

Hexachlorobenzene 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.

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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.

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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

CAS	Chemical Abstracts Service
HCB	hexachlorobenzene
IARC	International Agency for Research on Cancer
LC ₅₀	median lethal concentration
NOAEL	no-observed-adverse-effect level
TD ₀₅	tumorigenic dose ₀₅ , the intake or exposure associated with a 5% excess incidence of tumours in experimental studies in animals
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	118-74-1
Molecular formula:	C ₆ Cl ₆

1.2 Physicochemical properties (IPCS, 1997)

<i>Property</i>	<i>Value</i>
Melting point	230 °C
Boiling point	Sublimes at 322 °C
Vapour pressure	0.0023 Pa at 20 °C
Water solubility	5 µg/litre
Log octanol–water partition coefficient	5.2

1.3 Major uses

Historically, hexachlorobenzene (HCB) had many uses in agriculture; the major agricultural application for HCB used to be as a seed dressing for crops such as wheat, barley, oats and rye to prevent growth of fungi. The use of HCB in such applications was discontinued in many countries in the 1970s owing to concerns about adverse effects on the environment and human health. However, HCB may continue to be used for this purpose in some countries. At present, its main significance appears to be as a by-product of several chemical processes or an impurity in some pesticides (IPCS, 1997).

1.4 Environmental fate

HCB is distributed throughout the environment because it is mobile and resistant to degradation. Volatilization from water to air and sedimentation following adsorption to suspended particulates are the major removal processes from water. Although HCB is not readily leached from soils and sediments, some desorption does occur and may be a continuous source of HCB to the environment, even if inputs to the system cease. In the troposphere, HCB is transported over long distances by virtue of its persistence, but does undergo slow photolytic degradation (the half-life is approximately 80 days) (IPCS, 1997).

The bioaccumulative properties of HCB result from the combination of its physicochemical properties (high octanol–water partition coefficient) and its slow elimination due to limited metabolism related to its high chemical stability (IPCS, 1997).

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2. ANALYTICAL METHODS

HCB in water can be extracted with organic solvents (e.g., hexane) and then determined by gas chromatography using an electron capture detector. The detection limit of this method is 5 ng/litre (Ang et al., 1989).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

HCB is widely dispersed in ambient air and is generally present at low concentrations. Mean concentrations of HCB in air removed from point sources in Canada, Norway, Sweden, Germany, the USA, the Arctic and the Antarctic range from 0.04 to 0.6 ng/m³. Levels of HCB in air are generally similar between urban, rural and remote sites, reflecting the persistence and long-range transport of this substance (IPCS, 1997).

3.2 Water

Levels of HCB in fresh water in Europe and North America are generally below 1 ng/litre, although higher values have been reported in aquatic systems that receive industrial discharges and surface runoff. HCB has been detected infrequently, and at very low concentrations, in drinking-water supplies. Samples of drinking-water collected in 1980 from Canadian cities in the vicinity of Lake Ontario contained from 0.06 to 0.20 ng/litre, with a mean of 0.1 ng/litre. In other Canadian and US surveys, HCB was not detected (IPCS, 1997).

3.3 Food

HCB is commonly detected, at low levels, in food. Levels of HCB tend to be highest in fatty foods and/or those that have been treated with HCB-contaminated pesticides. The results of total diet studies in the USA from 1982 to 1991 indicate that HCB is detectable (detection limit 0.1 ng/g) in a small fraction of food items, most often dairy products, meats and peanuts/peanut butter. In the more recent surveys, conducted during 1990–1991, mean levels were less than 1 ng/g for all products (IPCS, 1997).

