan *et al.*, 1984). Steady-state blood levels are approximately 5–6 times that of alveolar air (Åstrand *et al.*, 1973; Monster, 1979) and increase with increasing air concentration, increasing alveolar ventilation and cardiac output (Åstrand *et al.*, 1973). The percentage uptake of inhaled 1,1,1-trichloroethane decreased rapidly from approximately 95% at the beginning of a four-hour exposure to 30% at the end (Monster, 1979).

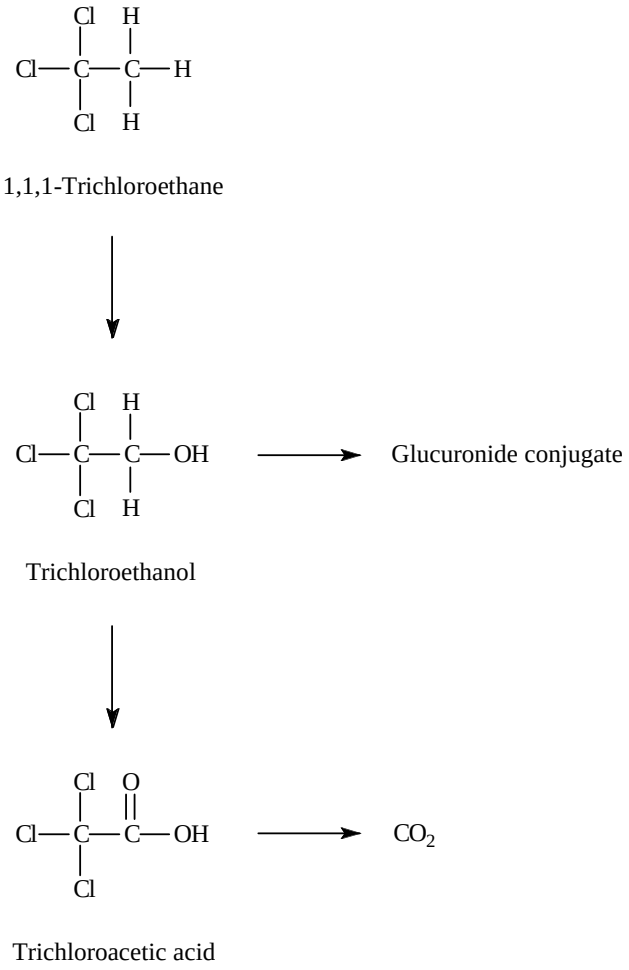
The absorption of 1,1,1-trichloroethane by the skin in humans has been shown to be dependent on the duration of exposure and the area of skin exposed (Fukabori *et al.*, 1977; Riihimaki & Pfaffli, 1978; Stewart & Dodd, 1964). 1,1,1-Trichloroethane vapours are absorbed through exposed skin to some extent, although absorption through the respiratory tract is expected to predominate during whole-body exposure to vapours. A quantitative examination of the relative magnitudes of percutaneous and respiratory absorption indicated that a whole-body exposure to 600 ppm [3280 mg/m^3] 1,1,1-trichloroethane for over 3.5 hours was equivalent to an inhalation exposure of only 0.6 ppm [3.3 mg/m^3] over the same time period (Riihimaki & Pfaffli, 1978).

After cessation of inhalation exposure, 1,1,1-trichloroethane is rapidly eliminated from the blood; 60–80% is eliminated within two hours after exposure and more than 95–99% within 50 hours (Åstrand *et al.*, 1973; Monster, 1979; Nolan *et al.*, 1984).

Blood concentrations of 1,1,1-trichloroethane in humans following dermal exposure are dependent on the duration of exposure. A two-hour exposure once a day resulted in higher blood levels than one-hour exposures twice a day (Fukabori *et al.*, 1977). At the end of a whole-body dermal exposure to 600 ppm [3280 mg/m^3] 1,1,1-trichloroethane vapour for 3.5 hours, the blood concentration of 1,1,1-trichloroethane reached a maximum of approximately 0.09 mg/L (Riihimaki & Pfaffli, 1978). This level quickly dropped after exposure ceased. In comparison, the steady-state blood concentration of 1,1,1-trichloroethane during inhalation exposure to 325 ppm [1770 mg/m^3] for four hours was approximately 4 mg/L (Åstrand *et al.*, 1973) and during exposure to 350 ppm [1910 mg/m^3] for six hours was approximately 2 mg/L (Nolan *et al.*, 1984).

