

Dichloroacetic Acid 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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Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
IARC	International Agency for Research on Cancer
IUPAC	International Union of Pure and Applied Chemistry
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NEU	nitrosoethylurea
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.:	79-43-6
Molecular formula:	Cl ₂ CHCOOH

The IUPAC name for dichloroacetic acid is dichloroethanoic acid.

1.2 Physicochemical properties¹(Verschuieren, 1977; Weast, 1988; Budavari et al., 1989)

<i>Property</i>	<i>Value</i>
Boiling point (°C)	194
Melting point (°C)	13.5
Density (g/cm ³)	1.56 at 20 °C
Vapour pressure (kPa)	0.133 at 44 °C
Water solubility (g/litre)	86.3
Log octanol–water partition coefficient	0.14

1.3 Organoleptic properties

No information is available on the taste or odour threshold of dichloroacetic acid in water.

1.4 Major uses

Dichloroacetic acid is used as a chemical intermediate in the synthesis of organic materials, as an ingredient in pharmaceuticals and medicines, as a topical astringent and as a fungicide (Verschuieren, 1977; Hawley, 1981; Budavari et al., 1989; Meister, 1989).

2. ANALYTICAL METHODS

The chloroacetic acids can be determined by either EPA Method 515.1 or draft EPA Method 552, which was developed for non-pesticidal haloacids and phenols (i.e., by capillary column/electron capture/gas chromatography). Data from a monitoring study of water supplies indicate that detection levels of 1 µg/litre are achievable.

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Chlorinated acetic acids are formed from organic material during water chlorination (Coleman et al., 1980); typical levels in finished drinking-water supplies range from

¹ Conversion factor in air: 1 ppm = 5.27 mg/m³.

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30 to 160 µg/litre (Jolley, 1985). Dichloroacetic acid was found in the distribution systems of six water supply companies at concentrations ranging from 8 to 79 µg/litre; it was detected in the finished water of 10 of 10 companies surveyed and at levels of 10 µg/litre or higher at 8 of them (Stevens et al., 1990).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Plasma dichloroacetic acid concentrations peaked in rats 30 min after dosing by gavage, suggesting rapid intestinal absorption (Stacpoole et al., 1987). Levels in liver and muscle increased following administration (Evans, 1982). In rats, dogs and humans given sodium dichloroacetate intravenously, average half-lives of the parent compound in the plasma were 2.97, 20.8 and 0.43 h, respectively; the apparent dose dependence of plasma clearance suggests that metabolic transformation becomes rate-limiting at high doses (Lukas et al., 1980). In the rat, dichloroacetate is rapidly metabolized by dechlorination to glyoxalate, which in turn is metabolized to oxalate (Crabb et al., 1981). In humans, urinary excretion of unchanged dichloroacetate was negligible after 8 h, and cumulative excretion was less than 1% of the total dose in all subjects (Lukas et al., 1980).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

LD₅₀s of 4480 and 5520 mg of dichloroacetic acid per kg of body weight have been reported in rats and mice, respectively (Woodard et al., 1941).

5.2 Short-term exposure

In a study in which Sprague-Dawley rats (five per sex per group) were given water containing 0, 30, 125, 500 or 1875 mg of dichloroacetate per litre (0, 2.4, 10, 40 or 150 mg/kg of body weight per day) for 14 days, none of the parameters monitored (e.g., body weight, lactate and pyruvate levels, blood glucose levels) was significantly altered. In this study, a NOAEL of 150 mg/kg of body weight per day was identified (Davis, 1986).

In a study in which sodium dichloroacetate was administered to Sprague-Dawley rats (10 per sex per dose) by gavage at dose levels of 0, 125, 500 or 2000 mg/kg of body weight per day for 3 months, body weight gain was significantly depressed in a dose-dependent manner at all dose levels. Minimal effects on haematological parameters were observed at the two highest doses. Mean relative weights of liver, kidneys and adrenals were significantly increased in a dose-dependent fashion. Brain and testes were the principal target organs; brain lesions characterized by vacuolation of the myelinated white tracts resembling oedema were observed in the cerebrum and cerebellum of treated rats of both sexes in all dose groups. Based on effects on organ weights and brain lesions, a LOAEL of 125 mg/kg of body weight per day, the lowest dose tested, was identified in this study (Katz et al., 1978, 1981).

Beagle dogs were given sodium dichloroacetate by capsule at 50, 75 or 100 mg/kg of body weight per day for 13 weeks. Both sexes exhibited dose-dependent weight losses. All dose levels were associated with a progressive depression in erythrocyte counts, erythrocyte volume fraction (haematocrit) and haemoglobin levels. Mean blood glucose, lactate and pyruvate levels were significantly reduced in all treated animals. There was an increased incidence of lung consolidation among treated dogs. Histopathological examination indicated that all treated dogs suffered slight to moderate vacuolation of white myelinated tracts in the cerebrum and to a lesser extent in the cerebellum. There was an increased incidence of haemosiderin-laden Kupffer's cells in the liver and cystic mucosal hyperplasia in the gallbladder at all dose levels. A LOAEL of 50 mg/kg of body weight per day can be identified from this study (Katz et al., 1978, 1981).

