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1,2-Dichloroethane in Drinking-water

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

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
cDNA	complementary DNA
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
IARC	International Agency for Research on Cancer
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOEL	lowest-observed-effect level
NOEL	no-observed-effect level
RNA	ribonucleic acid
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	107-06-2
Molecular formula:	$C_2H_4Cl_2$

1,2-Dichloroethane is also known as ethylene dichloride.

1.2 Physicochemical properties[1] *(IPCS, 1995)*

Property	*Value*
Melting point	-35 °C
Boiling point	83 °C
Density	1.23 g/cm^3 at 20 °C
Vapour pressure	8.53 kPa at 20 °C
Water solubility	8.69 g/litre at 20 °C
Log octanol–water partition coefficient	1.48

1.3 Organoleptic properties

The odour thresholds for 1,2-dichloroethane in air and water are 356 mg/m^3 and 7 mg/litre, respectively (Amoore & Hautala, 1983).

1.4 Major uses

US production of 1,2-dichloroethane was about 14.5 million tonnes in 1994 (ATSDR, 1999). The major use (about 90%) of 1,2-dichloroethane is in the production of vinyl chloride. 1,2-Dichloroethane is also used as an extraction and cleaning solvent, in the synthesis of other chlorinated solvents and as a lead scavenger in leaded petrol, although this use has declined with the phase-out of leaded petrol (IPCS, 1995). It is no longer registered as a fumigant on agricultural products in many countries. 1,2-Dichloroethane may also be released to the environment from the microbial degradation of other chlorinated alkanes (e.g., 1,1,2,2-tetrachloroethane) (ATSDR, 1999).

1.5 Environmental fate

1,2-Dichloroethane released to the environment volatilizes to the atmosphere. It is moderately persistent in air, with an estimated atmospheric lifetime between 43 and 111 days. In the troposphere, it undergoes photo-oxidation. Any 1,2-dichloroethane reaching the stratosphere may be photolysed to produce chlorine radicals, which may in turn react with ozone, but 1,2-dichloroethane is not expected to contribute significantly to the depletion of the stratospheric ozone layer (IPCS, 1995). 1,2-Dichloroethane may enter surface waters via effluents from industries that

[1] Conversion factor in air: 1 ppm = 4.05 mg/m^3.

manufacture or use the substance. Further, it may enter the atmosphere or groundwater following disposal in waste sites (IPCS, 1995). Biodegradation is not expected to be significant in aquatic systems (IPCS, 1998). 1,2-Dichloroethane may persist for long periods in groundwater, where volatilization is restricted (ATSDR, 1999).

2. ANALYTICAL METHODS

A purge-and-trap gas chromatographic procedure is used for the determination of 1,2-dichloroethane and other volatile organohalides in drinking-water (IPCS, 1995; ATSDR, 1999). Detection limits were given as 0.03 µg/litre for gas chromatography with photoionization detection (EPA Method 8021B) (ATSDR, 1999). Confirmatory analysis is by mass spectrometry, the detection limit being 0.06 µg/litre (EPA Method 8260B) (ATSDR, 1999).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Mean concentrations of 1,2-dichloroethane in surveys of ambient air in non-source-dominated areas in cities are 0.07–0.28 µg/m^3 in Canada, <0.004–3.8 µg/m^3 in Japan and 1.2 µg/m^3 in the United Kingdom and the Netherlands. Earlier surveys in the USA reported mean levels of 0.33–6.05 µg/m^3; however, peak levels near chemical manufacturing plants have ranged as high as 736 µg/m^3 (US EPA, 1985). Mean levels in residential indoor air are reported to be <0.1 µg/m^3 in Canada, 0.1–0.5 µg/m^3 in the USA (although one survey gave mean values of 20 µg/m^3) and 3.4 µg/m^3 in the Netherlands (IPCS, 1995, 1998; ATSDR, 1999).

3.2 Water

1,2-Dichloroethane is frequently detected in surface water, in particular near industrialized areas (IPCS, 1995; ATSDR, 1999). Typical background levels of 1,2-dichloroethane in non-industrialized areas are in general below 0.5 µg/litre (De Rooij et al., 1998). 1,2-Dichloroethane was detected in 26% of the river samples from Osaka, Japan, at a mean concentration of 0.09 µg/litre (Yamamoto et al., 1997). It was also detected in the River Rhine, Germany, at concentrations up to 5 µg/litre, in the River Elbe, Germany, at 0.03–1.27 µg/litre (mean 0.1 µg/litre) (Goetz et al., 1998) and in the Tees estuary in England at 0.7–4.0 µg/litre, the highest levels being in the vicinity of a 1,2-dichloroethane/vinyl chloride factory (Dawes & Waldock, 1994).