Metabolism appears to play a relatively minor role in the overall disposition of absorbed 1,1,1-trichloroethane in humans. Less than 10% of the absorbed dose is metabolized; a large fraction is excreted unchanged in exhaled air, regardless of the route of exposure. The major metabolites of 1,1,1-trichloroethane are water-soluble

Figure 1. Biotransformation of 1,1,1-trichloroethane



trichloroethanol and its glucuronide conjugate, trichloroacetic acid and carbon dioxide (Figure 1).

The total amount of trichloroethanol and trichloroacetic acid excreted in urine accounts for 77% of the predicted amount of metabolized 1,1,1-trichloroethane. Excretion of trichloroethanol and trichloroacetic acid in urine is slow in relation to exhalation of 1,1,1-trichloroethane and these metabolites may accumulate with repeated exposure (Nolan *et al.*, 1984). The kinetics of elimination of 1,1,1-trichloroethane from blood into exhaled air are exponential. Elimination half-times for the initial, intermediate and terminal phases have been estimated at 1–9 hours, 6–20 hours and > 26 hours (Monster, 1979; Nolan *et al.*, 1984). Half-times for elimination from blood have been estimated to be 10–27 hours for trichloroethanol and 70–85 hours for trichloroacetic acid (Monster,

1979; Nolan *et al.*, 1984). Daily occupational exposure to 1,1,1-trichloroethane has been shown to result in a progressive increase in levels of urinary metabolites. Levels decline over the weekend, after exposure ceases (Seki *et al.*, 1975).

4.1.2 *Experimental animals*

1,1,1-Trichloroethane is rapidly absorbed by experimental animals after inhalation exposure. The initial uptake is governed by tissue loading and metabolism. Because 1,1,1-trichloroethane is poorly metabolized, absorption is expected to be lower after a steady state is reached (Dallas *et al.*, 1989).

The relative concentrations of 1,1,1-trichloroethane in the blood of experimental animals correlate with the levels found in humans (Carlson, 1981; Eben & Kimmerle, 1974; McEwen & Vernot, 1974; Schumann *et al.*, 1982b) after comparable exposure regimens.

1,1,1-Trichloroethane inhaled by animals distributes primarily into fat, liver and, to a lesser extent, kidney and brain, and is rapidly cleared after cessation of exposure (Holmberg *et al.*, 1977; Savolainen *et al.*, 1977; Schumann *et al.*, 1982a; Takahara, 1986). A linear relationship between exposure concentration and tissue concentration was found (Holmberg *et al.*, 1977).

The concentration of 1,1,1-trichloroethane in blood was determined in rats after one gavage dose in water (Reitz *et al.*, 1988). The blood level of 1,1,1-trichloroethane peaked approximately five minutes after the dose was given and then quickly decreased following exposure, being negligible after two hours.

Metabolism has been shown to be saturable in animals over a range of exposure levels of 150–1500 ppm [820–8200 mg/m^3] (Schumann *et al.*, 1982a); thus, as the exposure level and absorbed dose increase, metabolism will contribute less to overall elimination of 1,1,1-trichloroethane.

The data on 1,1,1-trichloroethane metabolism by animals are consistent with the human data. Approximately 90% of the inhaled dose is excreted unchanged in expired air, while the remainder is eliminated as CO_2 in expired air and as trichloroethanol and trichloroacetic acid in the urine (Ikeda & Ohtsuji, 1972; Eben & Kimmerle, 1974; Schumann *et al.*, 1982a,b; Koizumi *et al.*, 1984). A similar pattern of metabolism and subsequent excretion occurred in acutely and chronically exposed mice; the majority of 1,1,1-trichloroethane was excreted unchanged in the expired air and a small percentage was metabolized.

