

Chloropicrin in Drinking-water

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

© World Health Organization 2003

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 2476; fax: +41 22 791 4857; email: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

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*:

- J.K. Fawell, Water Research Centre, United Kingdom
(inorganic constituents)
- U. Lund, Water Quality Institute, Denmark
(organic constituents and pesticides)
- B. Mintz, Environmental Protection Agency, USA
(disinfectants and disinfectant by-products)

The WHO coordinators were as follows:

Headquarters:

- H. Galal-Gorchev, International Programme on Chemical Safety
- R. Helmer, Division of Environmental Health

Regional Office for Europe:

- X. Bonnefoy, Environment and Health
- O. Espinoza, Environment and Health

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

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

CAS no.: 76-06-2

Molecular formula: CCl₃NO₂

The IUPAC name for chloropicrin is trichloronitromethane.

Physicochemical properties (1–3) [Conversion factor in air: 1 ppm = 6.68 mg/m³]

<i>Property</i>	<i>Value</i>
Boiling point	112 °C
Melting point	-64 °C
Density	1.65 g/cm ³ at 20 °C
Vapour pressure	2.27 kPa at 20 °C

Major uses

Chloropicrin is used as a reagent in the synthesis of organic chemicals, in the manufacture of methyl violet, and as a fumigant for stored grain; it has also been used as a chemical warfare agent (3,5).

Environmental fate

Chloropicrin in water is reduced to chloroform when reducing agents are added to remove excess chlorine (6). In the presence of light, it is degraded to carbon dioxide, chloride ion, and nitrate ion (7).

ANALYTICAL METHODS

Draft EPA Method 551 can be used for the determination of chloropicrin, by capillary-column/electron-capture/gas chromatography. Extremely low detection limits can be achieved.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Chloropicrin is formed in water by the reaction of chlorine with humic acids, amino acids, and nitrophenols. The presence of nitrates increases the amount formed (6). Chloropicrin has been detected in drinking-water; however, in the presence of reducing agents, it is converted into chloroform (6). In one study, the mean chloropicrin concentration was 0.6 µg/litre; the highest concentration observed was 5.6 µg/litre in 36 water supplies expected to have high concentrations of chlorination by-products (8).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

An oral LD₅₀ of 250 mg/kg of body weight was reported in rats (9). An LC₅₀ of 66 mg/m³ in mice was reported following a 4-h exposure to chloropicrin aerosol (10).

Short-term exposure

In a 6-week range-finding test, Osborne-Mendel rats (5 per sex per group) were given chloropicrin by gavage at doses of 0, 16, 25, 40, 63, or 100 mg/kg of body weight per day, 5 days per week. Groups of B6C3F₁ mice were treated in the same manner with doses of 10, 16, 25, 40, or 63 mg/kg of body weight per day. In rats, chloropicrin produced no mortality at 40 mg/kg of body weight per day or less, except for one female at 25 mg/kg of body weight per day. At 40 and 63 mg/kg of body weight per day, mean body weight was depressed by 11% and 38% in males and by 17% and 30% in females, respectively. In mice, there was no mortality at any dose tested. At 40 and 63 mg/kg of body weight per day, mean body weight was depressed by 12% and 20% in males and by 3% and 6% in females, respectively. In both species, a NOAEL of 25 mg/kg of body weight per day was identified (11).

Long-term exposure

The chronic toxicity of chloropicrin was investigated in a 78-week study on Osborne-Mendel rats and B6C3F₁ mice. Chloropicrin in corn oil was administered 5 days per week by gavage to animals (50 per sex per dose) at initial doses of 23 or 46 mg/kg of body weight per day for rats and 25 or 50 mg/kg of body weight per day for mice in a complex dosing regimen. Survival was decreased in both rats and mice. For rats, survival to the end of the study was 6% for high-dose males, 8% for low-dose males, 20% for high-dose females, and 22% for low-dose females. In both vehicle and untreated control groups, at least 50% of the animals survived past week 89. The associations between chloropicrin dose and accelerated mortality in mice were also significant when compared with the vehicle controls for both males and females (11).

Mutagenicity and related end-points

The mutagenicity of chloropicrin in five strains of *Salmonella typhimurium* and one strain of *Escherichia coli* was studied. Chloropicrin was either negative or weakly positive in the absence of the S9 fraction, but positive in one strain in its presence. Chloropicrin significantly increased the number of sister chromatid exchanges in cultured human lymphocytes *in vitro* in the absence of metabolic activation (13).

