

1,1,1-Trichloroethane in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters...”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

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Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer
LD ₅₀	median lethal dose
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	71-55-6
Molecular formula:	C ₂ H ₃ Cl ₃

1.2 Physicochemical properties¹ (1,2)

<i>Property</i>	<i>Value</i>
Melting point	-30.4 °C
Boiling point	74.1 °C
Density	1.339 g/cm ³ at 20 °C
Vapour pressure	13.3 kPa at 25 °C
Water solubility	0.3–0.5 g/litre at 25 °C
Log octanol–water partition coefficient	2.49

1.3 Organoleptic properties

1,1,1-Trichloroethane has a chloroform-like odour.

1.4 Major uses

1,1,1-Trichloroethane is widely and increasingly used as a cleaning solvent for electrical equipment, motors, electronic instruments and upholstery, as a solvent for adhesives, coatings and textile dyes, as a coolant and lubricant in metal cutting oils and as a component in inks and drain cleaners (1,2).

1.5 Environmental fate

1,1,1-Trichloroethane is found mainly in the atmosphere, where it has a half-life of approximately 2–6 years. It can be decomposed by photochemically produced hydroxyl radicals (1). In water, 1,1,1-trichloroethane is moderately soluble but can volatilize to air. It can be anaerobically dechlorinated by methane-producing bacteria to form 1,1-dichloroethane and decomposes to give ethanoic acid and 1,1-dichloroethene by abiotic reactions, with a half-life of 200–300 days. 1,1,1-Trichloroethane is mobile in soils and readily migrates to groundwater. Volatilization from surface soils is also likely. It does not bioaccumulate in animals (1).

2. ANALYTICAL METHODS

1,1,1-Trichloroethane in water is usually determined by a purge-and-trap gas chromatographic procedure (3). It can be detected by mass spectrometry, the detection limit being 0.3 µg/litre (4).

¹ Conversion factor in air: 1 ppm = 5.4 mg/m³.

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

The median concentration of 1,1,1-trichloroethane in air was $0.6 \mu\text{g}/\text{m}^3$ in rural and remote areas, $2.8 \mu\text{g}/\text{m}^3$ in urban and suburban areas and $6.5 \mu\text{g}/\text{m}^3$ in source-dominated areas (5). Mean air levels in cities in the USA ranged from 0.001 to $60 \mu\text{g}/\text{m}^3$ for urban air and from 0.36 to $1.08 \mu\text{g}/\text{m}^3$ for rural air (1). Air concentrations are typically higher in the northern hemisphere (average 0.06–0.1 $\mu\text{g}/\text{m}^3$) than in the southern hemisphere (average 0.02 $\mu\text{g}/\text{m}^3$) (6).

3.2 Water

1,1,1-Trichloroethane is not usually found at significant concentrations in surface water. It may be found in groundwater as a consequence of surface spills or poor handling practice. Tributaries of the Rhine contained 1,1,1-trichloroethane at levels of 0.05–2.2 $\mu\text{g}/\text{litre}$. Surface waters in Switzerland contained an average of 0.06 $\mu\text{g}/\text{litre}$. In Europe, groundwater levels were in the range 0.04–130 $\mu\text{g}/\text{litre}$ (6).

In the USA, the mean level of 1,1,1-trichloroethane in drinking-water was 0.02–0.6 $\mu\text{g}/\text{litre}$; in well water, the corresponding level was 9–24 $\mu\text{g}/\text{litre}$ (1). A mean concentration of 0.3 $\mu\text{g}/\text{litre}$ was reported for drinking-water in Italy (7). Surface water samples from 20 of 106 drinking-water systems analysed for 1,1,1-trichloroethane in the USA between 1977 and 1981 contained detectable levels of this compound (0.1–3.3 $\mu\text{g}/\text{litre}$, mean 0.6 $\mu\text{g}/\text{litre}$; detection limit 0.1 $\mu\text{g}/\text{litre}$). Of 316 groundwater systems tested, 15 contained 1,1,1-trichloroethane at levels ranging from the detection limit (0.5 $\mu\text{g}/\text{litre}$) to 142 $\mu\text{g}/\text{litre}$ (mean 13 $\mu\text{g}/\text{litre}$) (8).

3.3 Food

Small amounts of 1,1,1-trichloroethane were found in various foodstuffs in the United Kingdom; it was present in meats, oils and fats, tea, fruits and vegetables at levels ranging from 1 to 10 $\mu\text{g}/\text{kg}$ (9). The highest levels of 1,1,1-trichloroethane found in a survey in the USA were in fatty foods (19 $\mu\text{g}/\text{kg}$) and margarine (45 $\mu\text{g}/\text{kg}$) (10).