Metabolism following oral exposure is similar to metabolism following inhalation exposure. Reitz *et al.* (1988) found that approximately 3% of a dose ingested in drinking water by rats was metabolized and excreted as CO_2 in expired air or as metabolites in urine. Mice metabolized 1,1,1-trichloroethane more extensively than rats. This is consistent with the metabolic differences between rats and mice following inhalation exposure (Schumann *et al.*, 1982a), implying that mice may be the more sensitive species to effects of 1,1,1-trichloroethane that are based on biotransformation.

The pattern of excretion of 1,1,1-trichloroethane in animals is similar to that of humans. In rats exposed to 1,1,1-trichloroethane in the drinking water for eight hours (total dose of 116 mg/kg bw), the primary route of excretion was rapid elimination in expired air; only 3% of the ingested dose was metabolized (Reitz *et al.*, 1988). Virtually all of the ingested 1,1,1-trichloroethane was excreted within 30 hours after exposure.

Rapid elimination of 1,1,1-trichloroethane from blood after dermal exposure has been demonstrated in guinea-pigs (Jakobson *et al.*, 1982).

4.1.3 *Comparison of animals and humans*

In attempting to correlate the human and animal data, Nolan *et al.* (1984) validated a physiologically based pharmacokinetic model for 1,1,1-trichloroethane. The model predicted greater absorption, blood levels and metabolism of 1,1,1-trichloroethane in rodents than in humans. On the basis of toxicokinetic data, rats were suggested to be a better model than mice to evaluate potential health effects in humans.

The blood levels of 1,1,1-trichloroethane in human subjects were lower following exposure to 350 ppm [1910 mg/m^3] (approximately 2 mg/L) (Nolan *et al.*, 1984) than those found in rats and mice following exposure to 150 ppm [820 mg/m^3] (9.6 mg/L and 12.6 mg/L, respectively) (Schumann *et al.*, 1982b). The species differences between humans and rats are probably the result of a lower 1,1,1-trichloroethane blood:air partition coefficient and greater adipose tissue volume in humans (Dallas *et al.*, 1989).

4.2 Toxic effects

The toxicity of 1,1,1-trichloroethane has been reviewed (WHO, 1992; Agency for Toxic Substances and Disease Registry, 1995).

4.2.1 *Humans*

At least 30 fatalities have been associated with exposure to 1,1,1-trichloroethane, mostly due to deliberate inhalation or to accidental occupational exposure. Death was due to suffocation, the lungs showing acute oedema and congestion. Exposure to 1,1,1-trichloroethane impairs psychophysiological functions (IARC, 1979).

In a cross-sectional study of workers exposed to 1,1,1-trichloroethane in two textile mills (for 149/151, duration of exposure more than 12 months, for 135/151, estimated current exposure level (50–250 ppm [273–1365 mg/m^3])), no differences in the reported symptoms, electrocardiograms or laboratory examinations pertaining to liver function were observed (Kramer *et al.*, 1978). Case reports describing hepatic damage after exposure to 1,1,1-trichloroethane have been published (Cohen & Frank, 1994).

In an experimental inhalation exposure study at either stable or fluctuating exposure levels (time-weighted average, 200 ppm [1090 mg/m^3]), with or without 10-min peaks of exposure of 400 ppm [2180 mg/m^3]) combined with physical exercise, increased body sway but no change in visually evoked potentials or electroencephalography was observed in young healthy male volunteer participants (Laine *et al.*, 1996).

Case reports have been published on sensory neuropathies induced by exposure to 1,1,1-trichloroethane (House *et al*., 1996).

4.2.2 *Experimental systems*

1,1,1-Trichloroethane causes central nervous system depression in rats and liver damage has been reported only after exposure to nearly lethal doses. Continuous inhalation exposure for 14 weeks caused hepatotoxicity in mice (IARC, 1979). The very limited hepatic toxicity was substantiated in a long-term carcinogenicity study (United States National Cancer Institute, 1977), in which no gross or histopathological evidence of 1,1,1-trichloroethane-induced damage was observed in Osborne-Mendel rats (time-weighted average dosage 750 or 1500 mg/kg bw/day, five days per week for 78 weeks by gavage) or in B6C3F_1 mice (2807 or 5615 mg/kg bw/day for 78 weeks by gavage), although markedly shortened survival was noted at both dose levels in rats of both sexes and in female mice.

