

1,2-Dichloropropane (1,2-DCP) 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 coordinators was crucial in the development of this document and others in the Addendum:

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

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GENERAL DESCRIPTION

Identity

CAS no.: 78-87-5

Molecular formula: C₃H₆Cl₂

Physicochemical properties (WHO, 1993) [Conversion factor in air: 1 mg/m³ = 0.214 ppm]

<i>Property</i>	<i>Value</i>
Boiling point	96.8°C
Melting point	-100°C
Density	1.1595 g/cm ³ at 20°C
Vapour pressure	27.9 kPa at 19.6°C
Water solubility	2700 mg/litre at 20°C
Log octanol–water partition coefficient	1.99

Organoleptic properties

1,2-DCP has a chloroform-like odour. The odour threshold in water is 10 µ/litre.

Major uses

1,2-DCP is used primarily as an intermediate in the production of perchloroethylene and other chlorinated products (ATSDR, 1989). It is also used as a solvent for fats, oils, resins, waxes, and rubber, as an insecticide fumigant on grain and soil, and to control peach tree borers. Other uses are as dry cleaning fluid, paint remover, metal degreasing agent, and lead scavenger for antiknock fluids. 1,2-DCP is also a component of "MIX D/D," used as a pre-plant fumigant (WHO, 1993, 1996).

Environmental fate

The decomposition of 1,2-DCP in the atmosphere is rather slow; on the basis of reaction with hydroxyl radicals, the half-life of 1,2-DCP was >23 days. Phototransformation is likely to be the predominant process for the decomposition of 1,2-DCP, but vapour-phase photolysis was not detected after prolonged simulated sunlight irradiation in a reaction chamber (WHO, 1993, 1996).

In water, 1,2-DCP is relatively resistant to hydrolysis and has a half-life of 175–1400 days (WHO, 1993). No biodegradation was observed in a semi-continuous activated sludge process, and there was also no biodegradation in standard 4-week tests that simulate biodegradation in environmental waters (ATSDR, 1989). Volatilization is likely to be the major route of loss from water. The relatively low soil adsorption coefficient as well as the high water solubility suggest that 1,2-DCP is not appreciably adsorbed onto soil but migrates from it to groundwater. 1,2-DCP is persistent in soil. More than 98% of the 1,2-DCP applied to loam soil was recovered 12–20 weeks after treatment. Because of its high water solubility and low octanol–water partition coefficient (log *K_{ow}*), bioaccumulation is unlikely to occur (WHO, 1993, 1996). A bioconcentration factor of 18 is estimated, indicating that there is very low potential for bioaccumulation in the food-chain (ATSDR, 1989).

ANALYTICAL METHODS

1,2-DCP is usually determined by a purge-and-trap gas chromatographic method used for the determination of volatile organohalides in drinking-water. Subsequent thermal desorption is used for its quantification. Confirmatory analysis is done by halide-specific detectors (e.g. Hall electrolytic conductivity detector) and mass spectrometry (detection limit 0.02–0.17 μ /litre) (Lyman et al., 1982; WHO, 1996).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

1,2-DCP was monitored in 13 cities in Japan. Levels in ambient air were reported to range from 0.0065 to 1.4 μ /m³ (WHO, 1993). Levels in 1982 were reported to be non-detectable in rural/remote areas, 0.26 μ /m³ in urban/suburban areas, and 0.55 μ /m³ in source-dominated areas (WHO, 1996). An average concentration of 0.85–3.10 μ /m³ in ambient air was detected in 1981–1982 and 1986–1987 in cities in Germany (BUA, 1996).

Water

In a 1983 study in the USA, 1,2-DCP was found in wells at concentrations up to 440 μ /litre. In another study, 1,2-DCP concentrations as high as 51 μ /litre were found in groundwater (WHO, 1993). In Japan in 1989, 1,2-DCP was detected in 20 out of 78 water samples (river, lake, port, and bay areas), with levels ranging from 0.000 01 to 0.14 μ /litre (WHO, 1993). Levels of 0.7–19.0 μ /litre were found in potable water samples collected in 1990 in eight homes in three communities in Connecticut, USA (WHO, 1993). In the Netherlands in 1995, 1,2-DCP was found in raw drinking-water in 13 out of 169 supplies (range 0.06–2.1 μ /litre) and in drinking-water in 11 out of 52 groundwater supplies (range 0.05–0.12 μ /litre) (Rijkinstituut voor Volksgezondheid en Milieuhygiene [RIVM], Bilthoven, personal communication, 1996). In a waterworks monitoring program in Germany in 1990, 1,2-DCP concentrations of 0.3 μ /litre were found in drinking-water from Schleswig-Holstein (BUA, 1996).

