WHO/SDE/WSH/03.04/36
English only

1,3-Dichloropropene in Drinking-water

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

Originally published in **Guidelines for drinking-water quality,** 2nd ed. Vol.2. *Health criteria and other supporting information.* World Health Organization, Geneva, 1996.

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.

Acknowledgements

The work of the following coordinators was crucial in the development of this background document for development of WHO *Guidelines for drinking-water quality*:

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The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom of Great Britain and Northern Ireland and United States of America.

GENERAL DESCRIPTION

Identity

Compound	*CAS no.*
Isomer mixture	542-75-6
cis-Isomer	10061-01-5
trans-Isomer	10061-02-6

The molecular formula is $C_3H_4Cl_2$.

Physicochemical properties *(1,2)* [Data also from Dow Chemical Company. Conversion factor in air: 1 ppm = 4.54 mg/m^3]

Property	*cis-Isomer*	*trans-Isomer*
Boiling point (°C)	104	112
Density at 25 °C (g/cm^3)	1.22	1.22
Vapour pressure at 25 °C (kPa)	5.7	4.5
Water solubility at 25 °C (g/litre)	2.7	2.8
Log octanol–water partition coefficient	1.6	1.6

Major uses

1,3-Dichloropropene is a broad-spectrum soil fumigant used primarily for nematode control on crops grown in sandy soils.

Environmental fate

1,3-Dichloropropene is released to the environment when used as a fumigant. It volatilizes from both soil and surface waters to the atmosphere, where it can be photolytically degraded. Hydrolysis and microbial biodegradation also remove it from the environment (*2*).

ANALYTICAL METHODS

EPA Methods 524.2 (*3*) and 502.2 (*4*), which are standard purge-and-trap capillary-column gas chromatographic techniques for volatile organic compounds in water, should be suitable for the analysis of 1,3-dichloropropene. The detection limits for the compound are believed to range from 0.02 to 0.05 µg/litre.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

1,3-Dichloropropene was found in 41 of 1088 surface water samples and in 10 of 3949 groundwater samples in the USA. The 85th percentile values for all samples containing detectable levels of 1,3-dichloropropene were 1.3 µg/litre in surface water and 3.4 µg/litre in groundwater [STORET water quality file. US Environmental Protection Agency, Office of Water (data file search conducted in May 1988)]. These data have not been validated and must therefore be accepted with caution.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

1,3-Dichloropropene is absorbed through skin and respiratory and gastrointestinal systems (*1*). Oral administration in rats resulted in approximately 90% absorption of the administered

dose (*5*). Both *cis*- and *trans*-1,3-dichloropropene administered orally in rats were excreted primarily in the urine in 24–48 h (*5,6*). *cis*-1,3-Dichloropropene is probably biotransformed into an intermediate glutathione conjugate, and then follows the mercapturic acid pathway, and is excreted in the urine as a cysteine derivative. The main urinary metabolite (92%) of *cis*-1,3-dichloropropene was *N*-acetyl-*S*-[(*cis*)-3-chloroprop-2-enyl]cysteine (*6*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

The acute oral LD_{50}s of 1,3-dichloropropene in male and female rats are 713 and 740 mg/kg of body weight, respectively (*7*). In mice, the oral LD_{50} is 640 mg/kg of body weight. The dermal LD_{50} in rabbits ranges from 504 to 2100 mg/kg of body weight (*8*).

Short-term exposure

Exposure of rats to 1,3-dichloropropene by gavage (10 or 30 mg/kg, 6 days per week, for 13 weeks) resulted in increased kidney weight (*9*). Exposure by inhalation to 13.6 mg/m^3, 7 h per day, 5 days per week, for 6 months, resulted in discoloration of kidney and swelling of renal tubular epithelium (*7*).

Long-term exposure

Hyperplasia of the urinary bladder epithelium was observed as a result of inhalation exposure of $B6C3F_1$ mice to 1,3-dichloropropene at doses of 91 or 270 mg/m^3, 6 h per day, 5 days per week for 24 months (*10*). Hyperplasia of the urinary bladder epithelium and kidney hydronephrosis were seen in $B6C3F_1$ mice after gavage exposure to Telone II (in which 1,3-dichloropropene is the active ingredient) in corn oil at doses of 0, 50, or 100 mg/kg of body weight, 3 times per week for 104 weeks (*11*).

Reproductive toxicity, embryotoxicity, and teratogenicity

No studies on the reproductive toxicity of 1,3-dichloropropene by the oral route of administration are available. In a study in which male and female Wistar rats were exposed to technical D-D (28% *cis* isomer, 27% *trans* isomer) by inhalation at 0, 64, 145, or 443 mg/m^3 for 10 weeks, male and female mating, fertility, and reproductive indices were unaffected, litter sizes and weights were normal, and pup survival over 4 days was not affected (*12*). In a study of the effects of inhalation exposure to 1,3-dichloropropene on fetal development, pregnant Fischer 344 rats were exposed to 0, 91, 270, or 540 mg/m^3 1,3-dichloropropene for 6 h per day on gestation days 6–15. Effects included dose-related depression of maternal body weight gain, significant depression of feed consumption, decreases in water consumption at 540 mg/m^3, and significant increases in relative kidney weights and decreases in absolute liver weights at 270 mg/m^3 (*13*).