1,2-Dichloroethane has frequently been detected in the µg/litre range in the groundwater near waste disposal sites in several countries (ATSDR, 1999). Maximum values in the mg/litre range have also been reported (Lee et al., 1995; ATSDR, 1999).

1,2-Dichloroethane has been detected in drinking-water samples from a number of urban and rural locations in the USA, in particular from well water supplies, with maximum concentrations up to 24 µg/litre (ATSDR, 1999). In a study on drinking-

water in Taiwan, mean concentrations of 1,2-dichloroethane were reported as 18 µg/litre in tap water, 7 µg/litre in underground water, 3 µg/litre in mountain water and 59 µg/litre in bottled mineral water (Kuo et al., 1997a). About 90% of the surveyed households did not use tap water as a direct source of drinking-water but used mountain or bottled mineral water (Kuo et al., 1997b).

3.3 Food

In recent market basket surveys in the USA, Canada and Japan, 1,2-dichloroethane was mostly not detected. It was reported in only some samples of cereal, butter, cake, ice cream and milk at low ng/g levels or less (Daft, 1991; Heikes et al., 1995; IPCS, 1995; Miyahara et al., 1995; ATSDR, 1999). As 1,2-dichloroethane has low potential for bioaccumulation, food is unlikely to be a major source of exposure (IPCS, 1998).

3.4 Estimated total exposure and relative contribution of drinking-water

The greatest exposure of the general population is usually from the inhalation of ambient air (ATSDR, 1999). Exposure from drinking-water may be important in some countries and may exceed exposure by inhalation (ATSDR, 1999). Volatilization of 1,2-dichloroethane from water during showering or other water uses and from consumer products (cleaning agents, wallpaper and carpet glue) may also contribute to inhalation exposure.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

1,2-Dichloroethane is readily absorbed through the lungs, skin and gastrointestinal tract by both humans (Luznikov et al., 1985) and laboratory animals, and it appears to be readily distributed (IPCS, 1995; IARC, 1999). 1,2-Dichloroethane appears in the placenta, and it has been detected in human milk following occupational exposure (IPCS, 1995; IARC, 1999).

Available data suggest that 1,2-dichloroethane is metabolized via two principal pathways. The first involves a saturable microsomal oxidation mediated by cytochrome P-450 to 2-chloroacetaldehyde and 2-chloroethanol, followed by conjugation with glutathione. The second pathway entails direct conjugation with glutathione to form *S*-(2-chloroethyl)-glutathione, which may be non-enzymatically converted to a glutathione episulfonium ion; this ion can form adducts with proteins, DNA or RNA. Although DNA damage has been induced by the P-450 pathway *in vitro*, several lines of evidence indicate that the glutathione conjugation pathway is probably of greater significance than the P-450 pathway as the major route for DNA damage (IPCS, 1998; IARC, 1999). The major urinary metabolites identified in rats by administration by gavage or by inhalation were thiodiacetic acid (67–68%) and thiodiacetic acid sulfoxide (26–29%), and the rate of elimination was rapid (Reitz et al., 1982).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

1,2-Dichloroethane is moderately acutely toxic in experimental animals. For example, LC_{50}s for rats exposed by inhalation for 6 or 7.25 h ranged from 4000 to 6600 mg/m^3, whereas oral LD_{50}s for rats, mice, dogs and rabbits ranged from 413 to 2500 mg/kg of body weight (IPCS, 1995, 1998).

5.2 Short-term exposure

No significant changes in organ or body weights, histology or clinical chemistry and haematological parameters were observed in rats administered 1,2-dichloroethane doses of up to 150 mg/kg of body weight in corn oil by gavage, 5 times per week for 2 weeks (van Esch et al., 1977; Reitz et al., 1982).

The results of subchronic studies in several species of experimental animals indicate that the liver and kidneys are the target organs of 1,2-dichloroethane exposure; however, most of these studies were inadequate to serve as a basis for establishing reliable NOELs or LOELs, generally because of the inadequate documentation and the limited range of end-points examined in small groups of animals (IPCS, 1998).

Increases in relative liver weight have been observed in rats following subchronic oral administration of doses of 49–82 mg/kg of body weight per day and above for 13 weeks (van Esch et al., 1977; NTP, 1991).

