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Tetrachloroethene 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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GENERAL DESCRIPTION

Identity

CAS no.: 127-18-4
Molecular formula: C_2Cl_4
Tetrachloroethene is also known as tetrachloroethylene and perchloroethylene.

Physicochemical properties (*1–3*) [Conversion factor in air: 1 ppm = 6.78 mg/m^3]

Property	*Value*
Melting point	-19 °C
Boiling point	121 °C
Density	1.623 g/ml at 25 °C
Vapour pressure	2.53 kPa at 25 °C
Water solubility	150 mg/litre at 25 °C
Log octanol–water partition coefficient	2.86

Organoleptic properties

The odour thresholds for tetrachloroethene in water and air are 0.3 mg/litre and 7 mg/m^3, respectively (*3*).

Major uses

Tetrachloroethene is used primarily as a solvent in the dry-cleaning industry. It is also used as a degreasing solvent in metal industries, as a heat transfer medium, and in the manufacture of fluorohydrocarbons (*1,4*).

Environmental fate

Most tetrachloroethene released to the environment is found in the atmosphere, where photochemically produced hydroxyl radicals degrade it to phosgene and chloroacetyl chlorides with a half-life of 96–251 days (*3*). In water, it does not readily undergo hydrolysis or photolysis but is biodegraded by microorganisms to dichloroethene, vinyl chloride, and ethene. Tetrachloroethene can persist in waters where volatilization cannot occur. It volatilizes less readily from soil than from water and, with a soil adsorption coefficient of 72–534, is expected to be fairly mobile in soils. Degradation may occur in anaerobic soils. It does not appear to bioaccumulate in animals or food-chains (*3*).

ANALYTICAL METHODS

A purge-and-trap gas chromatographic procedure is used for the determination of tetrachloroethene in drinking-water (*5*). Mass spectrometry or electron capture, flame-ionization, and halide-sensitive detectors may be used for detection, the detection limits ranging from 0.1 to 1.9 µg/litre in water (*3,6*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Concentrations of tetrachloroethene in city air in the United Kingdom range from less than 0.7 to 70 µg/m^3 (*7*). In Munich, suburban and urban air concentrations were 4 and 6 µg/m^3,

respectively (*8*). Surveys in the USA indicated concentrations of less than 0.01 μg/m^3 in rural areas and up to 6.7 μg/m^3 in urban areas (*9*).

Water

A survey of drinking-water in the USA in 1976–77 detected tetrachloroethene in nine of 105 samples at levels ranging from 0.2 to 3.1 μg/litre (mean 0.81 μg/litre) (*10*). In other surveys of drinking-water supplies in the USA, it was found that 3% of all public water-supply systems that used well-water contained tetrachloroethene at concentrations of 0.5 μg/litre or higher, whereas those that used surface water contained lower levels (*2*). In the United Kingdom, it has been detected at levels of 0.4 μg/litre in municipal waters (*1,7*) and, in Japan, in approximately 30% of all wells, at concentrations ranging from 0.2 to 23 000 μg/litre (*3*). In Switzerland, tetrachloroethene concentrations as high as 954 μg/litre have been found in contaminated groundwater (*11*). Tetrachloroethene in anaerobic groundwater may degrade to more toxic compounds, including vinyl chloride (*3*).

Food

Tetrachloroethene concentrations in seafood in the United Kingdom ranged from 0.5 to 30 μg/kg (*7,12*). Those in other foodstuffs ranged from almost undetectable (0.01 μg/kg) in orange juice to 13 μg/kg in butter (*13*). Some foods (particularly those with a high fat content) stored or sold near dry-cleaning facilities may contain considerably higher concentrations (*14*).

Estimated total exposure and relative contribution of drinking-water

Based on a tetrachloroethene concentration in air of 6 μg/m^3, estimated exposure would be about 120 μg/day for an adult with an air intake of 20 m^3. If drinking-water contains 0.5 μg of tetrachloroethene per litre, the average daily exposure would be 1 μg for an adult consuming 2 litres of water per day. There are insufficient data on the levels of tetrachloroethene in foods to allow an average exposure to be determined.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The results from animal studies indicate that tetrachloroethene is rapidly and completely absorbed from the gastrointestinal tract (*3,15*). It reached near-steady-state levels in the blood of human volunteers after 2 h of continuous inhalation (*16*). Rats given a gavage dose of radiolabelled tetrachloroethene contained radioactivity in the liver, kidney, and fat (*15*). Occupationally exposed subjects had whole-blood levels as high as 2500 μg/litre, as compared with 0.4 μg/litre in controls (*17*).