3.4 Estimated total exposure and relative contribution of drinking-water

Total intake of HCB from ambient air, drinking-water and foods is estimated to range from approximately 0.0004 to 0.003 µg/kg of body weight per day for the general population, the principal route of exposure being through the diet (92%). The estimated contributions from air and drinking-water are much smaller (7% and 1%, respectively) (IPCS, 1997). The results of most studies of temporal trends of HCB levels in human adipose tissue or milk indicate that general population exposures have declined since the 1970s.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

More HCB is absorbed following administration in olive oil compared with administration as an aqueous suspension or the solid crystalline form (80% vs. 20%) (US EPA, 1988). Following administration to male rats, the highest concentrations were detected in adipose tissue, bone marrow, skin, the Harderian gland, nasal mucosa and the preputial gland (Ingebrigtsen, 1986).

HCB is metabolized slowly to give lower chlorinated benzenes, chlorinated phenols and other lower metabolites; glucuronide and glutathione conjugates have also been detected. Most is excreted in faeces as the parent compound, a small fraction, about 5%, being excreted in the urine as polar metabolites. Lactation is an effective method of HCB elimination for the cow and mouse, but not for humans (IPCS, 1997).

Levels of HCB in human adipose tissue are generally below 1 mg/kg. Concentrations tend to be slightly higher in fat tissue samples from European countries than in samples from elsewhere in the world; the highest levels reported in recent surveys are from Spain (mean levels of approximately 3–6 mg/kg) (IPCS, 1997). The body burden of HCB in the US population has been estimated to be 0.7 mg, based on a dietary intake of 0.2 µg/day and a mean concentration of 0.04 mg/kg in adipose tissue. The mean retention time of HCB has been estimated to be 15 years (ATSDR, 2000).

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Reported LC₅₀ values for inhalation exposure range from 1600 mg/m³ for the cat to 4000 mg/m³ for the mouse, with intermediate values reported for the rat and rabbit. The symptoms observed were convulsions, tremors, weakness, ataxia, paralysis and pathological changes in organs (IPCS, 1997).

5.2 Short-term exposure

The effects of short-term, repeated exposure to HCB are primarily hepatotoxic and neurological (IPCS, 1997). HCB was fed in the diet to Swiss mice (0, 100 or 200 mg/kg), Sprague-Dawley rats and Syrian golden hamsters (0, 200 or 400 mg/kg) for 90 days. It induced severe hyperplasia of lymphohaematopoietic centres, with frequent lymphocytic infiltrations into the liver and kidneys, as well as severe haemosiderosis in the spleen and liver. Toxic liver lesions, including several degenerations, peliosis, necroses leading to toxic hepatitis and cirrhosis that developed into neoplastic growths, were most severe in male hamsters and rats but were seldom seen in mice. The kidneys were also affected, showing toxic tubular nephrosis and nephritis (Erturk et al., 1986).

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5.3 Reproductive and developmental toxicity

Relatively low doses of HCB have been found to affect some reproductive tissues in female monkeys. Oral exposure of cynomolgus monkeys to 0.1 mg/kg of body weight per day for 90 days caused stratification of the ovarian germinal epithelium. Higher dosages (1.0 and 10.0 mg/kg of body weight per day) were associated with cellular degeneration of this surface epithelium (IPCS, 1997).

In a four-generation test with Sprague-Dawley rats, the NOAEL was 20 mg/kg in the diet (IPCS, 1997). Some teratogenic effects of HCB were observed in Wistar rats at doses of up to 120 mg/kg of body weight administered during organogenesis, but could not be reproduced (Khera, 1974). HCB was found to cause developmental effects in fetal CD-1 mice whose mothers ingested 100 mg/kg of body weight per day on days 7–16 of gestation (IPCS, 1997). HCB did not exhibit developmental effects in New Zealand rabbits (Villeneuve et al., 1974).

5.4 Mutagenicity and related end-points

HCB has not been found to be genotoxic in most studies conducted to date. For example, HCB was not found to be mutagenic in five strains of *Salmonella typhimurium*, with or without metabolic activation (Lawlor et al., 1979). It was negative in dominant lethal mutation studies with rats (Khera, 1974), but was shown to be mutagenic in *Saccharomyces cerevisiae* (Guerzoni et al., 1976). HCB gave negative results in the Ames test and sister chromatid exchange (Gorski et al., 1986).