Carcinogenicity

Osborne-Mendel rats (50 per sex per dose) and B6C3F₁ mice (50 per sex per dose) were given chloropicrin by gavage in corn oil 5 days per week for 78 weeks. A complex dosing regimen was employed in which varying doses were administered for varying intervals; there were also periods during which no chloropicrin was given. The overall time-weighted average doses for the 78-week period were 25 or 26 mg/kg of body weight per day for male rats, 20 or 22 mg/kg of body weight per day for female rats, 66 mg/kg of body weight per day for male mice, and 33 mg/kg of body weight per day for female mice. Post-dosing observation periods were 32 weeks (rats) or 13 weeks (mice). In rats, the incidence of neoplasms in exposed animals was not higher than that in controls. However, mortality in exposed rats was high, and it is likely that most animals did not survive long enough to be at risk from tumours with long latency period. A rapid decrease in survival after the first year of the study was also observed among the high-dose mice of both sexes. Although the mice did not exhibit any statistically significant incidence of tumours, two carcinomas and a papilloma of the squamous epithelium of the forestomach were reported, which were rare in historical controls. The authors concluded that the results of tests with rats did not permit an evaluation of carcinogenicity because of the short survival time of dosed animals, and that the results in mice did not demonstrate conclusive statistical evidence for carcinogenicity under the conditions of the study (11).

EFFECTS ON HUMANS

Inhalation of chloropicrin at 2 mg/m³ caused pulmonary effects following a 1-min exposure (9).

CONCLUSIONS

Because of the high mortality in the carcinogenesis bioassay and the limited number of endpoints examined in the 78-week study, the available data are considered inadequate to support the establishment of a guideline value for chloropicrin.

REFERENCES

1. Weast RC. *Handbook of chemistry and physics*. Cleveland, OH, CRC Press, 1988.
2. Verschueren K. *Handbook of environmental data on organic chemicals*. New York, NY, Van Nostrand Reinhold, 1977.
3. Budavari S, O'Neill M, Smith A, eds. *The Merck index. An encyclopedia of chemicals, drugs, and biologicals*, 11th ed. Rahway, NJ, Merck, 1989.
4. Hawley GG. *The condensed chemical dictionary*, 10th ed. New York, NY, Van Nostrand Reinhold, 1981:241.
5. Clayton GD, Clayton FE. *Patty's industrial hygiene and toxicology*. Vol. II, 2nd ed. New York, NY, Interscience, 1963:2082-2083.
6. Sayato Y, Nakamuro K, Matsui S. [Studies on mechanism of volatile chlorinated organic compound formation. III. Mechanism of formation of chloroform and chloropicrin by chlorination of humic acid.] *Suishitsu odaku kenkyu*, 1982, 5:127-134 (in Japanese).
7. Castro CE, Belser NO. Photohydrolysis of methyl bromide and chloropicrin. *Journal of agricultural and food chemistry*, 1981, 29:1005-1008.
8. Bull RJ, Kopfler FC. Formation and occurrence of disinfectant by-products. In: *Health effects of disinfectants and disinfection by-products*. Denver, CO, American Water Works Association Research Foundation, 1991:55-103.
9. Tatken RL, Lewis RJ Sr, eds. *Registry of toxic effects of chemical substances*, Vol. 2, 1981-82 ed. Cincinnati, OH, National Institute for Occupational Safety and Health, 1983 (DHHS (NIOSH) Publication No. 83-107).
10. Kawai M. [Inhalation toxicity of phosgene and trichloronitromethane (chloropicrin). *Sangyo igaku*, 1973, 15:406-407 (abstract, in Japanese).
11. National Cancer Institute. *Carcinogenesis bioassay of chloropicrin*. Washington, DC, US Department of Health, Education and Welfare, 1978 (Technical Report Series No. 65).
12. Moriya M et al. Further mutagenicity studies on pesticides in bacterial reversion assay systems. *Mutation research*, 1983, 116:185-216.
13. Garry VF, Nelson R, Markins M. Detection of genotoxicity of grain fumigants in human lymphocytes. *Environmental mutagenesis*, 1987, 9(Suppl. 8):38-39.