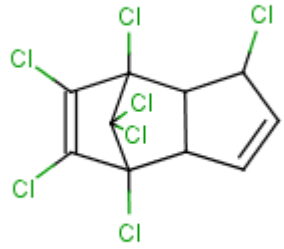
HEPTACHLOR

$C_{10}H_5Cl_7$

Chemical structure



Chemical formula[1]

Heptachlor (CAS Nr. 76-44-8) has a relative molecular mass of 373.5.
Technical heptachlor usually contains about 72% heptachlor, and 28% related compounds including about 18% trans-chlordane, 2% cis-chlordane, 2% nonachlor, 1% chlordene, 0.2% hexachlorobutadiene and 10 - 15 other compounds (EFSA, 2007).

Properties

Heptachlor is a persistent pesticide. This compound has very low volatility and is essentially insoluble in water (table 1). Its biodegradation in soil is very slow, with halftimes measured in decades. Heptachlor is therefore persistent in the environment and can be expected to accumulate in sediment long after application has ceased. In the environment heptachlor is rapidly converted to heptachlor epoxide and photoheptachlor. Heptachlor is lipophilic and persistent in the environment and tend to accumulate in the food chain; photoheptachlor is found in fish and marine mammals. The half-life of heptachlor-epoxide in the air soil and water has been estimated to be in the range of months to many years (EFSA, 2007).

Table 1: Properties of heptachlor (EFSA, 2007)

Solubility in water (mg/L)	0.10 (15°C), 0.18 (25°C)
Melting point (°C)	93, 98
Henry's law constant Pa.m3/mol (25°C):	233, 29.75, 29.73, 62, 38
log Koc(mL/g)	4.9
log Kow	6.1, 4.4-5.5, 5.94
Vapour pressure Pa (25°C):	$4.0\ 10^{-2}$, $5.3\ 10^{-2}$, $3.1 \cdot 10^{-2}$

Contamination source

Heptachlor was commercially introduced as a non-systemic contact insecticide in 1945. It was also a major constituent (about 10%) of technical chlordane. Heptachlor was used for agricultural purposes, soil and seed treatment, wood protection and termite- and household insect control. It has also been used in the control of malaria. In 1970, the use of heptachlor throughout the world was as follows: Africa, 5%; Asia, 15%; Canada and the USA, 5%; Europe, 60%; and South America, 15%. It has been banned for use in the European Union since 1984 and in most other countries worldwide because of the persistency in the environment of the two break-down products heptachlor epoxide and photoheptachlor (EFSA, 2007). The use of heptachlor has diminished substantially over the last two decades.

Heptachlor is among the 12 persistent organic pollutants being considered for international action to reduce or eliminate their releases under the Stockholm convention signed in 2001.

Analytical method

A number of well-proven, validated multi-residue methods are available for the quantitative determination of heptachlor and heptachlor epoxide in various environmental matrices, including

[1] http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/ChemInfo.jsp?calledFrom=lite&type=names

food, feed and other biological specimens (Muir and Sverko, 2006). Depending on the type of feed material, whether it is of plant or animal origin, the extraction and the extent of necessary subsequent clean up steps may differ considerably. While after grinding, solid materials are commonly extracted with boiling organic solvents using conventional Twisselmann, Soxhlet, accelerated solvent extraction (ASE) or microwave assisted extraction (MAE) procedures or by supercritical fluid extraction (SFE), liquid samples are mostly extracted by liquid/liquid partitioning. Co-extracted fat and other compounds which potentially may disturb the determination of heptachlor and heptachlor epoxide can be removed by gel permeation chromatography (GPC) and by adsorption chromatography on various solid phase materials (SPE), such as Florisil or alumina.

Clean up procedures that involve sulfuric acid need to be avoided when analyzing for heptachlor and heptachlor epoxide since acid treatment of samples may degrade these compounds (Andersen *et al.,* 2001). Due to the high electronegativity caused by the seven chlorine atoms of heptachlor and heptachlor epoxide, HRGC/ECD is the analytical method most commonly used (EFSA, 2007).

Toxicity

Heptachlor shows moderate acute toxicity and heptachlor epoxide and photoheptachlor are more toxic than heptachlor. In mammals, the main target organs are the nervous system and the liver, but also the reproductive and the immune system are affected. Heptachlor and heptachlor epoxide cause liver tumours in mice, but are not genotoxic (EFSA, 2007).

Toxicokinetic
Heptachlor, which is also a component of technical-grade chlordane, is biotransformed to its epoxide. Subsequent dechlorination reactions lead to hydroxylated compounds, which are excreted primarily as glucuronides. Minor metabolites include heptachlor and heptachlor epoxide.

