

## **Lindane in Drinking-water**

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

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## 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 first draft of Lindane in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Dr P. Toft, Canada, to whom special thanks are due.

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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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)  
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

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
HCH	hexachlorocyclohexane
LC <sub>50</sub>	median lethal concentration
LD <sub>50</sub>	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
USA	United States of America
WHO	World Health Organization

## Table of contents

1. GENERAL DESCRIPTION .....	1
1.1 Identity .....	1
1.2 Physicochemical properties of $\gamma$ -HCH.....	1
1.3 Organoleptic properties.....	1
1.4 Major uses.....	1
1.5 Environmental fate.....	1
2. ANALYTICAL METHODS .....	2
3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.....	2
3.1 Air .....	2
3.2 Water.....	2
3.3 Food .....	2
3.4 Estimated total exposure and relative contribution of drinking-water.....	3
4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS .....	3
5. EFFECTS ON EXPERIMENTAL ANIMALS AND <i>IN VITRO</i> TEST SYSTEMS.....	3
6. EFFECTS ON HUMANS.....	5
7. GUIDELINE VALUE .....	5
8. REFERENCES .....	6





## 1. GENERAL DESCRIPTION

### 1.1 Identity

CAS No.:	58-89-9
Molecular formula:	C <sub>6</sub> H <sub>6</sub> Cl <sub>6</sub>

In the production of hexachlorocyclohexane (HCH), a mixture of isomers is formed, consisting mainly of the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers. Lindane is the name given to 99% pure  $\gamma$ -hexachlorocyclohexane ( $\gamma$ -HCH).

### 1.2 Physicochemical properties of $\gamma$ -HCH<sup>1</sup> (Slooff & Matthijsen, 1988; ATSDR, 1989; IPCS, 1991)

Property	Value
Melting point	112.8 °C
Boiling point	288 °C
Density	1.85 g/cm <sup>3</sup> at 20 °C
Water solubility	7–17 mg/litre at 20 °C
Log octanol–water partition coefficient	3.2–3.7
Vapour pressure	$0.434 \times 10^{-2}$ Pa at 20 °C

### 1.3 Organoleptic properties

Odour thresholds of 12 mg/litre for lindane and 0.3 µg/litre for  $\beta$ -HCH have been reported (ATSDR, 1989).

### 1.4 Major uses

Lindane is used as an insecticide on fruit and vegetable crops (including greenhouse vegetables and tobacco), for seed treatment and in forestry. It is also used as a therapeutic pesticide (e.g., in the treatment of scabies) in humans and animals (ATSDR, 1989; IPCS, 1991). Several countries have restricted the use of lindane.

### 1.5 Environmental fate

In soil, lindane can be degraded under aerobic conditions; the half-life ranges from 88 to 1146 days.  $\gamma$ -Pentachlorocyclohexene, hexa-, penta-, tetra- and trichlorobenzenes and penta- and tetrachlorophenols are the degradation products most commonly found. Anaerobic degradation is more rapid than aerobic degradation under laboratory conditions (half-life 12–174 days). Under anaerobic conditions, the same chlorinated benzenes and hexenes are found, but not the phenols. Leaching of lindane to groundwater rarely occurs. In surface waters, lindane can be removed by evaporation. Ultraviolet light seems to transform  $\gamma$ -HCH into  $\alpha$ -HCH to some extent. Bacteria also

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<sup>1</sup> Conversion factor in air: 1 ppm = 11.89 mg/m<sup>3</sup>.

## ***LINDANE IN DRINKING-WATER***

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influence the isomerization of  $\gamma$ -HCH to  $\alpha$ -HCH. The degradation products found in soils have also been found in water (Slooff & Matthijsen, 1988; IPCS, 1991).

### ***2. ANALYTICAL METHODS***

Lindane in water can be determined by extraction with petroleum ether followed by gas chromatography. The limit of detection is 0.01  $\mu\text{g/litre}$  (IPCS, 1991).

### ***3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE***

#### ***3.1 Air***

Background levels of lindane in the range 0.01–0.7  $\text{ng/m}^3$  have been found in “unpolluted” remote areas, whereas levels in urban and agricultural areas range from 0.1 to 2  $\text{ng/m}^3$  (Slooff & Matthijsen, 1988; ATSDR, 1989; Gustavson et al., 1990).  $\alpha$ -HCH is present together with  $\gamma$ -HCH, often in higher concentrations (Slooff & Matthijsen, 1988; Gustavson et al., 1990; IPCS, 1991). In indoor air, levels range from 6  $\text{ng/m}^3$  (average for homes built on waste dumps) to 40–60  $\mu\text{g/m}^3$  after treatment for insect control (Slooff & Matthijsen, 1988; IPCS, 1991). Lindane can also be present in cigarette smoke (ATSDR, 1989).

#### ***3.2 Water***

Lindane enters water from direct application for the control of mosquitos, from use in agriculture and forestry, from precipitation and, to a lesser extent, from occasional contamination of wastewater from manufacturing plants. Normal levels in precipitation are 0.4–155  $\text{ng/litre}$ , but levels up to 43  $\mu\text{g/litre}$  have been measured in India (Gustavson et al., 1990).