Mutagenicity and related end-points

Tests of commercial formulations containing 1,3-dichloropropene or a mixture of pure *cis*- and *trans*-1,3-dichloropropene (*14*), and pure *cis*-1,3-dichloropropene (*15*) were positive in *Salmonella typhimurium* strains TA1535 and TA100 with and without metabolic activation, indicating that 1,3-dichloropropene is a direct-acting mutagen. Positive results have also been reported in TA1978 (with and without metabolic activation) for a commercial mixture of 1,3-dichloropropene and a mixture of the pure isomers (*14*). 1,3-Dichloropropene was negative in a reverse-mutation assay with *Escherichia coli* B/r Wp2 and in the mouse host-mediated test with *S. typhimurium* G46 (*16*).

Carcinogenicity

F344 rats were gavaged 3 times per week with Telone II in corn oil at doses of 0, 25, or 50 mg/kg of body weight (77 per sex per dose: 52 per sex per dose gavaged for 104 weeks in the main carcinogenicity study, plus 5 per sex per dose sacrificed after 9, 16, 21, 24, and 27 months of exposure to 1,3-dichloropropene in an ancillary study). There was no increase in mortality in treated animals. Neoplastic lesions included squamous cell papillomas of the forestomach (male rats: 1/52; 1/52; 9/52; female rats: 0/52; 2/52; 3/52), squamous cell carcinomas of the forestomach (male rats: 0/52; 0/52; 4/52), and neoplastic nodules of the liver (male rats: 1/52; 6/52; 7/52). The increased incidence of forestomach tumors was accompanied by a positive trend for forestomach basal cell hyperplasia in male and female rats of both treated groups. The highest dose level tested in rats (50 mg/kg of body weight) was approximately the maximum tolerated dose level (*11*).

$B6C3F_1$ mice (50 per sex per dose) were gavaged with Telone II in corn oil at doses of 0, 50, or 100 mg/kg of body weight, three times per week for 104 weeks. Because of excessive mortality from myocardial inflammation in control male mice approximately 1 year after the initiation of the study, conclusions concerning carcinogenicity were based on concurrent and National Toxicology Program (NTP) historical control data. Neoplastic lesions in female mice included squamous cell papillomas of the forestomach (0/50; 1/50; 2/50), squamous cell carcinomas of the forestomach (0/50; 0/50; 2/50), transitional-cell carcinomas of the urinary bladder (0/50; 8/50; 21/48), and alveolar/bronchiolar adenomas (0/50; 3/50; 8/50). The increased incidence of forestomach tumours was accompanied by an increased incidence of stomach epithelial cell hyperplasia in males and females at 100 mg/kg of body weight, and the increased incidence of transitional-cell carcinoma of the urinary bladder was accompanied by a positive trend for bladder hyperplasia in male and female mice of both treated groups. Incidences of neoplasms were not significantly increased in male mice (*11*).

In the NTP gavage studies (*11*), epichlorohydrin (1%), which can cause papillomas, carcinomas, and hyperplasia of the forestomach (*17*), was added as a stabilizer. It is possible that the gavage dosing procedure adopted in the NTP study produced epichlorohydrin concentrations at the site of application similar to those in the drinking-water study (*17*), albeit for much shorter periods. If this is true, it is possible that epichlorohydrin was involved in the development of the papillomas and carcinomas of the forestomach during the NTP study.

Exposure of Fischer 344 rats for 2 years to vapours of Telone II (0, 23, 91, and 270 mg/m^3) did not result in increases in tumour incidence (*18*). The only tumorigenic effect of a similar exposure of $B6C3F_1$ mice was an increased incidence in benign lung tumours (bronchioloalveolar adenomas) in males exposed to 270 mg/m^3 (*10*).

EFFECTS ON HUMANS

The only known human fatality occurred a few hours after the accidental ingestion of a D-D mixture at an unknown dosage. The symptoms were abdominal pain, vomiting, muscle twitching, and pulmonary oedema. Treatment by gastric lavage failed. Inhalation of 1,3-dichloropropene at concentrations above 6.8 g/m^3 resulted in gasping, coughing, substernal pain, and extreme respiratory distress (*19*).

A total of 64 male workers exposed to three compounds, including 1,3-dichloropropene, were evaluated to determine whether fertility was adversely affected. The exposed study population was divided into groups with up to 5 and more than 5 years of exposure. Sperm counts and percentage of normal sperm forms were the major variables evaluated. No adverse effects on fertility were observed *(20)*, but the study participation rate for the exposed group was only 64%.

GUIDELINE VALUE

IARC concluded that there was sufficient evidence for the carcinogenicity of 1,3-dichloropropene in experimental animals to classify it in Group 2B (possible human carcinogen) (*21*). It is also a direct-acting mutagen. Based on observation of lung and bladder tumours in female mice in a 2-year NTP gavage study (*11*) and using the linearized multistage model, the drinking-water concentrations (and hence the guideline values) associated with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} are estimated to be 200, 20, and 2 µg/litre, respectively.

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