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English only

Hexachlorobutadiene 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.

Acknowledgements

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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:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Dr P. Toft, Canada (*Pesticides*)
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
Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

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

CAS	Chemical Abstracts Service
Cys	cysteine
ECD	electron capture detection
GC	gas chromatography
GSH	glutathione
HCBD	hexachlorobutadiene
LD_{50}	median lethal dose
MS	mass spectrometry
NOAEL	no-observed-adverse-effect level
PCBD	*S*-(1,2,3,4,4-pentachloro-1,3-butadienyl)
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	87-68-3
Molecular formula:	C_4Cl_6

Synonyms of hexachlorobutadiene (HCBD) include perchlorobutadiene, 1,3-hexachlorobutadiene and 1,1,2,3,4,4-hexachloro-1,3-butadiene.

1.2 Physicochemical properties (IARC, 1979)

Property	*Value*
Physical state	Clear, colourless, liquid
Melting point	-22 to -19 °C
Boiling point	210 to 220 °C
Vapour pressure	0.02 kPa at 20 °C
Density	1.55 g/cm^3 at 20 °C
Water solubility	2.6 mg/litre
Log octanol–water partition coefficient	3.67

1.3 Organoleptic properties

The odour threshold for HCBD in air is 12 mg/m^3 (Ruth, 1986).

1.4 Major uses

HCBD is used as a solvent in chlorine gas production, an intermediate in the manufacture of rubber compounds, a lubricant, a gyroscopic fluid, a pesticide and a fumigant in vineyards (IARC, 1979).

1.5 Environmental fate

HCBD may not volatilize rapidly from water because of its low vapour pressure. Adsorption onto soil particles in water is important.

2. ANALYTICAL METHODS

The minimum detection limit of HCBD is 0.34 µg/litre by gas chromatography (GC) and 0.18 µg/litre by capillary GC with electron capture detection (ECD) after solid-phase micro-extraction (Almedia et al., 1997). The purge-and-trap gas chromatography/mass spectrometry (GC-MS) technique has a minimum detection limit of 0.01 µg/litre (Abdelghani et al., 1995). The minimum detection limit is 0.05 µg/litre by purge-and-trap GC-MS with ECD (Amaral et al., 1996) and 0.04 ng/litre when hexane is used for extraction from water samples (Meharg et al., 1998). Closed-loop stripping analysis with GC-MS can detect HCBD at ng/litre levels (Li et al., 1976).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

In a study of nine chemical plants, the highest levels of HCBD in air were found near those producing tetrachloroethene and trichloroethene (maximum 462 μg/m^3) (IARC, 1979).

3.2 Water

In Europe, HCBD was detected at 0.05–5 μg/litre in ambient water (IARC, 1979), at 0.1–5 μg/litre in the Rhine (IARC, 1979), at 0.2 μg/litre in Ebre River water (Amaral et al., 1996) and at 0.04 μg/litre in Hamber River water at 1 out of 280 points (Meharg et al., 1998); in the USA, it was detected at 0.9–1.9 μg/litre in Mississippi River water (IARC, 1979). It was also found in mud and soil at concentrations up to 800 μg/kg in Louisiana, USA (IARC, 1979). The concentrations of HCBD in water and soil in Louisiana were reported to be 0.01–0.48 μg/litre and 0.05–0.4 ng/g, respectively (Almedia et al., 1997). HCBD was not detected in ambient water and mud in Japan (minimum detection limits: water 0.02 μg/litre; mud 2–200 μg/g) (Japan Environment Agency, 1982). It has been detected at 6.4 μg/litre in the effluent from a European chemical plant and at 0.27 μg/litre in European drinking-water (IARC, 1979).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

In rats, about 95% of the ingested dose of HCBD is absorbed (Nash et al., 1984); it was found in the blood, liver and brain 3 h after a single injection and in the kidney, spleen and mesentery after 6 h (Gul'ko & Dranovskaja, 1974). When a mixture of chlorinated hydrocarbons, including HCBD, was administered orally to rats at doses of 2 or 4 mg/kg of body weight per day for up to 12 weeks, less than 7 mg of HCBD per kg of body weight accumulated in adipose tissue (Jacobs et al., 1974).

HCBD is metabolized in rats and mice via conjugation with glutathione (GSH), following by biliary excretion of *S*-(1,2,3,4,4-pentachloro-1,3-butadienyl)-GSH (PCBD-GSH) (Nash et al., 1984; Reichert et al., 1985; Dekant et al., 1986). The GSH conjugate of HCBD is further metabolized in the gastrointestinal tract and kidney to a number of water-soluble metabolites that are excreted mainly in the urine (Nash et al., 1984; Reichert et al., 1985). Experimental evidence suggests that the metabolism of PCBD-GSH involves, in part, degradation to PCBD-cysteine (PCBD-Cys), which is nephrotoxic via activation of the renal enzyme cysteine conjugate β-lyase (Jaffe et al., 1983; Nash et al., 1984; Reichert et al., 1985). PCBD-Cys is *N*-acetylated, presumably in a detoxification reaction, to give the mercapturic acid, *N*-acetyl-PCBD-Cys (Reichert & Schutz, 1986). The pathway for biotransformation of HCBD in experimental animals appears to be saturable (IPCS, 1994).

After a single oral administration of [^{14}C]HCBD to rats, the principal route of excretion was in the bile; 17–20% of the initial dose was excreted on each of the first 2 days. Extensive enterohepatic circulation must have occurred, because faecal elimination amounted to only 5% of the total dose of radioactivity per day (Nash et al., 1984). In another study, 42–67% and 11–31% of the radioactivity were excreted in the faeces and urine by 72 h, respectively (Reichert et al., 1985). Similar results were obtained in mice (67.5–76.7% in faeces, 6.6–7.6% in urine) (Dekant et al., 1988).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Oral LD_{50}s were reported to be 200–400 and 504–667 mg/kg of body weight in 50 adult female and male rats, respectively (Schwetz et al., 1977).