In a 13-week study in which 1,2-dichloroethane was administered in drinking-water, no histological evidence of toxicity was observed in male Fischer 344/N rats or Osborne-Mendel or Sprague-Dawley rats of either sex at the highest dose used (8000 mg/litre, corresponding to 515–727 mg/kg of body weight per day). Minimal histological damage was observed in the kidney of female Fischer 344/N rats. Equivalent doses (up to 480 mg/kg of body weight) given by gavage to Fischer 344 rats were more toxic than those given via drinking-water and caused substantial mortality. However, no histological damage to the liver or kidney was observed in the gavage experiments (Morgan et al., 1990; NTP, 1991). The NOEL of 1,2-dichloroethane administered to F344/N rats by gavage was given as 120 and 150 mg/kg of body weight per day in males and females, respectively, based on mortality and chemically related lesions in the forestomach (IPCS, 1995). The doses in drinking-water were not considered high enough to result in biologically significant toxic effects. The NOEL for $B6C3F_1$ mice exposed via drinking-water was considered to be 780 mg/kg of body weight per day (2000 mg/litre) in males, based on kidney lesions, and 2500 mg/kg of body weight per day (4000 mg/litre) in females, based on mortality.

In a 10-day toxicity study, male and female Sprague-Dawley rats (10 per group) were given 1,2-dichloroethane at dose levels of 10, 30, 100 or 300 mg/kg of body weight per day by gavage. Although 8 of 10 males and all females in the high-dose group

died, no haematological or clinical chemistry changes were observed. The main histopathological lesion exhibited was a minimal multifocal to diffuse inflammation of the mucosal and submucosal layers of the forestomach in the 100 mg/kg of body weight per day dose group. In a 90-day study at dose levels of 37.5, 75 and 150 mg/kg of body weight per day, no treatment-related effect on mortality or gross histopathology was observed. In the 75 and 150 mg/kg of body weight per day groups, there were slight but significant haematological findings and significant increases of relative brain, kidney and liver weights (Daniel et al., 1994).

Mice exposed to 1,2-dichloroethane at 4.9 or 49 mg/kg of body weight per day for 14 days by gavage exhibited a significant depression of leukocyte counts at the higher dose and a significant reduction in the number of antibody-forming cells and inhibition of cell-mediated immunity at both doses. No effects on other haematological parameters, body weights or the hepatic, renal or respiratory system were observed. Mice exposed to 1,2-dichloroethane at time-weighted average doses of 3, 24 or 189 mg/kg of body weight per day for 90 days in drinking-water experienced no significant adverse effects on haematological, immunological, hepatic, renal or respiratory parameters (Munson et al., 1982). Liver changes, including an increase in liver triglycerides and a 15% increase in fat accumulation in the liver, were observed in rats given 1,2-dichloroethane in the diet at 80 mg/kg of body weight per day for 5–7 weeks (Alumot et al., 1976).

5.3 Long-term exposure

Significantly increased mortality was reported in groups of rats and mice exposed to 1,2-dichloroethane by gavage in corn oil for 78 weeks at doses of 95 or 299 mg/kg of body weight per day, respectively (NCI, 1978). No treatment-related effects on growth or biochemical indices were observed in rats exposed to 1,2-dichloroethane at 250 or 500 mg/kg of diet (the higher dose is equivalent to about 26–35 mg/kg of body weight per day) for 2 years (Alumot et al., 1976).

5.4 Reproductive and developmental toxicity

In rats exposed to 1,2-dichloroethane at 250 or 500 mg/kg in the diet for 2 years, no effect was seen on male fertility or on reproductive activity in either sex (Alumot et al., 1976). No reproductive effects, as measured by fertility, gestation, viability or lactation indices, pup survival or weight gain, were found in a multigeneration reproduction study using male and female ICR Swiss mice that received 0, 5, 15 or 50 mg/kg of body weight per day in drinking-water (Lane et al., 1982). In a study in which male and female mice were exposed to 1,2-dichloroethane in drinking-water at doses of 0, 5, 15 or 50 mg/kg of body weight per day, no statistically significant developmental effects, as indicated by the incidence of fetal visceral or skeletal anomalies, were observed (Lane et al., 1982).

Administration of 1,2-dichloroethane be gavage (up to 2.4 mmol/kg of body weight per day) or by inhalation (up to 1200 mg/m^3) for 6 h per day on days 6 through 20 of gestation induced no embryo- or fetotoxicity, changes in fetal growth or teratological

effects. Maternal toxicity, as indicated by smaller weight gain, was observed at the highest inhalation dose level and the two highest oral dose levels (Payan et al., 1995; IARC, 1999).

5.5 Immunological effects

Effects on antibody levels and reversible effects on cell-mediated responses were noted in mice exposed to 1,2-dichloroethane in drinking-water at concentrations equivalent to doses of 3 mg/kg of body weight per day and above for 14 or 90 days (Munson et al., 1982).

5.6 Mutagenicity and related end-points

1,2-Dichloroethane has been consistently demonstrated to be genotoxic in numerous *in vitro* and *in vivo* assays for a wide range of end-points. It has been mutagenic in *Salmonella typhimurium*, especially in the presence of an exogenous activation system, and induces unscheduled DNA synthesis, induces gene mutation and forms adducts with DNA in mammalian cells *in vitro*. It binds to DNA in all reported *in vivo* studies in rats and mice. 1,2-Dichloroethane has also induced somatic cell and sex-linked recessive lethal mutations in *Drosophila melanogaster* (IPCS, 1995, 1998).