3.4 Estimated total exposure and relative contribution of drinking-water

Exposures to 1,1,1-trichloroethane are highly variable and should be evaluated on an individual basis. If an air concentration of $5 \mu\text{g}/\text{m}^3$ is assumed, the daily intake would be 100 μg for an adult breathing 20 m^3 of air per day. On the assumption of a 1,1,1-trichloroethane level of 0.6 $\mu\text{g}/\text{litre}$ in drinking-water, the daily intake will be 1.2 μg for an adult consuming 2 litres of drinking-water per day. If the average concentration in food is 5 $\mu\text{g}/\text{kg}$, the intake will be 10 $\mu\text{g}/\text{day}$ for an adult consuming 2 kg of food.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

1,1,1-Trichloroethane appears to be absorbed rapidly and completely from the lungs of human subjects (11). After 4 h of continuous exposure to 378 or 756 mg/m³, a steady-state lung retention of 30% was observed (12,13). The concentration of 1,1,1-trichloroethane in the expired air of humans after ingestion of 0.6 g/kg of body weight was equivalent to the expired air concentration following an inhalation exposure of 2700 mg/m³ (14).

After inhalation by humans, blood levels of 1,1,1-trichloroethane were highly correlated with alveolar air levels. Within 2 h of exposure, 60–80% was eliminated from the blood (12). One day after intraperitoneal administration of 1,1,1-trichloroethane at 700 mg/kg of body weight, rats retained 0.9% (as the parent compound) in the skin, 0.02% in the blood, 0.02% in the fat and 0.1% in other sites (15).

1,1,1-Trichloroethane is metabolized to a very limited extent in mammals (12); the proportion is probably less than 6% in humans. Metabolites include trichloroethanol, trichloroethane glucuronide and trichloroethanoic acid. Less than 3% of a single intraperitoneal injection of 1,1,1-trichloroethane was metabolized by rats (15). The metabolic fate of inhaled 1,1,1-trichloroethane in rats and mice was not altered on repeated exposure (16).

1,1,1-Trichloroethane was detected in the expired air of human subjects exposed to oral doses (14). Metabolites were excreted primarily in urine; very small amounts of trichloroethanol (1%) were excreted by the lungs (12). Over 99% of intraperitoneally injected 1,1,1-trichloroethane was excreted by rats via the pulmonary route (98.7% unchanged); less than 1% was excreted via the urine, primarily as the trichloroethanol glucuronide (15). Rats and mice exposed via inhalation to radiolabelled 1,1,1-trichloroethane for 6 h excreted more than 96% of the administered radioactivity during the first 24 h, primarily via exhalation (16).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

The acute oral LD₅₀ for 1,1,1-trichloroethane in several species ranged from 5.7 to 14.3 g/kg of body weight (17). A single oral dose of approximately 1.4 g/kg of body weight depressed the activities of hepatic cytochrome P-450 and epoxide hydratase in rats (18).

5.2 Short-term exposure

1,1,1-Trichloroethane at doses of 5 or 10 g/kg of body weight per day for 9 days produced fatalities, transient hyperexcitability and protracted narcosis in rats. There were no observed adverse effects at 0.5 g/kg of body weight per day. When 1,1,1-

trichloroethane was administered to rats by gavage 5 times a week for up to 12 weeks at doses of 0, 0.5, 2.5 or 5.0 g/kg of body weight, the animals given 2.5 or 5.0 g/kg of body weight exhibited reduced body weight gain and central nervous system effects. Although 35% of these rats died during the first 50 days of the experiment, only the group receiving 5.0 g/kg of body weight showed an increase in serum enzyme levels indicative of toxicity. No adverse effects were observed following ingestion of 0.5 g/kg of body weight for 12 weeks (19).

Male mice were exposed continuously to 1,1,1-trichloroethane by inhalation at levels of 1365 or 5460 mg/m³ for 14 weeks, while control mice were exposed to room air. Significant changes were observed in the centrilobular hepatocytes of mice in the high-dose group, namely vesiculation of the rough endoplasmic reticulum with loss of attached polyribosomes and increased smooth endoplasmic reticulum, microbodies and triglyceride droplets. The NOAEL in this study was 1365 mg/m³ (20).

Groups of 10 male or 10 female F344 rats and B6C3F₁ mice were exposed to 5000–80 000 mg of microencapsulated 1,1,1-trichloroethane per kg in their diet for 13 weeks in a study conducted according to GLP (21). At the end of this period, histopathology was carried out on a full range of organs. Female rats receiving the highest dose (5000 mg/kg of body weight per day) showed reduced liver weights, and males receiving the highest dose (4800 mg/kg of body weight per day) showed changes in the kidney that were consistent with hyaline droplet nephropathy. In mice, those receiving the middle dose and above (3500 mg/kg of body weight per day in males and 5600 mg/kg of body weight per day in females) showed lower body weights. The authors concluded that the NOAEL in rats and mice was 10 000 mg/kg in the diet (600 mg/kg of body weight per day in male rats, 650 mg/kg of body weight per day in female rats, 1770 mg/kg of body weight per day in male mice and 2820 mg/kg of body weight per day in female mice) (21).

