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English only

Heptachlor and Heptachlor Epoxide 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 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
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
IARC	International Agency for Research on Cancer
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
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

Compound	*CAS No.*	*Molecular formula*
Heptachlor	76-44-8	$C_{10}H_5Cl_7$
Heptachlor epoxide	1024-57-3	$C_{10}H_5Cl_7O$

Heptachlor is the common name for 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene. Heptachlor epoxide is the common name for 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2H-indene(1,2b)oxirene (*1*).

1.2 Physicochemical properties (1–7)

Property	*Heptachlor*	*Heptachlor epoxide*
Melting point (°C)	93	160–161.5 (99.5% pure)
Specific gravity	1.57–1.59	–
Vapour pressure at 25 °C (kPa)	53×10^{-6}	53×10^{-6}
Log octanol–water partition coefficient	3.87–5.44	4.43–5.40
Water solubility at 25 °C (mg/litre)	0.056	0.35

1.3 Organoleptic properties

Pure heptachlor is a white crystalline solid with a camphor-like odour.

1.4 Major uses

Heptachlor is applied as a soil treatment, as a seed treatment (maize, small grains and sorghum) or directly to foliage. It is used to control ants, cutworms, maggots, termites, thrips, weevils, wireworms and many other insect pests in both cultivated and uncultivated soils. Heptachlor also controls household insects and pests of humans and domestic animals (*5*). In many countries, heptachlor is banned or applied only by subsurface injection.

Heptachlor epoxide is not commercially available but is an oxidation product of heptachlor (*1*).

1.5 Environmental fate

Heptachlor is moderately persistent in soil, where it is mainly transformed into its epoxide. It may undergo significant photolysis, oxidation and volatilization (*6,8,9*). It binds to soil particles and migrates slowly (*10*). The soil half-life of heptachlor under certain conditions may be as long as 2 years (*11*). Heptachlor epoxide is very resistant to further chemical or biological changes in soil. It binds to soil particles and migrates slowly (*10*). Its half-life in various soils has been reported to be as long as several years (*12*).

Photolysis, oxidation, hydrolysis and biotic reactions do not appear to be important processes in reducing heptachlor epoxide levels in aquatic media (*6,8*), whereas volatilization seems to be significant (*13*).

2. ANALYTICAL METHODS

Heptachlor may be determined in water samples by liquid–liquid extraction followed by gas chromatography. Detection and measurement may be accomplished by electron capture or electrolytic conductivity gas chromatography. The sensitivity of the method is 1–10 ng/litre (*14*).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

In a survey carried out in the USA in 1971, heptachlor was found in samples from two of nine cities at a maximum level of 19.2 ng/m^3 (*15*). In air samples taken from 1972 to 1974 in a cotton-growing area of the USA, the maximum heptachlor level was 0.8 ng/m^3 (*16*).

3.2 Water

Heptachlor and heptachlor epoxide have been found in drinking-water at ng/litre levels (*17–19*). Heptachlor epoxide has been found in drinking-water, groundwater, land runoff and river water at seven locations in the USA and Europe and in sediments, lakes, rivers, tap water and effluent from a biological sewage treatment plant at 28 such locations (*19,20*).

3.3 Food

Heptachlor and heptachlor epoxide have been found in many food classes (*21,22*). Human milk can be contaminated with heptachlor epoxide (*23*). Based on a total diet study conducted by the US Food and Drug Administration, estimated daily intakes of heptachlor and heptachlor epoxide for men aged 25–30 were 0.007 µg and 0.184 µg, respectively (*24*).

3.4 Estimated total exposure and relative contribution of drinking-water

Diet is likely to be the greatest source of exposure to heptachlor epoxide.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Heptachlor is rapidly absorbed from the gastrointestinal tract of rats following intragastric administration (*25*). Heptachlor epoxide is distributed throughout the body of rats and dogs (*25,26*). Heptachlor is metabolized by rats to heptachlor epoxide, 1-hydroxychlordene and 1-hydroxy-2,3-epoxychlordene, which are the major faecal

metabolites. *In vitro* studies have shown that heptachlor epoxide formation is greater in rats than in humans and that metabolism is, in general, comparable in the two species. Faeces represent the major route of heptachlor elimination by rats (*27*).

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

In the rat, mouse, rabbit, guinea-pig, hamster and chicken, oral LD_{50}s for heptachlor range from 40 to 260 mg/kg of body weight (*28*).

5.2 Short-term exposure

Evidence of significant liver damage and altered liver function was reported in rats maintained on diets containing heptachlor at 7–12 mg/kg of body weight per day for up to 14 days and 1 mg/kg of body weight per day for 5–7 days (*29*,*30*).

