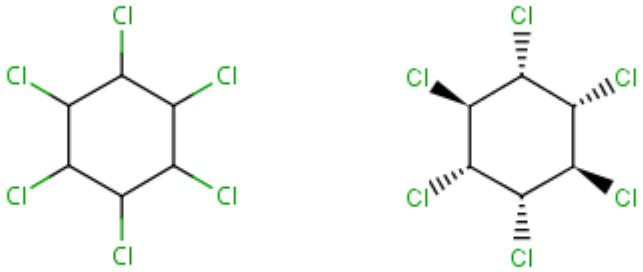
HEXACHLOROCYCLOHEXANE & LINDANE

C_6-H_6-Cl_6

Chemical structure



Chemical formulae of HCH[1] and Lindane[2]

Properties

Technical-grade hexachlorocyclohexane is a mixture of several hexachlorocyclohexane isomers. Each isomer has slightly different physical and chemical properties, including solubilities. The α isomer is practically insoluble in water but soluble in chloroform and benzene. The β isomer is very slightly soluble in water and slightly soluble in chloroform and benzene. The γ isomer (lindane) is practically insoluble in water but very soluble in chloroform, ethanol, acetone, ether, and benzene. The δ isomer is practically insoluble in water but soluble in ethanol, ether, and benzene. Technical-grade lindane (99% γ isomer) (HSDB 2009) is stable under normal temperature and pressure (Akron 2009). Physical and chemical properties of α-, β-, γ-, and δ-hexachlorocyclohexane (HCH) are listed in the following table.

Table 1: Properties of hexachlorocyclohexane (NTP, 2011)

Property	α-HCH	β-HCH	γ-HCH	δ-HCH
Molecular weight	290.8	290.8	290.8	290.8
Specific gravity	1.87	1.89	1.85	NA
Melting point	158°C	309°C	112.5°C	141.5°C
Boiling point	288°C	60°C at 0.50 mm Hg	323.4°C at 760 mm Hg	60°C at 0.36 mm Hg
Log K_{ow}	3.8	3.78	3.72	4.14
Water solubility	0.002 g/L[a]	0.0002 g/L[b]	0.0073 g/L[a]	0.0314 g/L[a]
Vapor pressure	4.5×10^{-5} mm Hg[a]	3.6×10^{-7} mm Hg[b]	4.20×10^{-5} mm Hg[b]	3.5×10^{-5} mm Hg[a]

Source: HSDB 2009. NA = not available. [a]At 25°C. [b]At 20°C

Contamination source

Technical hexachlorocyclohexane (HCH) is a mixture of various HCH isomers; alpha (α),beta (β), delta (δ) and gamma (γ) (also known as lindane). Both technical HCH and γ-HCH have been globally used as insecticides, and γ-HCH also for medical treatment in humans and animals. The insecticidal activity can be almost exclusively attributed to the γ-isomer. In some areas in the world these compounds are still in use. Because of the lipophilic properties and persistence in the environment, β-HCH followed by α-HCH and to a less extent γ-HCH may give rise to bioaccumulation and biomagnification through the food chain (EFSA, 2005).

Technical HCH contains a number of impurities, such as chlorinated benzenes,

[1]http://chem.sis.nlm.nih.gov.vdicp.health.fgov.be:8080/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=getAll3DMViewFiles&nextPage=jsp%2Fcommon%2FChemFull.jsp%3FcalledFrom%3Dlite&chemid=0000608731&formatType=_3D
[2]http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=getAll3DMViewFiles&nextPage=jsp%2Fcommon%2FChemFull.jsp%3FcalledFrom%3Dlite&chemid=0000058899&formatType=_3D

heptachlorocyclohexane and octachlorocyclohexane, which contribute to the unpleasant odour. Moreover, 2,3,7,8-tetrachloro-p-dioxin (2,3,7,8-TCDD) was found in technical HCH at a concentration of 13 µg/kg.

