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English only

Epichlorohydrin 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.

Acknowledgements

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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:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

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
ECH	epichlorohydrin
EPA	Environmental Protection Agency (USA)
GC	gas chromatography
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MS	mass spectrometry
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America
USSR	Union of Soviet Socialist Republics

Table of contents

1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	106-89-8
Molecular formula:	C_3H_5ClO

Synonyms of epichlorohydrin (ECH) include 1-chloro-2,3-epoxypropane, 3-chloro-1,2-epoxypropane, 1-chloropropene oxide and 3-chloropropene oxide.

1.2 Physicochemical properties[1] *(IARC, 1976; US EPA, 1987)*

Property	*Value*
Physical state	Colourless liquid
Melting point	-57.2 to -25.6 °C
Boiling point	116.2 °C
Vapour pressure	1.60 kPa at 20 °C
Density	1.18 g/cm^3 at 20 °C
Water solubility	66 g/litre at 20 °C
Log octanol–water partition coefficient	0.26

1.3 Major uses

ECH is used mainly for the manufacture of glycerol and unmodified epoxy resins and, to a lesser extent, in the manufacture of elastomers, water treatment resins, surfactants, ion exchange resins, plasticizers, dyestuffs, pharmaceutical products, oil emulsifiers, lubricants and adhesives (IPCS, 1984).

1.4 Environmental fate

ECH is released to the environment as a result of its manufacture, use, storage, transport and disposal. Its half-lives in neutral, acidic and alkaline solutions at room temperature are 148, 79 and 62 h, respectively. The rate of hydrolysis increases 7-fold when the temperature is raised to 40 °C (von Pringer, 1980).

2. ANALYTICAL METHODS

ECH in water can be determined by a purge-and-trap gas chromatographic/mass spectrometric (GC-MS) procedure (Neu & Sprenger, 1997) (detection limit 0.1 µg/litre) and by gas chromatography with flame ionization (JWWA, 1989) (detection limit 0.01 mg/litre) or electron capture detection (Pesselman & Felt, 1988) (detection limit 0.01 µg/litre). A GC-MS method can be used for the determination of ECH in ambient water and sediment (Japan Environment Agency, 1986) (detection limit 0.5 µg/litre).

[1] Conversion factor: 1 ppm = 3.78 mg/m^3.

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Data on ambient air levels of ECH are extremely limited and relate mainly to occupational exposure. At 100–200 m from a factory discharging ECH into the atmosphere in the former USSR, the airborne ECH concentration ranged from 0.5 to 1.2 mg/m^3. At 400 m, levels in 5 out of 29 samples exceeded 0.2 mg/m^3; at 600 m, ECH was detected (Fomin, 1966; IPCS, 1984).

3.2 Water

ECH can theoretically enter drinking-water supplies through the use of flocculating agents in which there are ECH residues and through leaching from epoxy resin coatings on pipes. No ECH residue was found in water kept in containers coated with epoxy resins (detection limit 3 µg/litre) (van Lierop, 1978).

3.3 Food

Migration into food of ECH used as a cross-linking agent in packing materials and epoxy resins is possible but is expected to be low (IPCS, 1984). No studies on its occurrence in food were identified. The compound has little potential for bioaccumulation in the food-chain (Santodonato et al., 1980).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The pharmacokinetics of ECH have been reviewed by IPCS (1984) and the US EPA (1987). ECH is rapidly and extensively absorbed following oral administration and may be absorbed following both inhalation and dermal exposure (Gingell et al., 1985).

Following oral administration of [^{14}C]ECH to rats, peak tissue levels were reached after 2 h in males and 2–8 h in females, depending on the tissue. The tissues containing the highest levels of radioactivity were the kidneys, liver, pancreas, spleen and adrenal glands. ECH is rapidly removed from blood. It is not likely to accumulate during chronic exposures. Metabolites of ECH, however, are much more persistent and have the potential to accumulate to a small extent during chronic exposures (Gingell et al., 1985).