Similarly, in another long-term carcinogenicity study (Quast *et al*., 1988), very slight microscopic hepatotoxic changes were observed in rats of both sexes at 6, 12 and 18 months, but no more at 24 months after exposure to 1500 ppm [8190 mg/m^3] 1,1,1-trichloroethane for 6 h per day on five days per week for two years. No toxic changes were observed in mice.

Administration of 1,1,1-trichloroethane to male Fischer 344/N rats (82.7 or 165.4 mg/kg bw) once daily for 21 days induced a slight increase in the relative liver weight, but no microscopic hepatic damage (United States National Toxicology Program, 1996).

A small but significant elevation of serum sorbitol dehydrogenase activity was observed in female Sprague-Dawley rats 18 h after an intraperitoneal dose of 1,1,1-trichloroethane of 909 mg/kg bw (1/8 of the LD_{50}), but not at a dose level of 455 mg/kg bw (Lundberg *et al*., 1986). After a single intragastric dose of 667 mg/kg bw 1,1,1-trichloroethane, a small increase in glutamic pyruvic transaminase but not sorbitol dehydrogenase or glutamate dehydrogenase activities was observed in female Wistar rats (Liangfu & Tianju, 1992).

When 82.7 or 165.4 mg/kg bw 1,1,1-trichloroethane was administered to male Fischer 344/N rats by gavage once daily for 21 days, a decrease in the total urine output and an increase in the urinary alanine aminotransferase activity were observed at the high dose. However, no sign of hyaline nephropathy, or any other microscopic effect on the kidney, was observed (United States National Toxicology Program, 1996).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

When female Long-Evans rats were exposed to 1,1,1-trichloroethane by inhalation (11 470 ± 1100 mg/m^3 for 6 h per day) for two weeks before mating and through day 20 of gestation (York *et al*., 1982), no maternal toxicity was observed, and the only sign of

fetotoxicity was decreased fetal weight in the groups exposed during gestation only. Increased incidence of skeletal and soft tissue variations was observed in fetuses from the group exposed both before mating and during gestation (but not in groups exposed only during either of the periods alone). No teratogenic effects or effects on behaviour, as measured by the open field, running wheel activity or amphetamine challenge tests, or on pup survival were observed.

In a two-generation reproduction study (Lane *et al.*, 1982), ICR Swiss mice were continuously administered 1,1,1-trichloroethane in the drinking-water (580, 1750 or 5830 mg/L with the aim of producing daily doses of 100, 300 or 1000 mg/kg bw) starting five weeks before the mating of the F_0 generation. No treatment-related effects on fertility, gestation, viability, pup survival, weight gain or terata were observed.

In a reproduction study in CD rats, male and female breeders were exposed to 1,1,1-trichloroethane in drinking water (3, 10, or 30 mg/L) for 14 days before cohabitation and during the cohabitation. Sperm-positive females remained on the same regimen during pregnancy and lactation until postnatal day 21. No significant changes in reproductive competence, teratogenic effects or postnatal growth or development changes were noted, with the exception of a slight increase in mortality from implantation to postnatal day 1, caused by a high mortality in one litter (George *et al.*, 1989).

When pregnant CD-1 mice were exposed to 2000 ppm [10 900 mg/m^3] 1,1,1-trichloroethane for 17 h on days 12 through 17 of gestation, no effect on the pregnancy outcome was observed (Jones *et al.*, 1996). However, pups from treated dams gained less weight, exhibited delays in developmental landmarks and acquisition of the righting reflex, had poorer performance on tests of motor coordination and exhibited delays in negative geotaxis than sham or untreated pups. The findings were similar when the dams were exposed to 8000 ppm [43 700 mg/m^3] for 3 h per day on days 12 through 17 of gestation.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

1,1,1-Trichloroethane did not induced SOS response in the *umu* test using *Salmonella typhimurium* strain TA1535/pSK1002 but did induce mutations in *S. typhimurium* strains TA100 and TA1535 in the presence or absence of exogenous metabolic activation. It induced reverse mutations in *Escherichia coli* in the presence of exogenous metabolic activation in one of three studies. It did not induce DNA damage, gene conversion, mutation or aneuploidy in *Saccharomyces cerevisiae*. It did not induce genetic crossing-over or aneuploidy in *Aspergillus nidulans*, mutation in *Tradescantia* or sex-linked recessive lethal mutation in *Drosophila melanogaster*.

