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Chlordane 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:

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

ADI	acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
FAO	Food and Agriculture Organization of the United Nations
HSDB	Hazardous Substances Data Bank
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
PTDI	provisional tolerable daily intake
UNEP	United Nations Environment Programme
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	57-47-9
Molecular formula:	$C_{10}H_6Cl_8$

The IUPAC name for chlordane is 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene. Chlordane is a mixture of isomers, mainly *cis*- and *trans*-chlordane. Technical chlordane contains 60–75% chlordane isomers and at least 25 other compounds, including heptachlor ($C_{10}H_5Cl_7$) and nonachlor ($C_{10}H_5Cl_9$).

1.2 Physicochemical properties (ATSDR, 1989; Worthing, 1991)

Property	*Value*
Melting point	106–107 °C (*cis*); 104–105 °C (*trans*)
Density	1.59–1.63 g/cm^3 at 25 °C
Water solubility	0.1 mg/litre at 25 °C
Log octanol–water partition coefficient	5.5 (pure chlordane)
Vapour pressure	61×10^{-3} Pa at 25 °C (technical) 1.3×10^{-3} Pa at 25 °C (refined)

1.3 Organoleptic properties

A taste threshold of 500 µg/litre (HSDB, 1985) and an odour threshold of 0.5 µg/litre (Sigworth, 1965) have been reported for chlordane in water.

1.4 Major uses

Chlordane is a versatile, broad-spectrum contact insecticide used mainly for non-agricultural purposes (primarily for the protection of structures, but also on lawn and turf, ornamental trees and drainage ditches). It is also used on corn, potatoes and livestock. When used for termite control, it is applied to the soil by subsurface injection. The use of chlordane has been increasingly restricted in many countries (FAO, 1985; ATSDR, 1989; Worthing, 1991).

Chlordane was designated as a persistent organic pollutant in 1997 by the Governing Council of the United Nations Environment Programme (UNEP, 1997).

1.5 Environmental fate

Chlordane is very resistant to chemical and biological degradation. It is highly immobile and migrates very poorly. Dissipation of chlordane from soils is mainly due to volatilization. The soil half-life is about 4 years (Rao & Davidson, 1982). In spite of its very low mobility in soil, chlordane may be a low-level source of contamination in groundwater when applied by subsurface injection. Once in water bodies, it is not removed by photodegradation, hydrolysis or biodegradation. Chlordane can be

dissipated from surface water by volatilization, sorption to bottom and suspended sediments and particulates and uptake by aquatic organisms (IPCS, 1984; US EPA, 1987).

2. ANALYTICAL METHODS

Chlordane can be determined by extraction with pentane followed by gas chromatography with electron capture detection. The detection limit in tap water and river water is about 0.01 µg/litre (US EPA, 1982).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Chlordane levels range from less than 0.1 to 60 ng/m^3 in urban air and from 0.01 to 1 ng/m^3 in rural air. Chlordane is a contaminant of indoor air when used for termite control; levels exceeding 1 µg/m^3 have been measured (ATSDR, 1989).

3.2 Water

In the USA, chlordane is rarely present in drinking-water; when found, it is mainly at levels below 0.1 µg/litre (US EPA, 1987). Levels of chlordane in drinking-water and groundwater that are higher than its solubility have been reported (FAO, 1985).

3.3 Food

Chlordane has been found in meat, eggs and milk. Some chlordane metabolites have been found in human milk. Food is considered to be the major source of exposure of the general population to chlordane (IPCS, 1984).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

When *cis*-chlordane was administered orally, at least 2–8% of the dose was absorbed by rats and at least 30% by rabbits (Barnett & Dorough, 1974). It is also absorbed by the pulmonary and dermal routes in rats (Nye & Dorough, 1976). Chlordane and its metabolites, mainly oxychlordane, are quickly distributed throughout the body and stored at the highest levels in adipose tissue (Barnett & Dorough, 1974). Oxychlordane has been detected in adipose tissue in the general human population (Barquet et al., 1981).

Various faecal metabolites from both *cis*- and *trans*-chlordane have been identified. A metabolic scheme involving dehydrogenation, epoxidation, hydroxylation and dechlorination reactions has been presented. A glucuronide conjugate was found in urine (Tashiro & Matsumura, 1978). Lactation is a route of excretion of chlordane in females; chlordane is present in breast milk mainly as oxychlordane (Strassman & Kutz, 1977).

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Chlordane is moderately toxic in acute exposure. Oral LD_{50}s of 335–430 mg/kg of body weight have been found in rats and mice, whereas the oral LD_{50} in hamsters was 1720 mg/kg of body weight. Cows seem to be more sensitive, with oral LD_{50}s of 25–90 mg/kg of body weight. Acute exposure to chlordane produces ataxia, convulsions, respiratory failure and cyanosis (IPCS, 1984).