5.2 Short-term exposure

Weanling Wistar rats given HCBD by gavage for 13 weeks at dose levels of 0, 0.4, 1, 2.5, 6.3 or 15.6 mg/kg of body weight per day exhibited an increase in relative kidney weight at the two highest doses and degeneration of the proximal renal tubules at and above 2.5 mg/kg of body weight per day (females) or 6.3 mg/kg of body weight per day (males). Increased cytoplasmic basophilia of hepatocytes associated with an increase in liver weight occurred in males at the two highest doses (Harleman & Seinen, 1979).

5.3 Long-term exposure

The kidney was the primary target organ in a study in which Sprague-Dawley rats were given HCBD in the food for 2 years at dose levels of 0, 0.2, 2 or 20 mg/kg of body weight per day. Effects included a treatment-related increase in relative and absolute kidney weights in males at 20 mg/kg of body weight per day, an increased incidence of multifocal or disseminated renal tubular epithelial hyperplasia in rats at 20 and possibly at 2 mg/kg of body weight per day and focal adenomatous proliferation of renal tubular epithelial cells in some males at 20 mg/kg of body weight per day and some females at 20 and 2 mg/kg of body weight per day. No discernible ill effects attributable to treatment were found at 0.2 mg/kg of body weight per day, which was the NOAEL in this study (Kociba et al., 1977).

5.4 Reproductive and developmental toxicity

In a 148-day study in which groups of 10–17 male and 20–34 female adult rats per group were fed diets containing HCBD at doses of 0, 0.2, 2.0 or 20 mg/kg of body weight per day for 90 days prior to mating, 15 days during mating and subsequently throughout gestation (22 days) and lactation (21 days), there were no treatment-related effects on pregnancy or neonatal survival. The body weights of 21-day-old weanlings in the highest dose group were slightly but significantly lower than those of

controls. No toxic effects were observed in neonates at doses of 0.2 or 2.0 mg/kg of body weight per day (Schwetz et al., 1977).

When oral doses of 8.1 mg of HCBD per kg of body weight per day were given to pregnant rats throughout gestation, ultrastructural changes in neurocytes and higher levels of free radicals in the brain and spinal cord were seen in the offspring, which also had lower body weights and shorter crown–rump lengths than controls (Badaeva et al., 1985).

Pups of rats injected intraperitoneally with 10 mg of HCBD per kg of body weight per day on days 1–15 of gestation experienced 3 times as many soft tissue anomalies as controls, although no particular type of anomaly was predominant (Harris et al., 1979).

5.5 Mutagenicity and related end-points

Negative results have been reported in most (Reichert et al., 1983; Vamvakas et al., 1988) but not all (Reichert et al., 1984) tests for the mutagenicity of HCBD in Ames test *Salmonella* strains. Metabolites and derivatives of HCBD were mutagenic to *Salmonella typhimurium* with metabolic activation (Reichert & Schutz, 1986; Wild et al., 1986), and some putative metabolites were mutagenic in this test without such activation (Dekant et al., 1986). Although HCBD is negative in a number of standard assays, it induces mutations in *Salmonella* in conditions designed to favour the formation of GSH conjugation products. Because of the conditions under which the active metabolites are formed, it has given variable results in a range of *in vivo* and *in vitro* assays (IPCS, 1994).

5.6 Carcinogenicity

Administration of HCBD in the diet at doses of 20 mg/kg of body weight per day for 2 years caused renal tubular adenomas and adenocarcinomas in SD rats. No renal tubular neoplasms were observed in rats ingesting 2.0 or 0.2 mg/kg of body weight per day. The authors concluded that HCBD-induced renal neoplasms developed only at doses higher than those causing discernible renal injury (Kociba et al., 1977). Induction of lung adenomas was not observed in male strain A mice following intraperitoneal administration of HCBD (4 or 8 mg/kg of body weight) 3 times per week until a total of 52 or 96 mg had been administered (Theiss et al., 1977). HCBD did not act as an initiator in an initiation/promotion experiment in mouse skin, nor did it cause tumours in the skin or systemically after repeated application to the skin (Van Duuren et al., 1979).

6. EFFECTS ON HUMANS

Farm workers exposed intermittently for 4 years to HCBD exhibited higher incidences of hypotension, myocardial dystrophy, nervous disorder, liver function disorders and respiratory tract lesions (Kiasniuk et al., 1969).

7. GUIDELINE VALUE

Kidney tumours were observed in a long-term oral study in rats. HCBD has not been shown to be carcinogenic by other routes of exposure. IARC (1987) has placed HCBD in Group 3. Both positive and negative results for HCBD have been obtained in bacterial assays for point mutation; however, several metabolites have given positive results.

On the basis of the available metabolic and toxicological information, it was considered that a TDI approach was most appropriate for derivation of a guideline value. A TDI of 0.2 µg/kg of body weight was therefore calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for limited evidence of carcinogenicity and the genotoxicity of some metabolites) to the NOAEL of 0.2 mg/kg of body weight per day for renal toxicity in a 2-year feeding study in rats (Kociba et al., 1977; IPCS, 1994). This gives a guideline value of 0.6 µg/litre, based on an allocation of 10% of the TDI to drinking-water.

A practical quantification level for HCBD is of the order of 2 µg/litre, which is above the guideline value. However, the most probable source of HCBD in drinking-water is from its use in the manufacture of chlorine, and concentrations in drinking-water can, therefore, be controlled by specifying the HCBD content of such chemicals coming into contact with water.

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