5.3 Long-term exposure

Male and female rats were fed diets containing heptachlor epoxide at 0, 5, 10, 20, 40, 80, 160 or 300 mg/kg for 2 years. Concentrations of 80 mg/kg or higher resulted in 100% mortality in 2–20 weeks. At 40 mg/kg, all the females died within 54 weeks, but there was no effect on male mortality up to 104 weeks. Diets containing 20 mg/kg or less did not produce any sign of illness in male or female rats, but an increase in liver weight was observed in male rats dosed with more than 10 mg/kg and females given 5 mg/kg (*31*).

Diets containing 0, 0.5, 2.5, 5.0 or 7.5 mg of heptachlor epoxide per kg were given to groups of five dogs for 60 weeks. No deaths attributed to heptachlor epoxide occurred. The weights of the male dogs increased in inverse proportion to the concentration of the compound in the diet, whereas those of the females were normal. Liver weights increased at 5.0 mg/kg and above. Degenerative liver changes were seen in only one dog at 7.5 mg/kg. From this study, a NOAEL of 2.5 mg/kg of diet, equivalent to 0.06 mg/kg of body weight per day, can be derived (*31*).

In a 2-year study, dogs fed heptachlor epoxide in the diet at concentrations of 0, 1, 3, 5, 7 or 10 mg/kg exhibited an increase in liver weight at the highest concentration and an increase in the incidence of histopathological changes in the liver (enlargement and vacuolation of centrilobular or scattered hepatocytes) at all but the lowest concentration. Similar histopathological changes persisted during 6 months of the recovery period. The NOAEL was 1 mg/kg of diet, equivalent to 0.025 mg/kg of body weight per day (*32*).

5.4 Reproductive and developmental toxicity

According to a poorly documented multigenerational study in rats fed heptachlor, litter size and viability were reduced and cataracts occurred in pups (*33*). No

indications of teratogenicity have been found in rats, rabbits, chickens or beagle dogs exposed to heptachlor (*28*). Rats fed 19.5 mg of heptachlor per kg of diet for 90 days showed a decrease in androgen receptor sites, nucleic acids and proteins in the ventral prostate (*34*).

Fertility was inhibited in female mice by three heptachlor injections of 25 mg/kg of body weight given at a rate of one per week. There was also an increase in estrogen metabolism and a decrease in the uterotropic activity of estrogen. Inhibition of the response of rat uterus to estrogen was seen; the LOAEL was 5 mg/kg of body weight for 7 days (*35*).

In a two-generation reproduction study in dogs fed heptachlor epoxide in the diet at concentrations of 1, 3, 5, 7 or 10 mg/kg, there was an increase in the mortality of F_2 pups at all but the lowest concentration. The NOAEL based on this finding was 1 mg/kg, equivalent to 0.025 mg/kg of body weight per day (*32*).

5.5 Mutagenicity and related end-points

Heptachlor did not induce dominant lethal mutations in mice. In one study, it induced unscheduled DNA synthesis in human fibroblast cultures but not repair synthesis in cultured rodent cells. It inhibited intercellular communication in rodent cell systems but was not mutagenic in cultured rat liver cells. It did not induce sex-linked recessive mutations in *Drosophila* or gene conversion in yeast. It was mutagenic in plants but not in bacteria. In one study, positive results were reported for technical-grade but not commercial-grade heptachlor. Heptachlor did not produce plasmid DNA breakage (*36*).

5.6 Carcinogenicity

Heptachlor containing about 20% chlordane produced neoplasms in mice following oral administration; the results of studies on rats were inconclusive. Oral administration of heptachlor increased the incidence of liver tumours induced in mice by the oral administration of *N*-nitrosodiethylamine (*36*).

6. EFFECTS ON HUMANS

Clinical case-studies of acute exposure (via the oral, dermal or inhalation route) to chlordane-containing heptachlor document a pattern of central nervous system effects similar to that found in animals (e.g., irritability, salivation, laboured respiration, muscle tremors, convulsions) (*37*,*38*). Heptachlor does not appear to be carcinogenic in humans (*39–42*).

7. CONCLUSIONS

IARC reviewed the data on heptachlor in 2000 and concluded that the evidence for carcinogenicity was sufficient in animals and inadequate in humans, classifying it in Group 2B (*43*). JMPR has evaluated heptachlor on several occasions and in 1991

established an ADI of 0.1 µg/kg of body weight on the basis of a NOAEL of 0.025 mg/kg of body weight per day from two studies in the dog, incorporating an uncertainty factor of 200 (100 for inter- and intraspecies variation and 2 for the inadequacy of the database) (*32*). This ADI was converted into a PTDI with the same numerical value by JMPR in 1994 (*44*).

The main source of exposure of the general population to heptachlor and heptachlor epoxide seems to be food. A health-based value of 0.03 µg/litre can be calculated with an allocation of 1% of the PTDI to drinking-water. However, because heptachlor and heptachlor epoxide occur at concentrations in drinking-water well below those at which toxic effects are expected to be observed, it is not considered necessary to derive a guideline value. It should also be noted that concentrations below 0.1 µg/litre are generally not achievable using conventional treatment technology.

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