Metabolic products appear to be similar in humans and experimental animals (*1,18,19*). Tetrachloroethene is metabolized by a cytochrome P-450-mediated oxidation to tetrachloroethene oxide and trichloroacetyl chloride to form trichloroethanoic acid and trichloroethanol. In mice, trichloroethanoic acid is the major metabolite formed, whereas it is formed in relatively small amounts in rats (*20*). In humans, only 1.8% of the retained dose was converted into trichloroethanoic acid; 1.0% was converted into an unknown metabolite in 67 h (*21*).

Saturation of metabolism has been observed both in inhalation studies in rats (*22*) and in gavage studies in mice (*23*). After saturation of metabolism via the oxidative pathway, a second metabolic pathway through conjugation with glutathione to form a highly reactive trichlorovinylthiol compound has been shown to occur in rat kidney, activated by renal ß-lyase enzyme. This metabolic pathway appears to be absent in humans (*22*) and to be significant only in male rats (*24*).

Tetrachloroethene is eliminated from the body primarily via the lungs; the half-life is about 65 h (*1,25*). Trichloroethanoic acid is eliminated via the urine with a half-life of 144 h (*1,26*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

LD_{50}s of 3835 and 3005 mg/kg of body weight were found for male and female rats to which single doses of tetrachloroethene were administered by gavage. Acute effects are dominated by central nervous system depression (*27*).

Short-term exposure

Groups of male Swiss-Cox mice were given oral doses of tetrachloroethene in corn oil at 0, 20, 100, 1000, or 2000 mg/kg of body weight, 5 days per week for 6 weeks (equivalent to 0, 14, 70, 700, or 1400 mg/kg of body weight per day). Mice treated with doses as low as 70 mg/kg of body weight per day exhibited significantly increased liver triglyceride levels and liver-to-body-weight ratios. At higher doses, hepatotoxic effects included decreased DNA content, increased serum alanine aminotransferase, decreased glucose-6-phosphatase serum levels, and hepatocellular necrosis, degeneration, and polyploidy. The NOAEL was 14 mg/kg of body weight per day (*23*).

Sprague-Dawley rats (20 per sex per dose) were given tetrachloroethene in drinking-water at doses of 14, 400, or 1400 mg/kg of body weight per day for 90 days. Males in the high-dose group and females in the mid- and high-dose groups exhibited depressed body weights. Increased liver- and kidney-to-body-weight ratios (equivocal evidence of hepatotoxicity) were also observed at the two highest doses (*27*).

There was moderate fatty degeneration of the liver in mice following a 4-h exposure to air containing 1340 mg of tetrachloroethene per m^3 (*28*). Exposure to this same level for 4 h per day, 6 days per week for up to 8 weeks increased the severity of the lesions (*29*).

Long-term exposure

Male and female Osborne-Mendel rats and $B6C3F_1$ mice were exposed to tetrachloroethene by corn oil gavage for 78 weeks at doses ranging from 471 to 1072 mg/kg of body weight per day. Increased mortality and nephropathy, as shown by degenerative tubule changes, fatty changes, and cloudy swelling, were observed in all treated animals (*30*).

Exposure of F344 rats to tetrachloroethene administered by inhalation at doses of 0, 1.36, or 2.72 g/m^3 for 103 weeks, 5 days per week, resulted in a significant reduction in survival, increased renal karyomegaly in both sexes, and renal tubular cell hyperplasia in males at both doses. Similar exposure of $B6C3F_1$ mice to 0, 1.36, or 2.72 g/m^3 resulted in reduced survival and increased renal nephrosis, tubular cell karyomegaly, and renal casts, as well as hepatic degeneration and necrosis (*31*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Inhalation exposures to tetrachloroethene have resulted in maternal and fetal toxicity in mice, rats, and rabbits (*3*).