5.3 Long-term exposure

Decreases in survival and body weight gain were noted in mice and rats given 1,1,1-trichloroethane by gavage in corn oil, 5 days per week for 78 weeks. The rats were given doses of 750 or 1500 mg/kg of body weight per day, and the mice were administered doses of 2800 or 5600 mg/kg of body weight per day (22).

5.4 Reproductive and developmental toxicity

In a multigenerational study, no dose-dependent effects on fertility, gestation or viability indices were seen in mice exposed to 1,1,1-trichloroethane in their drinking-water at dose levels of 100, 300 or 1000 mg/kg of body weight from pre-mating to lactation (23). In a teratogenicity study specifically designed to examine the heart, in which COBS CD9SD0BR outbred albino rats were given 1,1,1-trichloroethane in their drinking-water at average concentrations over the study of 2.7, 8.5 or 27.1 mg/litre, there were no indications of any cardiac malformations (24).

5.5 Mutagenicity and related end-points

It was reported in several studies that 1,1,1-trichloroethane was not mutagenic in *Salmonella typhimurium* when tested with or without metabolic activation (1), but no attempt was made in the testing procedure to prevent volatilization of the test compound. 1,1,1-Trichloroethane was mutagenic in various strains of *S. typhimurium* when tested with or without metabolic activation (1,25), but not in *Saccharomyces cerevisiae* or *Schizosaccharomyces pombe* (26). In several mammalian cell lines, exposure to 1,1,1-trichloroethane led to an increased frequency of transformed cells (1).

In an NTP study (21), 1,1,1-trichloroethane was not mutagenic in *S. typhimurium* TA98, TA100, TA1535 or TA1537 with or without metabolic activation. In the mouse lymphoma assay for trifluorothymidine resistance, it was negative in one test and gave an equivocal positive result in a second test with metabolic activation. The induction of sister chromatid exchange in Chinese hamster ovary cells was considered equivocal due to an unrepeated and questionable response in a single trial in the presence of a metabolizing system. The cells treated in the absence of this system showed no response. The overall weight of evidence appears to indicate that 1,1,1-trichloroethane does not possess significant genotoxic activity.

5.6 Carcinogenicity

Male and female rats (750 or 1500 mg/kg of body weight) and male and female mice (2800 or 5600 mg/kg of body weight) were given 1,1,1-trichloroethane in corn oil by gavage 5 times per week for 110 weeks (rats) or 78 weeks (mice). The incidence and types of tumours observed in treated animals were similar to those observed in controls. Because of the decreased survival time in both mice and rats, the authors concluded that this bioassay was not adequate to assess carcinogenicity in either species (2,22).

Rats (375 or 750 mg/kg of body weight) and mice (1500 or 3000 mg/kg of body weight) were given 1,1,1-trichloroethane in corn oil by gavage 5 times per week for 103 weeks. No treatment-related tumours were observed in male rats, and the study was inadequate for the evaluation of female rats because of the high mortality rate. Although there was a significant dose-response trend and increased incidence of hepatocellular carcinomas in male and high-dose female mice, the study was judged to be inadequate for assessment of carcinogenicity (27).

6. EFFECTS ON HUMANS

Large oral doses of 1,1,1-trichloroethane have produced nausea, vomiting and diarrhoea in humans. Acute inhalation exposures result in neurological effects (1). Impaired test performance occurs above 945 mg/m³, while dizziness, light-headedness and incoordination can occur above 2.7 g/m³. Concentrations of 54 g/m³ result in general anaesthesia. Acute pulmonary congestion and oedema were often found in fatalities resulting from inhalation (28,29). Fatty vacuolation was also found in the

liver of exposed subjects (28). High concentrations of 1,1,1-trichloroethane in air can produce respiratory failure and cardiac arrhythmia (1), while chronic exposure to low levels had no effect on parameters of serum and urine chemistry indicative of liver and kidney damage in humans (1).

7. CONCLUSIONS

IARC has placed 1,1,1-trichloroethane in Group 3 (not classifiable as to its carcinogenicity to humans) (30). Based on the lowest NOAEL of 600 mg/kg of body weight in male rats in the oral study conducted by the US NTP (21) and applying an uncertainty factor of 1000 (10 each for inter- and intraspecies variation and 10 for the use of a short-term study), a TDI of 0.6 mg/kg of body weight can be determined. Assuming a 60-kg adult drinking 2 litres of water per day and allocating 10% of the TDI to drinking-water, a health-based value of 2 mg/litre (rounded value) can be derived. However, because 1,1,1-trichloroethane occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value.

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