5.2 Long-term exposure

In a 2-year study, dogs fed chlordane at 0, 7.5, 75, 375 or 750 µg/kg of body weight per day showed altered liver enzyme activities and slightly increased relative liver weight at the two highest doses. The NOAEL in this study was 75 µg/kg of body weight per day (Wazeter, 1967).

F-344 rats (80 per sex per dose) were fed technical chlordane in the diet at 0, 1, 5 or 25 mg/kg for 130 weeks. Absolute and relative liver weights were increased in all treated groups compared with controls. Serum bilirubin levels were increased in mid- and high-dose male rats. Histopathological examination revealed a significantly increased incidence of hepatocellular swelling in both sexes at the high dose and in some of the mid- and low-dose males. A NOAEL of 1 mg/kg of diet, or approximately 0.05 mg/kg of body weight per day, was indicated by this study (FAO/WHO, 1987).

5.3 Reproductive and developmental toxicity

Male rats exposed for 90 days to 19.5 mg/kg of diet (about 1 mg/kg of body weight per day) showed changes in the ventral prostate (Shain et al., 1977). Chlordane reduced litter viability and delayed growth in multigenerational studies in rats and mice; in these studies, the NOAEL was 30 mg/kg of diet and the LOAEL was 50 mg/kg of diet. At lower doses, significant effects appeared only in the third and fourth generations (Ambrose et al., 1953; Keplinger et al., 1968). Effects were also seen in pups born to untreated dams but nursed by treated dams (Ambrose et al., 1953). Female mice exposed on days 1–19 of pregnancy to 8 mg/kg of body weight gave birth to apparently healthy progeny in which cell-mediated immunity was significantly reduced at adult age (Spyker-Cranmer et al., 1982).

5.4 Mutagenicity and related end-points

Chlordane was positive in *Saccharomyces cerevisiae* for mitotic gene conversion after metabolic activation (Blevins & Sholes, 1978) and in maize for reverse mutation (Gentile et al., 1982). It was mutagenic to Chinese hamster V79 cells and induced sister chromatid exchange in intestinal cells of fish treated *in vivo* (IARC, 1991). Chlordane was negative in *Bacillus subtilis* and *Salmonella typhimurium* for reverse

mutation (Probst et al., 1981; Gentile et al., 1982), in primary cultures of rat, mouse and hamster hepatocytes for unscheduled DNA synthesis and in mice for the dominant lethal assay (Maslansky & Williams, 1981). It was not mutagenic to cultures of human fibroblasts, and studies on DNA damage in transformed human cells yielded conflicting results (IARC, 1991).

5.5 Carcinogenicity

Chlordane gave positive results in carcinogenicity studies conducted in three strains of mice, one of which has a very low frequency of spontaneous liver lesions (Epstein, 1976; NCI, 1977; Becker & Sell, 1979). In all of these studies, chlordane exposure resulted in very high incidences of hepatic carcinomas in both male and female mice. In carcinogenicity studies on three strains of rats, chlordane did not exhibit generally carcinogenic effects (Ingle, 1952; NCI, 1977; Research Institute for Animal Science in Biochemistry and Toxicology, 1983); however, it produced an increased incidence of hepatocellular adenomas in F-344 SPF male rats (Ihui et al., 1983).

6. EFFECTS ON HUMANS

Neurological symptoms, including headache, dizziness, vision problems, incoordination, irritability, excitability, weakness, muscle twitching and convulsions, were consistently mentioned in a compilation of case reports and personal reports of humans accidentally exposed by inhalation or ingestion to unquantified concentrations of chlordane. A woman died 9 days after ingestion of 104 mg/kg of body weight (ATSDR, 1989). Following ingestion of drinking-water contaminated with chlordane at concentrations of up to 1.2 g/litre, 13 persons showed gastrointestinal and/or neurological symptoms (IPCS, 1984).

7. GUIDELINE VALUE

IARC (2001) re-evaluated chlordane in 2000 and concluded that there was inadequate evidence for its carcinogenicity in humans and sufficient evidence for its carcinogenicity in animals, classifying it in Group 2B.

JMPR re-evaluated chlordane in 1986 and established an ADI of 0.5 µg/kg of body weight by applying an uncertainty factor of 100 to a NOAEL of 50 µg/kg of body weight per day derived from a long-term dietary study in rats (FAO/WHO, 1987). The ADI was converted into a PTDI with the same value by JMPR in 1994 (FAO/WHO, 1995).

Although levels of chlordane in food have been decreasing, it is highly persistent and has a high bioaccumulation potential. An allocation of 1% of the JMPR PTDI to drinking-water gives a guideline value of 0.2 µg/litre (rounded figure).

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