Estimated total exposure and relative contribution of drinking-water

At an air concentration of 0.26 μ /m³, the exposure to 1,2-DCP will be 5.2 μ /day for an adult, assuming an air intake of 20 m³/day. Using the recently measured drinking-water concentrations ranging from 0.05 to 19 μ /litre, the maximal daily exposure for an adult consuming 2 litres of water per day is 38 μ .

KINETICS AND METABOLISM IN LABORATORY ANIMALS

After oral as well as inhalation exposure, 1,2-DCP is rapidly absorbed, metabolized, and excreted. The majority of the radioactivity is excreted within 24 hours. Elimination after oral or inhalation exposure occurs mainly via the urine (37–52%) and expired air (37–40%). It has been suggested that in rats, 1,2-DCP is dechlorinated and oxidized to epoxide intermediates, which are consequently hydrolysed and conjugated to form *N*-acetyl-*S*-(2-hydroxypropyl) cysteine. Three *N*-acetylcysteine conjugates of dichloropropane were identified as the major urinary metabolites after oral or inhalation exposure (Timchalk et al., 1989; WHO, 1996).

EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

1,2-DCP has a low acute toxicity in experimental animals. In rats, oral LD₅₀ values ranged from 1000 to 2000 mg/kg of body weight. The 8-hour LC₅₀ for inhalation is 9520 mg/m³ (ATSDR, 1989). The dermal LD₅₀ after a single application to the skin of rabbits was 8.75 mg/kg of body weight (WHO, 1993, 1996). Single oral doses of 1,2-DCP caused salivation,

lacrimation, dyspnoea, lethargy, reduced motility, haemorrhage in the gastrointestinal tract, haemolytic anaemia, and liver and kidney damage.

1,2-DCP does not cause any skin irritation in rabbits but is slightly irritating to the rabbit eye (BUA, 1996).

Short-term exposure

When rats were exposed to 1,2-DCP in corn oil at 0, 100, 250, 500, or 1000 mg/kg of body weight per day for 1, 5, or 10 days, the liver was the primary target organ. Central nervous system depression, decreased body-weight gain, and increased renal non-protein sulfhydryl levels were seen at 250 mg/kg of body weight per day and higher. Liver damage, as reflected by enzyme changes and morphological alterations, was observed at 500 and 1000 mg/kg of body weight per day. However, rats demonstrated an adaptive resistance to 1,2-DCP over 10 consecutive days of exposure, resulting in hepatic lesions being less severe at 10 days than at 5 days. However, nuclear enlargements in hepatocytes were observed at all dose levels at 5 and 10 days (Bruckner et al., 1989).

In a 13-week study in which male rats were administered 1,2-DCP by gavage in corn oil at 0, 100, 250, 500, or 750 mg/kg of body weight per day for 5 days/week, increased mortality occurred at 500 and 750 mg/kg of body weight per day. Significant growth retardation was observed at all dose levels. Effects indicating haemolytic anaemia, such as decreased haematocrit, decreased haemoglobin concentration, increased serum bilirubin, haemosiderosis and hyperplasia of the erythropoietic elements of the spleen, and increased liver and spleen weights, were observed. At the lowest dose of 100 mg/kg of body weight per day, haemosiderosis and splenic hyperplasia were still present. Relative spleen and liver weights were increased at doses =250 mg/kg of body weight per day. Upon histopathology, changes in the liver were observed, such as mild hepatitis at 750 mg/kg of body weight per day and periportal vacuolization and active fibroplasia at 500 mg/kg of body weight per day. At 500 and 750 mg/kg of body weight per day, testicular degeneration, including reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymis, occurred. A NOAEL could not be established in this study. The LOAEL was 100 mg/kg of body weight per day (71.4 mg/kg of body weight per day when corrected for 5 days/week dosing) (Bruckner et al., 1989).

In 13-week studies in mice and rats, 1,2-DCP was administered by gavage, in corn oil, at dose levels of 0, 30 (mice only), 60, 125, 250, 500, or 1000 (rats only) mg/kg of body weight per day for 5 days/week. Increased mortality was observed in rats at 500 (50%) and 1000 (100%) mg/kg of body weight per day. At 500 mg/kg of body weight per day, mean body weights were decreased 16% in males and 8% in females at the end of the study. High-dose rats showed congestion of the liver in males and females and necrosis and fatty changes in the liver in females. No mortality occurred in mice, and only marginal body-weight depression was seen at the highest dose. No dose-related histological effects were seen (NTP, 1986).