HCHs belong to the group of organochlorine pesticides. Since the beginning of commercial production in the early 1950s, γ-HCH became one of the most widely utilized insecticides worldwide. It has been used as a spray for foliage, in soil applications, for seed treatment and in baits for rodent control. Furthermore, it has been applied on a variety of fruits, seed grains, vegetable crops, in forestry and for poultry and other livestock. Aside from agricultural applications, it has been used for wood and timber protection and also in human medicine for treatment of head lice (EFSA, 2005).
Besides γ-HCH, also technical grade HCH was applied in many countries as an insecticide. It is estimated that total of 382,000 tonnes of technical grade HCH and 81,000 tonnes of γ-HCH were used in Europe from 1970 to 1996. This is equivalent to an estimated cumulative use of 259,000 tonnes α-HCH, 20,000 tonnes β-HCH and 135,000 tonnes γ-HCH.

Analytical method

A number of well-proven and validated methods for analysis of HCH isomers in various environmental and biological matrices are available. Currently, high resolution gas chromatography with electron capture detection (GC/ECD) is the analytical method of choice not only to differentiate between the different isomers but also to separate them from possible interfering co-extractants (EFSA, 2005).

Toxicity

With respect to acute exposure, γ-HCH is the most toxic followed by α-, δ-, and β-HCH. At chronic exposure, however, β-HCH is the most toxic followed by α-, γ-, and δ-HCH. The increased toxicity of β-HCH following chronic exposures is most likely due to its longer biological half-life and its accumulation over time in the body (ATSDR, 2003).

γ-HCH
LD50s were 88 - 190 and 59 - 562 mg/kg bw/day in rats and mice, respectively (EFSA, 2005).
Orally dosed γ-HCH is moderately neurotoxic in mice and rats with NOAELs of 6 - 7 mg/kg bw/day in acute and sub-chronic studies (FAO/WHO, 2002).
Numerous cases of fatal human poisoning and non-fatal illness caused by γ-HCH have been reported (Hayes, 1982). Symptoms of γ-HCH intoxication are seizures, convulsions, vomiting and dizziness (Davies *et al*., 1983; Kurt *et al*., 1986; Petring *et al*., 1986; Berry *et al*., 1987)

In short- and long-term oral studies of toxicity and studies of reproductive toxicity in rats, γ-HCH was found to be toxic to kidney and liver. Renal toxicity of γ-HCH was specific to male rats and a consequence of accumulation of $\alpha_2$micro-globulin, a protein that is not found in humans and this effect is therefore not of relevance for humans (FAO/WHO, 2002). Partially reversible hepatocellular hypertrophy was observed in a number of studies on rabbits, rats and mice. In a 2-year study of toxicity and carcinogenicity in rats, increased liver weight, hepatocellular hypertrophy and increased spleen weight were observed with a NOAEL of 10 mg/kg of diet (equal to 0.47 mg/kg bw/day) (Amyes, 1990).
γ-HCH is not carcinogenic in rats or dogs, but increased incidences of adenomas and carcinomas of the liver were observed at a dose of 23 mg/kg bw/day in a specific strain of mice, agouti and pseudoagouti mice; whereas other strains of mice did not show a clear tumourigenic response to γ-HCH (FAO/WHO, 2002).

γ-HCH at non-cytotoxic concentrations was not genotoxic *in vivo* or *in vitro (EFSA, 2005)*.

γ-HCH had anti-estrogenic properties in several studies in mice and rats with effects at doses of 5 mg/kg bw/day or higher (FAO/WHO, 2002).
In developmental studies in rats, including a multi-generation study, reduced survival and decreased body weight were observed in addition to increased incidence of supernumerary ribs and delay in tooth eruption and hair growth (FAO/WHO, 2002). The critical effect in these studies was neurotoxicity with a NOAEL of 0.8 mg/kg bw/day. In its derivation of an ADI, JMPR considered the existing database adequate to also characterize the potential hazard of γ-HCH to foetuses, infants as well as children. They established an ADI of 0 – 0.005 mg/kg bw on the basis of the NOAEL of 0.47 mg/kg bw/day, in the long-term study of toxicity and carcinogenicity in rats using a uncertainty

factor of 100. An acute RfD of 0.06 mg/kg bw was also established on the basis of the NOAEL of 6 mg/kg bw/day in the study of acute neurotoxicity in rats, using a uncertainty factor of 100 (FAO/WHO, 2002).

α-HCH
Acute oral LD50 values for α-HCH lie between 0.5 - 5 g/kg bw in rats and mice. Signs of intoxication were mainly from the nervous system (EFSA, 2005).