ECH has two electrophilic centres, C1 and C3, and may thus bind to cellular nucleophiles such as glutathione. This binding is catalysed by glutathione-*S*-epoxide transferase, which causes a considerable increase in reaction rate. The major metabolites in urine were identified as *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine, formed by conjugation with glutathione, and α-chlorohydrin, accounting for about 36% and 4% of the administered dose, respectively (Gingell et al., 1985, 1987).

Following oral administration and inhalation, ECH metabolites are rapidly excreted in the urine and expired air. Urinary excretion is approximately twice that in expired air. Only minor amounts (4%) are excreted in the faeces. Excretion of unmetabolized ECH has not been detected (Gingell et al., 1987).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

ECH is a strong irritant and acutely toxic following oral, percutaneous, subcutaneous and respiratory exposure. Death is due to effects on the central nervous system and the respiratory centre (Freuder & Leake, 1941). Oral LD_{50}s were reported to range from 90 to 260 mg/kg of body weight in rats (US EPA, 1997).

5.2 Long-term exposure

There was a gradual increase in mortality following the oral administration of ECH in water by gavage to weanling Wistar rats of both sexes, 5 days per week for 2 years; clinical symptoms included dyspnoea, weight loss, a decrease in leukocytes and hyperplasia in the forestomach at 2 and 10 mg/kg of body weight per day (Wester et al., 1985).

Lifetime inhalation of ECH by non-inbred male SD rats for 6 h per day, 5 days per week, caused weight loss, high mortality, severe inflammatory changes in the nasal cavity, lung congestion and pneumonia, tubular dilatation and dose-dependent tubular degeneration in the kidney at 38 and 114 mg/m^3 (Laskin et al., 1980).

5.3 Reproductive and developmental toxicity

The sperm of rats that had received an oral dose of 25 or 50 mg of ECH per kg of body weight showed an increased percentage of abnormal sperm heads at the higher dose and a reduced number of sperm heads at the lower dose; no microscopic changes in the testes or changes in their weight were observed (Cassidy et al., 1983). When male rabbits and male and female rats were exposed for 6 h per day, 5 days per week, to ECH vapour at concentrations of 0, 19.7, 93.4 or 189.0 mg/m^3 for 10 weeks, a dose-related transient infertility was induced at the two highest dose levels in male rats but not in female rats or male rabbits. Microscopic examination did not reveal any abnormalities in the reproductive organs. The sperm of the rabbits was investigated, but no adverse effects were found (John et al., 1983a).

Female rats received oral doses of 0, 40, 80 or 160 mg of ECH per kg of body weight per day and female mice received 0, 80, 120 or 160 mg of ECH per kg of body weight per day in cottonseed oil between days 6 and 15 of pregnancy. Although the highest dose levels were toxic to the dams, no embryotoxic, fetotoxic or teratogenic effects were observed (Marks et al., 1982). Similar negative results were obtained when female rats and rabbits inhaled ECH vapour at concentrations of 0, 9.4 or 94.5 mg/m^3 for 7 h per day between days 6 and 15 or 18 of pregnancy (John et al., 1983b).

5.4 Mutagenicity and related end-points

ECH induced base change-type mutations in *Salmonella typhimurium* and *Escherichia coli* in the absence of metabolic activation (Bridges, 1978). It has been shown to cause chromosomal aberrations in mammalian cells *in vitro* (IPCS, 1984) but was negative in the mouse micronucleus assay (Kirkhart, 1981) and in the mouse dominant lethal assay (Epstein et al., 1972). It was reported to cause chromosomal aberrations in mouse bone marrow cells *in vivo* (Sram et al., 1981).