In a neurotoxicity study, F344 rats were administered 1,2-DCP by gavage at dose levels of 0, 20, 65, or 200 mg/kg of body weight per day, 5 days/week for 13 weeks. After 13 weeks, extensive neurohistopathology as well as histopathology of liver, kidneys, and spleen were performed on four rats per group. The remaining 11 rats per group were observed for another 9 weeks, after which 5 rats per group were subjected to gross pathological examination. Male body weight was reduced in rats at 200 mg/kg of body weight per day; the reduction was still evident at the end of the recovery period. No substance-related changes were found in the results of the neurological tests or of the neurohistopathological examination (Johnson & Gorzinski, 1988).

Long-term exposure

Long-term toxicological studies with 1,2-DCP are not available. The available carcinogenicity studies with mice and rats are described below (see section 5.6).

Reproductive and developmental toxicity

Testicular degeneration and an increased number of degenerate spermatogonia in the epididymis were seen in the 13-week oral gavage study in rats described above (see section 5.2) at doses of 500 and 750 mg/kg of body weight per day. The NOAEL for testicular toxicity in this study was 250 mg/kg of body weight per day (179 mg/kg of body weight per day when corrected for 5 days/week dosing) (Bruckner et al., 1989).

In an oral two-generation study, rats were given 1,2-DCP in drinking-water at concentrations of 0, 240, 1000, or 2400 mg/litre (equivalent to 0, 33.6, 140, or 336 mg/kg of body weight per day). A decrease in water consumption (50% less than controls) as well as decreased body-weight gain in parental males and females (both generations) were observed at the highest dose. In F₀ females, red blood cell counts, haemoglobin concentration, and haematocrit were decreased at 2400 mg/litre. In parental males and females, increased hepatocellular granularity was observed at all dose levels. At 2400 mg/litre, neonatal body weight was decreased and neonatal mortality was slightly increased. No treatment-related changes in the reproductive organs or in other reproductive indices, including fertility, mating index, conception index, viable litters, gestation length, litter size, live pups, and sex ratio, were noted. The NOAEL in this study was 1000 mg/litre (equivalent to 140 mg/kg of body weight per day). According to the authors, the increased hepatocellular granularity is considered to be an adaptive change associated with the metabolism of 1,2-DCP and is not an indication of toxicity. Moreover, the US EPA (Kirk et al., 1990) as well as the IPCS (WHO, 1993) mentioned the observed effect but established the same NOAEL of 1000 mg/litre for this study.

Teratogenicity studies are available in rats and rabbits. Rats were administered 1,2-DCP by gavage at doses of 0, 10, 30, or 125 mg/kg of body weight per day on days 6 through 15 of gestation. Toxic effects were seen in dams at the highest dose level (decreases in growth, food consumption, muscle tone, and extensor flux reflex). In fetuses, the incidence of delayed ossification of skull bones was increased at 125 mg/kg of body weight per day. The NOAEL for maternal and fetal effects in the study was 30 mg/kg of body weight per day (Kirk et al., 1995).

Rabbits were dosed by gavage at 0, 15, 50, or 150 mg/kg of body weight per day on days 7 through 19 of gestation. Effects similar to those in the rat study were found: maternal toxicity (anorexia, anaemia) at 150 mg/kg of body weight per day and increased incidence of delayed ossification of skull bones in fetuses at 150 mg/kg of body weight per day. The NOAEL for maternal and fetal effects in rabbits was 50 mg/kg of body weight per day (Kirk et al., 1995).

Although maternal toxicity was apparent in these studies, no indication of teratogenicity was observed in rat or rabbit fetuses at any dose level. Significant increases in the incidence of delayed ossification of skull bones are considered secondary to decreased maternal body-weight gain.

Mutagenicity and related end-points

In *in vitro* mutagenicity studies, 1,2-DCP was positive in *Salmonella typhimurium* strains TA100 and TA1535, both with and without metabolic activation. In the *S. typhimurium* strains TA98, TA1537, and TA1538, no mutagenicity of 1,2-DCP could be detected (BUA, 1996; WHO, 1996). These results indicate that 1,2-DCP can cause base pair substitution.