In a 90-day study rats given 0, 2, 10, 50 or 250 mg α-HCH/kg diet showed growth depression at the highest dose (equivalent to 12.5 mg α-HCH/kg bw/day). Liver hypertrophy was seen at a dose of 10 mg/kg diet (equivalent to 0.5 mg/kg bw/day). The NOAEL was 2 mg α-HCH/kg diet (equivalent to 0.1 mg/kg bw/day). Signs of immunosuppression (reduced levels of immunoglobulines) were seen at 2.5 mg α-HCH/kg bw/day (Kuiper *et al.,* 1985).

No adequate long-term toxicity studies or studies on reproduction and teratogenicity have been identified for α-HCH.

Mutagenicity data for α-HCH are limited. α-HCH was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation (Lawlor and Haworth, 1979; Nishimura, 1982).

Studies on initiation-promotion show that α-HCH is a tumour promoter in the liver of mice and rats (WHO-IPCS, 1992). Several long-term studies (> 24 and up to 107 weeks) have been carried out in rodents. In rats and mice given 100 to 600 mg α-HCH/kg diet hyperplastic nodules and/or hepatocellular adenomas were found in mice only. Two mice studies and one rat study, using dose levels of up to 160 mg/kg diet (mice) and 640 mg/kg diet (rats) did not show any increase in the incidence of tumours. The absence of mutagenic activity in *in vitro* studies indicates that the α-HCH-induced tumourigenicity observed in mice has a non-genetic mechanism (WHO-IPCS, 1992).
The major urinary metabolite of α-HCH in rats, 2,4,6-trichlorophenol, was reported by IARC (1987) to be carcinogenic for animals (classified as a chlorophenol in group 2B).

β-HCH
Oral LD50s for β-HCH were 8 and 16 g/kg bw/day for rats and mice, respectively. Signs of intoxication were mainly from the nervous system. However, β-HCH penetrates the blood brain barrier less readily than the other isomers (EFSA, 2005).

In a 90-day study in rats given β-HCH liver changes similar to those induced by α-HCH were seen at 2.5 mg β-HCH/kg bw/day. Some gonadal effects were also seen at doses of 7.5 and 12.5 mg/kg bw/day. The NOAEL was 2 mg β-HCH/kg diet (equivalent to 0.1 mg β-HCH/kg bw/day) (EFSA, 2005).

In a long-term rat study reported in 1950 doses of 10, 100 or 800 mg β-HCH/kg diet (equivalent to 0.5, 5 and 40 mg/kg bw/day, respectively) all led to liver enlargement and histological changes.

The carcinogenic potential of β-HCH has been investigated in two studies on mice. In one study, 200 mg β-HCH/kg diet (equivalent to 40 mg/kg bw/day) was given for 110 weeks, and liver enlargement, hyperplastic changes, and an increase in benign and malignant tumours were reported. In the other study, where 500 mg β-HCH/kg diet were administered for 24 weeks, no tumours were observed. In several initiation promotion studies in rats β-HCH was shown to be a tumour promoter in rat liver (WHO-IPCS, 1992). A possible link between human exposure to HCH and breast cancer has been examined in several epidemiological studies. Most of them were equivocal or had very limited power to assess this hypothesis. A non-significant trend (P = 0.24) between β-HCH in serum and breast cancer risk was observed during a 17-year follow-up of a Copenhagen cohort (Høyer *et al*., 1998). Cross sectional studies have not supported this finding (Calle *et al*., 2002).

Mutagenicity data for β-HCH are limited. β-HCH was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation (Lawlor and Haworth, 1979; Nishimura, 1982). β-HCH was positive in an *in vivo* bone marrow metaphase test in rats (Shimazu *et al*., 1976; IARC, 1979).

In a two-generation reproduction study on rats exposed to β-HCH liver changes were found. A dose level of 10 mg/kg diet resulted in increased mortality and infertility. The NOAEL was 2 mg β-HCH/kg diet (equivalent to 0.1 mg β-HCH/kg bw/day). No compound-related teratogenic effects were found in an extension to this study.