5.5 Long-term toxicity and carcinogenicity

A range of non-neoplastic effects from long-term exposure to HCB, which are primarily hepatotoxic, have been observed at relatively low doses (IPCS, 1997).

The carcinogenicity of HCB has been assessed in several bioassays in rats, mice and hamsters. A statistically significant increase of liver cell tumours (hepatomas) was reported in groups of 30–60 male and female Syrian golden hamsters fed 50, 100 or 200 mg of HCB per kg (4, 8 or 16 mg/kg of body weight per day) in their diets for life. The incidence of “haemangioendotheliomas” of the liver was significantly increased in both sexes. Groups of Swiss mice were fed diets containing HCB (>99.5% pure) at 0, 50, 100 or 200 mg/kg. Liver cell tumours were found in the two highest dose groups but not in controls or in the group receiving 50 mg/kg (IPCS, 1997).

The potential carcinogenicity to rats of combined *in utero*, lactational and oral exposure to HCB was investigated in a two-generation study. Groups of 40 or more weanling male and female Sprague-Dawley rats were fed diets containing 0, 0.32, 1.6, 8 or 40 mg of HCB per kg. After 3 months, the rats were bred, and the pups were continued on the same diet for their lifetimes. Adrenal pheochromocytomas were noted at the highest dose, including a significantly increased incidence of parathyroid adenomas in males (IPCS, 1997).

Sprague-Dawley rats were fed diets containing 0, 75 or 150 mg/kg for up to 2 years. Statistically significant increases in the incidence of hepatomas/haemangiomas, renal cell adenomas, hepatocellular carcinomas and bile duct adenomas were observed at both doses in animals surviving beyond 12 months (IPCS, 1997).

6. EFFECTS ON HUMANS

IARC has found the evidence for carcinogenicity of HCB in humans to be inadequate, as no report of a direct association between HCB and human cancer is available. Hepatocellular carcinoma has been associated with porphyria; however, although abnormal porphyrin metabolism persisted at least 20 years after an epidemic of porphyria cutanea tarda in Turkey, caused by the consumption of grain treated with HCB, no excess cancer occurrence was reported in this population 25 years after the accident (IARC, 1987).

In a small ecological study of cancer incidence (129 cases in all) in the inhabitants of a village in Spain located near a chlorinated solvents factory, there were statistically significant excesses of thyroid neoplasms and soft-tissue sarcomas in males, compared with the province as a whole, although these were based on only two and three cases, respectively (IPCS, 1997).

7. CONCLUSIONS

IARC (2001) has evaluated the evidence for carcinogenicity of HCB in animals and humans and assigned it to Group 2B. Because HCB has been shown to induce tumours in three animal species and at a variety of sites, a linearized low-dose extrapolation model was used to calculate concentrations in drinking-water associated with upper-bound excess lifetime cancer risks of 10^{-4} , 10^{-5} and 10^{-6} . On the basis of liver tumours observed in female rats in a 2-year dietary study (Erturk et al., 1986) and applying the linearized multistage model, concentrations of 10, 1 and 0.1 µg/litre in drinking-water corresponding to upper-bound excess lifetime cancer risks of 10^{-4} , 10^{-5} and 10^{-6} , respectively, can be derived. A health-based value of 1 µg/litre in drinking-water, corresponding to an upper-bound excess lifetime cancer risk of 10^{-5} , can thus be calculated.

An alternative approach for deriving exposure values when dealing with neoplastic effects is based on the TD₀₅ approach (IPCS, 1997). Using this approach, IPCS (1997) derived a health-based guidance value of 0.16 µg/kg of body weight per day. If one were to assume a 1% allocation of this guidance value to drinking-water (IPCS, 1997), then this would correspond to a 60-kg adult consuming 2 litres of drinking-water containing approximately 0.05 µg/litre.

Because the health-based values derived from both of these approaches are considerably higher than the concentrations at which HCB is detected in drinking-water (i.e., sub-ng/litre), when it is detected, it is not considered necessary to establish a guideline value for HCB in drinking-water.

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