5.3 Long-term exposure

Male B6C3F₁ mice (50 per dose) received dichloroacetate in their drinking-water at 0, 0.05, 0.5, 3.5 or 5.0 g/litre (0, 7.6, 77, 410 or 486 mg/kg of body weight per day) for 60 weeks. Other groups of mice received dichloroacetate at 7.6 or 77 mg/kg of body weight per day for 75 weeks. In the highest-dose mice, water consumption was reduced to 60% of that of controls. Body weight was decreased at the two highest dose levels, and relative liver weight was increased at the three highest dose levels. An increase in kidney weight was seen only at 410 mg/kg of body weight per day. No effects were seen on testes or spleen weight. The NOAEL for the 60- and 75-week studies was 7.6 mg/kg of body weight per day (DeAngelo et al., 1991).

5.4 Mutagenicity and related end-points

Dichloroacetic acid was reported to cause strand breaks in DNA when administered *in vivo* to rats and mice in one study (Nelson & Bull, 1988) but not in a second study at higher doses (Chang et al., 1989).

5.5 Carcinogenicity

The carcinogenic potential of dichloroacetate was investigated in B6C3F₁ mice (50 males per dose) that received this compound in their drinking-water for 60 weeks at concentrations of 0, 0.05, 0.5, 3.5 or 5.0 g/litre (0, 7.6, 77, 410 and 486 mg/kg of body weight per day). Other groups of mice received dichloroacetate at 7.6 or 77 mg/kg of body weight per day for 75 weeks. Hyperplastic nodules were seen in 58% of the mice that received 410 mg/kg of body weight per day and in 83% of the mice that received 486 mg/kg of body weight per day. The incidences of hepatocellular adenomas were 100% and 80%, and those of hepatocellular carcinomas 67% and 83%, respectively. Incidences in the other dose groups were similar to those in controls (DeAngelo et al., 1991).

The carcinogenic potential of dichloroacetic acid in mice was investigated in a complex regimen that included pretreatment with nitrosoethylurea (NEU) at various

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doses. Male B6C3F₁ mice were supplied with drinking-water containing 0, 2000 or 5000 mg of dichloroacetate per litre (0, 400 or 1000 mg/kg of body weight per day). Non-initiation protocols (without NEU) were used only at the high dose level. The incidence of hepatocellular carcinomas was 0% in the control group (no NEU or dichloroacetic acid) and 81% at 1000 mg/kg of body weight per day (no NEU). With dichloroacetic acid and a low dose of NEU, the tumour incidences were 66–72% for the high and low doses. The authors concluded that dichloroacetic acid was carcinogenic at a dose of 1000 mg/kg of body weight per day without prior initiation (Herren-Freund & Pereira, 1986).

Dichloroacetic acid exposure via drinking-water resulted in the induction of liver tumours in male B6C3F₁ mice. Groups of mice received dichloroacetic acid at 0, 1 or 2 g/litre (approximately 0, 137 or 295 mg/kg of body weight per day, based on the authors' calculations of total dose for each group) for 37 or 52 weeks. Hepatocellular carcinomas were seen only in 5 of 24 males (21%) that received the highest dose for 52 weeks (Bull et al., 1990).

6. EFFECTS ON HUMANS

Diabetic or hyperlipoproteinaemic patients received a daily oral dose of 3–4 g of dichloroacetate for 6–7 days. Some patients experienced mild sedation, but no other laboratory or clinical evidence of adverse effects was noted during or immediately after the treatment phase. Biochemical effects included significantly reduced fasting blood glucose levels, marked decreases in plasma lactate and alanine, significantly decreased plasma cholesterol levels, decreased triglyceride levels, elevated plasma ketone bodies and elevated serum uric acid levels (Stacpoole et al., 1978).

Daily oral doses of 50 mg of dichloroacetate per kg of body weight were administered to two young males to treat severe familial hypercholesterolaemia (Moore et al., 1979). In both patients, total serum cholesterol levels decreased significantly. No adverse clinical or laboratory signs were detected in one patient, but the second complained of tingling in his fingers and toes after 16 weeks. Physical examination revealed slight decreases in the strength of facial and finger muscles, diminished to absent deep tendon reflexes and decreased strength in all muscle groups of the lower extremities. Electromyographic studies revealed denervation changes in foot and distal leg muscles. Mild slowing of conduction velocity was noted in both posterior tibial nerves, and no measurable response was obtained in the peroneal or sural nerves. Six months after discontinuation of the treatment, the neuropathic effects had improved, although serum cholesterol levels returned to high levels (Stacpoole et al., 1979).

7. PROVISIONAL GUIDELINE VALUE

In several bioassays, dichloroacetate has been shown to induce hepatic tumours in mice. No adequate data on genotoxicity are available. Because the evidence for the carcinogenicity of dichloroacetate is insufficient, a TDI of 7.6 µg/kg of body weight was calculated based on a study in which no effects were seen on the livers of mice

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exposed to dichloroacetate at 7.6 mg/kg of body weight per day for 75 weeks (DeAngelo et al., 1991) and incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity). With an allocation of 20% of the TDI to drinking-water, the provisional guideline value is 50 µg/litre (rounded figure).

The guideline value is designated as provisional because the data are insufficient to ensure that the value is technically achievable. Difficulties in meeting a guideline value must never be a reason to compromise adequate disinfection.

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