In one study, 1,1,1-trichloroethane bound to calf thymus DNA and microsomal RNA and protein when incubated in the presence of rat or mouse liver microsomes.

Table 1. Genetic and related effects of 1,1,1-trichloroethane

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, *Prophage*, induction, SOS response, strand-breaks or cross-links	–	–	666	Nakamura *et al*. (1987)
SAF, *Salmonella typhimurium*, forward mutation	NT	–	1000	Skopek *et al*. (1981)
SAF, *Salmonella typhimurium*, forward mutation (Ara test)	–	–	375	Roldán-Arjona *et al*. (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	70	Simmon *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG, vapour	Nestmann *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	144	Gocke *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	150	Nestmann *et al*. (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Falck *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	266×10^3 mg/m^3	Shimada *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	–	500	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	+	5	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG, vapour	Nestmann *et al*. (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Gatehouse (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	144	Gocke *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	80	Nestmann *et al*. (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Falck *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	266	Shimada *et al*. (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Nestmann *et al*. (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Gatehouse (1981)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Falck *et al*. (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Nestmann *et al*. (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Falck *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Nestmann *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	134	Norpoth *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Gatehouse (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Falck *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	5	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	5	Strobel & Grummt (1987)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	NT	+	268	Norpoth *et al*. (1980)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	1000	Gatehouse (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	1000	Falck *et al*. (1985)
SSD, *Saccharomyces cerevisiae*, differential toxicity	–	–	750	Sharp & Parry (1981a)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	–	–	125	Jagannath *et al*. (1981)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	–	–	750	Sharp & Parry (1981b)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	NT	–	2600	Zimmermann & Scheel (1981)
ANG, *Aspergillus nidulans*, strain P1 genetic crossing-over	–	NT	1300	Crebelli *et al*. (1988)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	–	–	1488	Mehta & von Borstel (1981)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	–	–	500	Parry & Sharp (1981)
SCN, *Saccharomyces cerevisiae* D61.M, aneuploidy	–	NT	6000	Whittaker *et al*. (1990)
ANN, *Aspergillus nidulans* strain P1, aneuploidy	–	NT	1300	Crebelli *et al*. (1988)
TSM, *Tradescantia* species, mutation	–	NT	27.5×10^3 mg/m^3	Schairer & Sautkulis (1982)
DMX, *Drosophila melanogaster*, Basc strain, sex-linked recessive lethal mutations	–		3335 µg/mL feed	Gocke *et al*. (1981)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	133	Shimada *et al*. (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	?	NG	Tennant *et al*. (1986)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	680	Mitchell *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	?	536	Myhr & Caspary (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	NT	–	10	Perry & Thomson (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	?	?	1000	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	–	160	Galloway *et al*. (1987)
TBM, Cell transformation, BALB/c-3T3 mouse cells	+	NT	4	Tu *et al*. (1985)
TRR, Cell transformation, Fischer rat embryo cells,	+	NT	13	Price *et al*. (1978)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	+	NT	11×10^3 mg/m^3	Hatch *et al*. (1983)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
MVM, Micronucleus test, NMRI mouse bone marrow *in vivo*	–		2000 ip × 2	Gocke *et al*. (1981)
MVM, Micronucleus test, B6C3F_1 mouse bone marrow *in vivo*	–		67 ip × 2	Salamone *et al*. (1981)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	–		43 ip × 2	Tsuchimoto & Matter (1981)
BID, Binding (covalent) to calf thymus DNA *in vitro*	NT	+	7.6	Turina *et al*. (1986)
BIP, Binding(covalent) to RNA or protein *in vitro*	NT	+	7.6	Turina *et al*. (1986)
BVD, Binding (covalent) to DNA, male Wistar rat and BALB/c mouse liver, kidney, lung and stomach *in vivo*	(+)		1.2 ip × 1	Turina *et al*. (1986)
BVP, Binding (covalent) to RNA or protein, male Wistar rat and BALB/c mouse liver, kidney, lung and stomach *in vivo*	+		1.2 ip × 1	Turina *et al*. (1986)
SPM, Sperm morphology, mice *in vivo*	–		1340 ip × 5	Topham (1980)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal

1,1,1-Trichloroethane did not induce unscheduled DNA synthesis in rat primary hepatocytes. It showed inconclusive evidence of gene mutation at the *tk* locus in mouse lymphoma L5178Y cells in the presence of an exogenous metabolic activation system. Results for induction of sister chromatid exchanges were also inconclusive. 1,1,1-Trichloroethane increased the frequency of chromosomal aberrations in Chinese hamster ovary cell cultures and induced morphological transformation in BALB/c 3T3 and in Fischer rat and virally-enhanced Syrian hamster embryo cells *in vitro*.

1,1,1-Trichloroethane bound to DNA, RNA and protein in liver, lung, kidney and stomach of mice and rats given a single intraperitoneal injection but did not induce micronuclei in mouse bone marrow following two injections, or abnormal sperm morphology in mice given five daily intraperitoneal injections.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,1,1-Trichloroethane is a solvent. It has been detected in waste-, ground-, drinking- and ambient water as well as in ambient and urban air.

5.2 Human carcinogenicity data

An increased risk for central nervous system and multiple myeloma was reported from a cohort study of workers exposed to 1,1,1-trichloroethane in Finland. These findings were not confirmed by two case–control studies carried out in the United States and Canada, while an increased risk for cancer of the lung and kidney was shown in the Canadian study.

5.3 Animal carcinogenicity data

1,1,1-Trichloroethane was tested for carcinogenicity by oral administration in rats in two experiments and in mice in one experiment. Although leukaemia was seen in both sexes of rats in one study and a few liver tumours occurred in male mice, the results of these studies were considered to be inadequate for evaluation. 1,1,1-Trichloroethane was tested by inhalation in rats in two experiments and in mice in one experiment. No chemically related increase in tumour incidence was observed in either rats or mice in one adequate study. Another inhalation study was considered to be inadequate.

In a multistage study for γ-glutamyltranspeptidase (γ-GT)-positive foci in the liver of male rats, neither single administration of 1,1,1-trichloroethane by gavage after a two-thirds partial hepatectomy followed by treatment with phenobarbital (initiation study) nor repeated administration of 1,1,1-trichloroethane by gavage after a two-thirds partial hepatectomy and initiation with *N*-nitrosodiethylamine (promotion study) increased the number of γ-GT-positive foci.

5.4 Other relevant data

Absorption of 1,1,1-trichloroethane vapour is mainly through the respiratory tract. It is rapidly eliminated from blood. Metabolism plays a minor role in this process, more than 90% being eliminated unchanged, both in exposed people and rodents. The main metabolites are trichloroethanol, trichloroacetic acid and carbon dioxide.

1,1,1-Trichloroethane is neurotoxic and hepatotoxic, following exceptionally high exposure concentrations of people and also in rodents. No structural damage has been reported in reproductive toxicity studies in rats and mice, but delayed development, particularly of neurological attributes, has been reported in one study with mice.

1,1,1-Trichloroethane covalently bound to DNA, RNA and protein in mice and rats but did not induce micronuclei or abnormal sperm head morphology in mice *in vivo*. It induced chromosomal aberrations and cell transformation in mammalian cell cultures and it showed inconclusive evidence of sister chromatid exchange induction. It did not induce unscheduled DNA synthesis or gene mutation in mammalian cells *in vitro*. 1,1,1-Trichloroethane did not cause mutation in plants or sex-linked mutation in *Drosophila*. It did not induce DNA damage, gene conversion, mutation or aneuploidy in yeast or genetic crossing-over or aneuploidy in fungi, but it was mutagenic to some bacterial strains.

5.5 Evaluation

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

There is *inadequate evidence* for the carcinogenicity of 1,1,1-trichloroethane in experimental animals.

Overall evaluation

1,1,1-Trichloroethane is *not classifiable as to its carcinogenicity to humans (Group 3).*

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