In surface waters, levels of 0.01–0.1  $\mu\text{g/litre}$  have been reported (Slooff & Matthijsen, 1988; ATSDR, 1989; IPCS, 1991). Particularly high concentrations, up to 12  $\mu\text{g/litre}$ , are found in wastewater-contaminated rivers (Gustavson et al., 1990). Concentrations in groundwaters have been reported to range from 3 to 163  $\text{ng/litre}$  (ATSDR, 1989; Gustavson et al., 1990).

#### ***3.3 Food***

HCH isomers are found in dairy products, meat, fish, poultry, garden fruits, oils and fats, leafy and root vegetables and sugar. Spices and herbs contain the highest levels of  $\alpha$ - and  $\beta$ -HCH, whereas pork and beef fat contain the highest levels of  $\gamma$ -HCH (up to 3200 and 1700  $\mu\text{g/kg}$  of fat, respectively). Most animal fats and eggs contain less than 10  $\mu\text{g}$  of  $\gamma$ -HCH per kg (Slooff & Matthijsen, 1988; ATSDR, 1989; IPCS, 1991). Breast milk contains  $\beta$ - and occasionally  $\gamma$ -HCH at mean levels of 3 and 6  $\mu\text{g/kg}$  of milk, respectively (National Board of Health, 1987; ATSDR, 1989).

### ***3.4 Estimated total exposure and relative contribution of drinking-water***

Daily intake of HCH isomers in adult diets in the USA in 1981–1982 was reported to be 10 ng/kg of body weight for total HCH (8 ng of  $\alpha$ -HCH and 2 ng of  $\gamma$ -HCH per kg of body weight) (ATSDR, 1989). In the Netherlands, the daily intake from food has been calculated to be 1  $\mu$ g for the  $\alpha$ -,  $\beta$ - and  $\gamma$ -isomers, or approximately 15 ng/kg of body weight (Slooff & Matthijsen, 1988; IPCS, 1991). Intake from air may be considerable for people living in houses treated for pest control purposes.

## ***4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS<sup>2</sup>***

After oral administration, [<sup>14</sup>C]lindane was rapidly absorbed from the gastrointestinal tract of mice and rats and was extensively distributed throughout the body. In mice, radiolabel was detected in fat, brain, kidney, muscle, liver, adrenals and ovary tissue after administration in the diet. Adipose tissue had the highest concentration of lindane. A similar distribution pattern was observed in rats. The major route of excretion was urine, with a small proportion of an oral dose eliminated in the faeces. The half-life of lindane in rats was estimated to be 3–5 days, approximately 80% of the administered dose being excreted within 8 days.

Lindane undergoes extensive metabolism in mammals, proceeding through a pathway involving stepwise dehydrogenation, dechlorination and dehydrochlorination, which may be followed by conjugation with sulfate or glucuronide.

## ***5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS<sup>3</sup>***

Lindane was moderately acutely toxic when given orally, with LD<sub>50</sub> values of 56–250 mg/kg of body weight in mice and 140–190 mg/kg of body weight in rats. The LD<sub>50</sub> and LC<sub>50</sub> values after dermal and inhalation administration to rats were 1000 mg/kg of body weight and 0.002 mg/litre, respectively. Lindane did not irritate the skin or eye in rabbits and did not sensitize the skin of guinea-pigs. WHO has classified lindane as “moderately hazardous.”

Lindane induces a number of metabolizing enzymes, including the cytochrome P-450 system, glutathione-S-transferase and uridine diphosphate-glucuronosyl transferase. In contrast, it inhibits, for example, epoxide hydrolysis at concentrations of 100 ppm and more.

Lindane was toxic to the kidney and liver after administration orally, dermally or by inhalation in short-term and long-term studies of toxicity and studies of reproductive toxicity in rats. The renal toxicity of lindane was specific to male rats and was

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<sup>2</sup> This section is taken from FAO/WHO (2002).

<sup>3</sup> This section is taken from FAO/WHO (2002).

## ***LINDANE IN DRINKING-WATER***

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considered not to be relevant to human risk assessment, since it is a consequence of accumulation of  $\alpha_2\mu$ -globulin, a protein that is not found in humans. Hepatocellular hypertrophy was observed in a number of studies in mice, rats and rabbits and was reversed only partially after recovery periods of up to 6 weeks. In a 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 10 mg/kg in the diet (equal to 0.47 mg/kg of body weight per day) on the basis of increased liver weight, hepatocellular hypertrophy, increased spleen weight and deaths at 100 mg/kg (equal to 4.7 mg/kg of body weight per day).

Body weights and decrements in body weight gain were reported in rats and rabbits, but not in mice. Decreased body weight gain occurred at concentrations of 100 mg/kg (equal to 4.7 mg/kg of body weight per day) and higher.

In rats given lindane at a concentration of 400 mg/kg in the diet (equal to 35 mg/kg of body weight per day), marginal increases in blood phosphorus and calcium and a 45–110% increase in cholesterol concentration, a 20–54% increase in urea concentration and a statistically significant increase in platelet count were seen. In general, the haematological changes seen were marginal.