5.5 Carcinogenicity

Male Wistar rats that received 18, 39 or 89 mg of ECH per kg of body weight per day in drinking-water for 81 weeks developed forestomach tumours characterized as squamous cell papillomas and carcinomas at the two highest doses and hyperplasia at all three doses (Konishi et al., 1980). Similar findings were reported in a 104-week study in which Wistar rats were given 0, 2 or 10 mg of ECH per kg of body weight per day by gavage in distilled water (Van Esch & Wester, 1982). Male SD rats exposed for 30 days to ECH at 378 mg/m^3 of air, 6 h per day, 5 days per week, developed squamous cell carcinomas in the nasal cavities during subsequent lifetime observation (Laskin et al., 1980). In 100 rats, lifetime exposure to 113 mg/m^3 yielded only one malignant squamous cell carcinoma of the nasal cavity and one nasal papilloma. Subcutaneous injection of ECH in ICR/Ha Swiss mice induced local sarcomas and adenocarcinomas (Van Duuren et al., 1974).

6. EFFECTS ON HUMANS

Acute toxic responses following dermal exposure are characterized by initial redness and itching or burning sensation. With time, the redness intensifies and the tissue becomes swollen and blistered. The initial symptoms following exposure to vapour are local irritation, burning of the eyes and throat, swelling of the face, nausea, vomiting and severe headache (Schultz, 1964).

In a case-study, long-term effects due primarily to damage to the liver and kidneys were still present 2 years after exposure (Schultz, 1964). In workers occupationally exposed to ECH, increased incidences of chromatid and chromosomal breaks in peripheral lymphocytes and decreases in blood cell counts were observed (Sram et al., 1980).

An epidemiological study was undertaken on 863 workers with probable exposure to ECH at two chemical plants (Enterline et al., 1990). All deaths due to cancer and leukaemia and death from most other causes were compared with estimated levels of exposure to ECH. The most consistent relationship was between exposure level and heart disease.

The fertility status of 64 glycerol workers in the USA exposed to ECH, allylchloride and 1,3-dichloropropane was compared with that of a control group of 63 workers

who had not handled chlorinated hydrocarbons for more than 5 years. No association was found between levels, duration or intensity of exposure and sperm characteristics or hormone levels (Venable et al., 1980). A similar negative result for sperm count and hormone levels was obtained for a group of 128 workers from two plants compared with other chemical plant workers who had not been exposed to any chemical known to be toxic to the testes. In one of these plants, most of the employees were exposed to ECH concentrations below 3.8 mg/m^3. The number of non-participating employees was high in both plants, namely 172 in total (Milby et al., 1981).

7. PROVISIONAL GUIDELINE VALUE

The major toxic effects of ECH are local irritation and damage to the central nervous system. In rats, it induces squamous cell carcinomas in the nasal cavity and forestomach tumours by the inhalation and oral routes, respectively. It has been shown to be genotoxic *in vitro* and *in vivo*. IARC (1987) has placed ECH in Group 2A (probably carcinogenic to humans).

Although ECH is a genotoxic carcinogen, the use of the linearized multistage model for estimating cancer risk was considered inappropriate because tumours are seen only at the site of administration, where ECH is highly irritating. A TDI of 0.14 µg/kg of body weight was therefore calculated by applying an uncertainty factor of 10 000 (10 for the use of a LOAEL instead of a NOAEL, 100 for inter- and intraspecies variation and 10 reflecting carcinogenicity) to a LOAEL of 2 mg/kg of body weight per day for forestomach hyperplasia in a 2-year study in rats by gavage (administration 5 days per week) (Wester et al., 1985). This gives a guideline value of 0.4 µg/litre (rounded figure) based on an allocation of 10% of the TDI to drinking-water. The guideline value is designated as provisional because of the uncertainties surrounding the toxicity of ECH and the use of a large uncertainty factor in deriving the guideline value.

A potential source of EHC in drinking-water is the presence of free ECH in chemicals and materials used in contact with drinking-water. Concentrations in drinking-water can be controlled by specifying the ECH content of products coming into contact with the water. The analytical determination of ECH in drinking-water is very difficult.

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