1,2-DCP was mutagenic in mouse lymphoma cells in the thymidine kinase test and in an *in vitro* test in *Aspergillus nidulans* (forward mutation to 8-azaguanine resistance) (Myhr & Caspary, 1991; WHO, 1996). Negative results were obtained in a test studying the induction of somatic segregation in *Aspergillus nidulans* (Crebelli et al., 1984).

Other *in vitro* studies for sister chromatid exchanges in Chinese hamster ovary cells and V79 cells were positive both without and with metabolic activation, as was a test for chromosomal aberrations in Chinese hamster ovary cells (Galloway et al., 1987; von der Hude et al., 1988).

A test for DNA repair in *S. typhimurium* TA1535 (umu test) yielded negative results both with and without metabolic activation (BUA, 1996). In the SOS chromotest with *Escherichia coli* strain PQ37, 1,2-DCP was not genotoxic in concentrations up to the solubility limit (~2700 mg/litre), either with or without S9 mix (von der Hude et al., 1988). 1,2-DCP (0.1–10 mmol/litre) did not induce unscheduled DNA synthesis in human lymphocytes (Perocco et al., 1983).

Negative results were obtained in two *in vivo* studies: a test for sex-linked recessive lethal mutations in *Drosophila melanogaster* with oral and inhalatory administration and a dominant lethal test in Sprague-Dawley rats, dosed for 14 weeks via drinking-water (WHO, 1993).

Carcinogenicity

Two carcinogenicity studies are available (NTP, 1986). Groups of male and female B6C3F₁ mice and female F344/N rats were administered 1,2-DCP by gavage at 0, 125, or 250 mg/kg of body weight per day, 5 days/week for 103 weeks. Groups of male rats were administered 0, 62, or 125 mg/kg of body weight per day according to the same protocol. Mortality was increased in high-dose female mice and rats. An increased incidence of liver lesions (hepatomegaly, focal and centrilobular necrosis) was observed in male mice at both dose levels. The incidence of hepatocellular tumours (combined adenomas and carcinomas) in treated groups of mice was higher than that in the concurrent control groups, but was within the historical control range.

Female rats in the highest dose group showed decreased survival, and body weight was decreased in both male (14%) and female rats (24%) at the highest dose. In the same group, the incidence of liver lesions (foci of clear cells and necrosis) was increased. The incidence of mammary gland adenocarcinomas was slightly increased in female rats (1/50, 2/50, and 5/50 in the control, low-dose, and high-dose groups, respectively). There were no effects on tumour incidences in male rats.

EFFECTS ON HUMANS

Several cases of acute poisoning resulting from accidental or intentional (suicide) overexposure to 1,2-DCP have been reported. Effects have been mainly on the central nervous system, liver, and kidneys. Haemolytic anaemia and disseminated intravascular coagulation as well as effects on the respiratory system, heart, and blood have also been described (WHO, 1993, 1996).

Several cases of dermatitis and skin sensitization following occupational dermal exposure to solvent mixtures containing 1,2-DCP have been reported (WHO, 1993, 1996).

PROVISIONAL GUIDELINE VALUE

1,2-DCP was evaluated by IARC in 1986 and 1987 based on NTP studies. The substance was classified in Group 3 (not classifiable as to its carcinogenicity to humans) based on limited

evidence for its carcinogenicity to experimental animals and an inability to evaluate its carcinogenicity to humans.

Results from *in vitro* assays for mutagenicity were mixed. The *in vivo* studies, which were limited in number and design, were negative. In accordance with the IARC evaluation, the evidence from the long-term carcinogenicity studies in mice and rats was considered limited, and it was concluded that the use of a threshold approach for the toxicological evaluation of 1,2-DCP was appropriate.

The 13-week toxicity study in which male rats were administered 1,2-DCP by gavage in corn oil for 5 days/week was considered to be the most appropriate study for derivation of a guideline value. A LOAEL of 100 mg/kg of body weight per day (71.4 mg/kg of body weight per day when corrected for 5 days/week dosing) was observed for changes in haematological parameters. Using an uncertainty factor of 5000 (100 for inter- and intraspecies variation, 10 for the use of a LOAEL instead of a NOAEL, and 5 for limitations of the database, including the limited data on *in vivo* genotoxicity and use of a subchronic study), a TDI of 14 µ/kg of body weight is derived. With an allocation of 10% of the TDI to drinking-water and assuming a 60-kg body weight and drinking-water consumption of 2 litres/day, the provisional guideline value is 40 µ/litre (rounded figure). The guideline value is considered to be provisional owing to the magnitude of the uncertainty factor and the fact that the database has not changed since the previous guideline value was derived.

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