Acute administration by oral, dermal, intraperitoneal or intramuscular routes or by inhalation elicited effects characteristic of toxicity to the central nervous system — namely, hypoactivity, dyspnoea, ataxia, convulsions and tremors. In addition, neurotoxic effects were observed after short- or long-term administration, including sensitivity to touch, aggressive behaviour, languor, piloerection, hunched posture, increased motor activity and paralysis of the hindquarters (rabbits only). In a study of acute neurotoxicity in rats, the NOAEL was 6 mg/kg of body weight on the basis of increased forelimb grip strength and decreased grooming behaviour. In a 90-day study of neurotoxicity, the NOAEL was 100 mg/kg (equal to 7.1 mg/kg of body weight per day) on the basis of hypersensitivity to touch and hunched posture. In a study of developmental neurotoxicity, the NOAEL for maternal toxicity was 50 mg/kg (equal to 4.2 mg/kg of body weight per day) on the basis of decreased body weight, decreased food consumption and increased reactivity to handling, while the NOAEL for developmental toxicity was 10 mg/kg (equal to 0.8 mg/kg of body weight per day) on the basis of reduced pup survival, decreased body weight and body weight gain during lactation, increased motor activity and decreased motor reflex.

Lindane did not induce a carcinogenic response in rats or dogs, but increased incidences of adenomas and carcinomas of the liver were observed in agouti and pseudoagouti mice at a dose of 23 mg/kg of body weight per day in a study of the role of genetic background in the latency and incidence of tumorigenesis. No tumours were observed in black mice in this study or in any other strain of mice. In another study, a slightly increased incidence of lung adenomas was observed in female mice at the highest dose (21 mg/kg of body weight per day); however, there was a limited dose–response relationship, and this tumour is common in the strain of mice used, the incidence (27%) only slightly exceeding that in other control groups (19%).

Lindane was not genotoxic *in vivo* or *in vitro*. Genotoxicity was found only at cytotoxic concentrations or in the presence of lindane precipitate. The Meeting concluded that lindane is not genotoxic.

In a multigeneration study of reproductive toxicity in rats, the NOAEL for parental toxicity was 150 mg/kg (equal to 13 mg/kg of body weight per day), the highest dose tested. The NOAEL for reproductive toxicity was 20 mg/kg (equal to 1.7 mg/kg of body weight per day), on the basis of a decreased litter viability index and delays in tooth eruption and hair growth.

Oral administration of lindane to pregnant rats resulted in a NOAEL for maternal toxicity of 5 mg/kg of body weight per day on the basis of decreased body weight gain and food consumption. In this study, the NOAEL for developmental toxicity was 5 mg/kg of body weight per day on the basis of an increased incidence of supernumerary ribs. In a study of developmental toxicity in rabbits, a NOAEL for maternal toxicity was not identified; the LOAEL for maternal toxicity was 5 mg/kg of body weight per day, on the basis of tachypnoea and lethargy after several days of administration. The NOAEL for developmental toxicity was 10 mg/kg of body weight per day, on the basis of an increased incidence of fetuses with 13 ribs.

JMPR reviewed several published studies of the effect of lindane on the endocrine system. Although lindane had anti-estrogenic properties in several studies, effects were reported only at doses of 5 mg/kg of body weight per day or more.

In view of the report of immunotoxicity in mice, a 39-week study was conducted in which mice were given lindane (purity 99%) to examine its effects on the total number of leukocytes and on the relative proportion of lymphocyte populations. In females, administration at a dietary concentration of 160 mg/kg (equal to 24 mg/kg of body weight per day) resulted in a 55% increase in the natural killer cell population. In the absence of effects on other lymphocyte parameters, JMPR concluded that lindane is not immunotoxic.

## **6. EFFECTS ON HUMANS<sup>4</sup>**

In an epidemiological study designed to assess the potential association between breast cancer and exposure to chlorinated pesticides, no correlation with lindane was found.

## **7. GUIDELINE VALUE**

In the absence of genotoxicity and on the basis of the weight of the evidence from the studies of carcinogenicity, the Meeting concluded that lindane is not likely to pose a carcinogenic risk to humans.

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<sup>4</sup> This section is taken from FAO/WHO (2002).

## ***LINDANE IN DRINKING-WATER***

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JMPR established an ADI of 0.005 mg/kg of body weight on the basis of the NOAEL of 10 mg/kg, equal to 0.47 mg/kg of body weight per day, in the long-term study of toxicity and carcinogenicity in rats, in which an increased incidence of periportal hepatocellular hypertrophy, increased liver and spleen weights and increased mortality occurred at higher doses, and a safety factor of 100.

Although exposure to lindane from food is decreasing, there may be substantial exposure from its use in public health and as a wood preservative. Therefore, 1% of the ADI of 5 µg/kg of body weight was allocated to drinking-water. The guideline value is therefore 2 µg/litre (rounded figure).

### **8. REFERENCES**

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