A weak estrogenic effect has been described for β-HCH with the uterus as a target organ. The mechanism and significance of this effect are uncertain. β-HCH did not displace 17-β- estradiol from its receptor (WHO-IPCS, 1992), but seems to indirectly activate the estrogen receptor, possibly via c-ErbB2 activation. β-HCH promotes transformation and invasiveness of MCF-7 human breast cancer cells (Zou and Matsumura, 2003).

Carcinogenicity
α- and β-HCH are tumour promoters in rat liver. HCHs were classified by IARC in group 2B (possibly carcinogenic) on the basis of inadequate evidence for carcinogenicity to humans, sufficient (for technical grade and the alpha-isomer) and limited evidence for carcinogenicity to animals (for β- and γ-HCHs) (IARC, 1987).
In the European Union, lindane was not classified for carcinogenicity.

Establishment of Health Based Reference Values
No ADI has been established by JMPR for the technical grade HCH.
JMPR (FAO/WHO,2002) established an ADI of 0.005 mg/kg bw/day for lindane on the basis of the NOAEL of 0.47 mg/kg bw/day, in the long-term study of toxicity and carcinogenicity in rats using a uncertainty factor of 100. An acute RfD of 0.06 mg/kg bw was also established on the basis of the NOAEL of 6 mg/kg bw/day in the study of acute neurotoxicity in rats, using a uncertainty factor of 100 (FAO/WHO, 2002).
In 1992 Health Canada set a group TDI for all HCH isomers of 0.3 µg/kg bw (Feeley, 2005, EFSA, 2005).

Occurrence in food

Lindane bioaccumulates in fatty tissues. It is found in human milk, dairy product, animal fat, fish and eggs.

Content of α-HCH, β-HCH and lindane in food samples taken by Fromberg et al. (2011) from 1998 to 2003 in Denmark are presented in table 1.
Concentration of α-HCH and β-HCH measured by Macgregor et al. (2010) in eels in Scotland riviers (2004-2008) were low, generally below 3 µg/kg ww. Concentration of HCH (sum) measured by Szlinder-Richert et al. (2010) in eels in Poland ranged between 0.6 and 6.0 ng/g ww.
Martinez et al. (1997) in Spain detected lindane in pasteurized milk at the levels of 0.007 mg/kg milk fat.

Table 1: Content of α-HCH, β-HCH and lindane in food samples taken by Fromberg et al. (2011) from 1998 to 2003 in Denmark

Foodstuff	Mean α-HCH (µg/kg fish and egg and µg/kg fat for other foods).	Mean β-HCH (µg/kg fish and egg and µg/kg fat for other foods).	Mean lindane (µg/kg fish and egg and µg/kg fat for other foods).
Chicken fat	0.4	0.3	1.1
Turkey fat	0.3		0.8
Beef fat		0.3	0.6
Pork fat	0.4		0.4
Milk, Danish	0.3		0.4
Cheese, Danish			1.0
Cheese, foreign	0.5	0.4	1.9
Butter, Danish			0.6
Butter, foreign		0.3	
Butter fat, mixed			1.0
Eel, farmed, raw	1.8	2.1	3.0
Greenland halibut, raw	1.2		

Herring, raw	0.4	0.5	0.9
Herring, pickled	0.6	0.5	
Herring, smoked	0.4	0.5	0.5
Lumpsucker, raw	1.0	0.8	2.6
Mackerel, raw	0.6		0.7
Mackerel, smoked	0.8		
Mackerel, tinned in tomato	0.2	0.3	0.5
Rainbow trout, farmed, raw	0.4	0.4	0.9
Salmon, raw	0.4	0.5	1.3
Trout, marine farmed, raw	0.7	0.6	1.0
Fish oil	1.7	1.7	1.6
Cod liver oil	4.6	0.3	1.6

The continuous decline of exposure to HCHs is also substantiated by numerous investigations of human milk specimens from different areas of the world. Analyses of more than 2000 individual human milk samples from women living in Western Germany collected and analyzed between 1984 and 2001 indicate that the level of β-HCH has declined by more than 85% during this period and currently amounts on average to about 0.020 mg/kg milk fat (EFSA, 2005).
B-HCH was detected in 22% of the Belgian mothers human milk collected in 2006 during the fourth World Health Organization Human biomonitoring campaigns (Colles et al., 2008). Mean concentration was 11.0 ± 7.7 ng/g fat.