In a single study, 1,2-dichloroethane induced mainly micronuclei not staining for the presence of kinetochore (indicative of aneuploidy) in human MCL-5 cells that stably express cDNAs encoding human CYP1A2, CYP2A6, CYP3A4, CYP2E1 and epoxide hydrolase and in h2E1 cells, which contain a cDNA for CYP2E1. AHH-1 cells constitutively expressing CYP1A1 showed an increase in the frequency only of non-kinetochore-staining micronuclei (Doherty et al., 1996). 1,2-Dichloroethane induced DNA damage in all seven mouse organs tested by the alkaline single-cell gel electrophoresis (comet) assay (Sasaki et al., 1998).

5.7 Carcinogenicity

1,2-Dichloroethane administered by gavage to Osborne-Mendel rats (time-weighted average doses of 47 or 95 mg/kg of body weight per day) and B6C3F_1 mice (time-weighted average doses of 97 or 195 mg/kg of body weight per day in males and 149 or 299 mg/kg of body weight per day in females), 5 days per week for 78 weeks, was reportedly carcinogenic to both species (NCI, 1978). Statistically significant increases in the incidence of squamous cell carcinomas of the forestomach and haemangiosarcomas of the circulatory system were observed in male rats, and female rats showed a statistically significant increased incidence of adenocarcinoma of the mammary glands. Statistically significant increases in the incidence of mammary adenocarcinomas and endometrial stromal polyps or sarcomas were seen in female mice, and the incidence of alveolar/bronchiolar adenomas was increased in male and female mice.

In a bioassay in which 1,2-dichloroethane was administered in drinking-water to male B6C3F_1 mice at concentrations of 835 or 2500 mg/litre (the higher dose is equivalent

to about 470 mg/kg of body weight per day) for 52 weeks, either alone or following initiation with diethylnitrosamine (Klaunig et al., 1986), no increase was seen in the incidence of tumours compared with controls. However, this was not a lifetime study, and there was a high incidence of spontaneous tumours in the controls. In addition, 1,2-dichloroethane appears to be more toxic by gavage than by exposure to drinking-water (Munson et al., 1982).

Carcinogenicity bioassays using oral exposure resulted in an increase in the incidence of tumours at several sites.

6. EFFECTS ON HUMANS

Deaths due to ingestion or inhalation of 1,2-dichloroethane in humans have been attributed to circulatory and respiratory failure; repeated exposures in the occupational environment have been associated with anorexia, nausea, abdominal pain, irritation of the mucous membranes, dysfunction of liver and kidney and neurological disorders (IARC, 1999).

Five cohort studies (Hogstedt et al., 1979; Austin & Schnatter, 1983a; Sweeney et al., 1986; Benson & Teta, 1993; Olsen et al., 1997) and one nested case–control study of brain tumours (Austin & Schnatter, 1983b) have examined the risk of cancer among workers with potential exposure to 1,2-dichloroethane. Excesses of lymphatic and haematopoietic cancers were observed in three studies and of stomach cancer in one study, while an excess of pancreatic cancer was observed in one study. All the cohort studies included workers with potential exposure to multiple agents and were not able to examine the excess risk associated with 1,2-dichloroethane (IARC, 1999). An epidemiological study found a positive association between exposure to 1,2-dichloroethane in public drinking-water and major cardiac defects (Bove, 1996; Bove et al., 1995), but the study population was also simultaneously exposed to elevated levels of many other organic contaminants, and the results should be interpreted with caution (ATSDR, 1999).

Increased lymphocyte sister chromatid exchange frequency has been reported in workers with exposure to levels of 1,2-dichloroethane around 4 mg/m^3 (Cheng et al., 2000).

7. GUIDELINE VALUE

IARC (1999) has classified 1,2-dichloroethane in Group 2B (possible human carcinogen). It has been shown to produce statistically significant increases in a number of tumour types in laboratory animals, including the relatively rare haemangiosarcoma, and the balance of evidence indicates that it is genotoxic. Data indicate that 1,2-dichloroethane is less potent when inhaled.

On the basis of haemangiosarcomas observed in male rats in a 78-week gavage study (NCI, 1978) and applying the linearized multistage model, concentrations in drinking-water of 300, 30 and 3 µg/litre, corresponding to upper-bound excess cancer risks of

10^{-4}, 10^{-5} and 10^{-6}, respectively, were calculated. The guideline value of 30 µg/litre is consistent with the value derived from IPCS (1998), based on a 10^{-5} risk level.

The guideline value is achievable by currently available treatment technologies (e.g., aeration and granular activated carbon).

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