Mutagenicity and related end-points

Short-term studies indicate that tetrachloroethene induces single-strand DNA breaks in the mouse but does not cause chromosomal aberrations in rat bone marrow or human lymphocytes (*1,30,32*). *In vitro* assays in *Salmonella typhimurium*, *Escherichia coli*, and *Saccharomyces cerevisiae* were negative both with and without microsomal activation.

Carcinogenicity

The exposure by inhalation (6 h per day, 5 days per week for 103 weeks) of F344/N rats to 0, 1.36, or 2.72 g/m^3 tetrachloroethene produced a small (but not statistically significant) increase in the combined incidence of renal tubular-cell adenomas and adenocarcinomas in males but not in females. In both sexes, there was an increase in the incidence of mononuclear cell leukaemias at both doses, but the incidence was also unusually high in concurrent as compared with historical controls (*31*).
It has been suggested that the induction of kidney tumours in male rats is the combined result of the formation of a highly reactive metabolite and cell damage produced by renal accumulation of hyaline droplets (*33,34*).

The exposure by inhalation (6 h per day, 5 days per week for 103 weeks) of B6C3F$_1$ mice at 0, 1.36, or 2.72 g/m^3 resulted in an increase in hepatocellular carcinomas in both males and females (*31*). In an earlier bioassay, in which tetrachloroethene was administered by gavage in corn oil, there was an increase in the incidence of hepatocellular carcinomas in both male and female mice but not in Osborne-Mendel rats. In this experiment, survival was reduced in both species as a result of pneumonia, and impurities later shown to be carcinogenic were present in the tetrachloroethene (*30*).

Hepatotoxic and related carcinogenic effects of tetrachloroethene in mice appear to be due to trichloroethanoic acid, which is formed in greater amounts by mice than by rats or humans (*19,35*). In addition, mice are more sensitive than rats to trichloroethanoic acid, a peroxisome proliferator in mice (*36*).

EFFECTS ON HUMANS

Oral doses of 4.2–6 g of tetrachloroethene administered to patients to control parasitic worm infections caused central nervous system effects, such as inebriation, perceptual distortion, and exhilaration (*37*). Several developmental effects, such as eye, ear, central nervous system, chromosomal, and oral cleft anomalies, were associated with exposure to tetrachloroethene and other solvents in contaminated drinking-water supplies (*38*). Inhalation exposures have been associated in female dry-cleaning workers with reproductive effects, including menstrual disorders and spontaneous abortions (*39,40*).

A few case reports and small-scale epidemiological and clinical studies involving a group of men occupationally exposed to tetrachloroethene at levels of 1890–2600 mg/m^3 suggest an association between such exposure and serious central nervous system problems (*1,41–43*). However, workers were often simultaneously exposed to several solvents (*44*). Evidence for the carcinogenicity of tetrachloroethene was obtained by observing laundry and dry-cleaning workers, but was rated as inadequate by IARC (*45*). Although an increased incidence of cancer was reported in several cohort and proportionate mortality studies (*1,46–48*) and increased risks of cancer in workers exposed to tetrachloroethene were found in case–control studies (*49,50*), study limitations, such as concomitant exposures to other chemicals and small sample size, make it difficult to reach a definite conclusion.

GUIDELINE VALUE

IARC (*45*) has concluded that there is sufficient evidence of carcinogenicity in animals to classify tetrachloroethene in Group 2B: possible human carcinogen. It reportedly produces liver tumours in mice, with some evidence of mononuclear cell leukaemia in rats and kidney tumours in male rats. However, overall evidence indicates that this compound is not genotoxic.

In view of the overall evidence for nongenotoxicity and evidence for a saturable metabolic pathway leading to kidney tumours in rats, it is appropriate to use a NOAEL with a suitable uncertainty factor for calculation of the TDI. A 6-week gavage study in male mice and and a 90-day drinking-water study in male and female rats both indicated a NOAEL for hepatotoxic effects of 14 mg/kg of body weight per day (*23,27*). A TDI of 14 µg/kg of body weight was calculated by applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for carcinogenic potential). In view of the database on tetrachloroethene and considerations regarding the application of the dose via drinking-water in one of the two critical studies, it was deemed unnecessary to include an additional uncertainty factor to reflect the length of the study. The guideline value is 40 µg/litre (rounded figure) for a drinking-water contribution of 10%.

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