Dietary exposure assessment

Food is the main source of exposure to HCHs for the general population.

Fromberg et al. (2011) have estimated the dietary intake of α-HCH, β-HCH and lindane for Danish adults to 0.6, 0.6, 0.8 ng/kg bw/day (mean), 0.9, 0.9, 1.2 ng/kg bw/day (P90) and 1.0, 1.0, 1.4 ng/kg bw/day (P95). Calculated estimation for children was 1.1, 1.1, 1.5 ng/kg bw/day (mean), 1.8,1.7, 2.4 ng/kg bw/day (P90) and 2.1, 2.1,2.7 ng/kg bw/day (P95).

Recent representative dietary intake studies for European countries are scarce. Ongoing market basket studies performed between 1994 and 2003 in the Czech Republic, where HCHs were produced and used for a long time, indicate a decline of daily dietary intakes. While in 1994 the median daily intake for α-, β-, γ- and δ-HCH was 4.3, 8.4, 19.0 and 12.0 ng/kg bw, respectively (Ruprich *et al.*, 1995), the corresponding intake values in 2002 were reported as 1.6, 2.1, 6.4 and 4.4 ng/kg bw, respectively (Ruprich *et al.*, 2003).

Daily dietary intake from 8 countries (Finland, Guatemala, Japan, The Netherlands, Switzerland, Thailand, the United Kingdom and the United States) showed mean intakes for HCH that were generally <0.04 µg/kg bw (Ahmed, 1999).

Mean dietary exposure of adult population in France to lindane is estimated between 0.001 µg/kg bw/day (0-0.007) (LB) and 0.18 µg/kg bw/day (0.17-0.19) (UB). Mean exposure of children is estimated between 0.002 µg/kg bw/day (0-0.008) (LB) and 0.24 µg/kg bw/day (0.23-0.29) (UB).
Mean dietary exposure of other HCH for French adult is estimated to 0.21 µg/kg bw/day (0.19-0.22) U(UB)) and for children is estimated to 0.24 µg/kg bw/day (0.23-0.25) (UB) (ANSES, 2011).

Risk characterization

ANSES (2011) has calculated an EDI (mean % of TDI) between 0.0 and 4.8% for the French children and between 0.0 and 3.5% for the French adults on basis of a TDI of 0.005 mg/kg bw/day.

Studies conducted in Guatemala, Japan, The Netherlands, Switzerland, the United Kingdom and the United States reported mean daily intake around <0.1% of the ADI (Ahmed, 1999).
Dietary exposure of the Danish population to lindane is in the low ng/kg bw/day range which is four orders of magnitude below the tolerable daily intake (TDI) of 5000 ng/kg bw/day (table 2).

Table 2: Lindane dietary exposure for adult and children and percentage of the TDI

Population	Dietary exposure (ng/kg bw/day)	%TDI (5000 ng/kg bw/day) (WHO, 2002)
Danish adults[1] - mean	0.8	0.02
Danish adults[1] - P90	1.2	0.02
Danish adults[1] - P95	1.4	0.03
Danish children[1] - mean	1.5	0.03
Danish children[1] - P90	2.4	0.05
Danish children[1] - P95	2.7	0.05
Czech Republic[2] - Median	6.4	1.13
France- adults[3] - Mean	1-180	0.02-3.6
France- children[3] - Mean	2-240	0.04-4.8

[1]Fromberg et al., 2011
[2]Ruprich et al., 2003
[3]ANSES, 2011

Legislation

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC which will repeal the four Council Directives

Recommendations

The CONTAM Panel of EFSA made the following recommendations for HCH in feed (EFSA, 2005):

- A European reporting system, allowing for exposure assessment of undesirable substances in feed is missing, and detailed data describing the background contamination of feedingstuffs and food of animal and plant origin are lacking
- Concentration levels for individual substances rather than condensed summaries for compound groups would be mandatory for a better understanding of the occurrence situation of undesirable substances in different feed materials and compound feeds as a prerequisite for a meaningful risk assessment and finally for a derivation of a possible temporal trend of the respective compounds in the feed chain.

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