Acute toxicity
Heptachlor shows moderate acute toxicity compared with other organochlorine pesticides. LD_{50}s are in the range of 40 – 162 mg/kg bw for rats and mice (EFSA, 2007). The dose response curve for mortality is quite steep. The main acute target is the central nervous system showing hyper excitability, tremors, convulsions, and paralysis. Liver toxicity has also been reported.

Repeated toxicity
Upon repeated exposure to heptachlor in mice and rats liver enlargement and histopathological signs of enlargement of centrilobular- and midzonal hepatocytes were seen. Such effects were seen at doses of 1.3 and 2 mg/kg bw/day and above this dose in mice and rats, respectively. Clinical effects and effects on the liver have been observed in experiments in dogs.
Heptachlor induces hepatic and gonadal microsomal oxidative enzymes and also steroid hormone metabolism.

Carcinogenicity
Available epidemiological studies on cancer mortality do not show a clear relationship to human heptachlor body burden.
Chlordane, technical-grade chlordane, heptachlor, technical-grade heptachlor, heptachlor epoxide and a mixture of heptachlor and heptachlor epoxide have been tested for carcinogenicity by oral administration in several strains of mice and rats. In the studies in mice, increased incidences of hepatocellular neoplasms (including carcinomas) were seen in both males and females. Increased incidences of thyroid follicular-cell adenomas and carcinomas were seen in one study each with chlordane and technical-grade heptachlor in rats. In initiation–promotion studies in mice, administration of chlordane or heptachlor after N-nitrosodiethylamine resulted in increased incidences of hepatocellular tumours (IARC, 2001).

Heptachlor has been evaluated by the International Agency for Research on Cancer (IARC, 2001). There is *inadequate evidence* in humans for the carcinogenicity of heptachlor. There is *sufficient evidence* in experimental animals for the carcinogenicity of heptachlor. Heptachlor is possibly carcinogenic to humans (Group 2B).

In the European Union, heptachlor was classified as Carc. Cat.3; R40 according to Dir 67/548/EEC and as Carc.2 H351 according to CLP Regulation (EC) No. 1272/2008.

Genotoxicity
No data were available on the genetic and related effects of chlordane or heptachlor in humans. Both compounds inhibited gap-junctional intercellular communication and induced gene mutations in rodent cells. Likewise, both compounds induced unscheduled DNA synthesis in human fibroblasts but not in rodent hepatocytes. Heptachlor did not induce mutations in hepatocytes of *lacI* transgenic mice treated *in vivo*. Neither chlordane nor heptachlor caused dominant lethal mutation in mice. Neither chlordane nor heptachlor was mutagenic to bacteria, and only chlordane damaged bacterial or plasmid DNA (IARC, 2001). Hence it can be concluded that heptachlor and its epoxide show mostly negative responses in genotoxicity testing.

Reproductive toxicity
Chlordane and heptachlor are toxic to reproduction and development in mice, rats and mink.
Fertility studies in rats injected with heptachlor subcutaneously resulted in LOAELs of 5 mg/kg bw per day for suppression of sex hormone levels, disruptions in female cyclicity, and delays in mating behaviour.
In developmental toxicity studies in rats and beagle dogs, there were usually no clinical signs of maternal toxicity (dose-related alterations in weight gain) until mortality occurred (NOAEL for maternal toxicity = 3 mg/kg bw per day). In one study, reduced litter sizes were noted, but postnatal mortality of the pups was the most obvious finding (NOAEL for pre- or postnatal survival of pups = 6 mg/kg bw per day). Studies evaluating effects on reproductive organs did not note such effects. No teratological effects were observed. Recent developmental toxicity studies in rats showed both neurotoxicity and immunotoxicity with NOAELs and LOAELs, respectively, of 0.030 mg/kg bw/day (WHO-IPCS, 2006).

Neurotoxicity
There is accumulating evidence that the nervous system and its development are influenced by cyclodiene pesticides. Heptachlor and the more potent heptachlor epoxide appear to act on the $GABA_A$ receptor by binding to the chloride channel thereby blocking the inhibitory actions of the GABA neurotransmitter. The profile of effects produced by repeated heptachlor administration to female rats consisted of altered activity, hyperexcitability, and autonomic effects (NOAEL = 2 mg/kg bw per day). Neurotoxicological studies on perinatal heptachlor exposure in the rat (0.03, 0.3, or 3 mg/kg bw/day) suggested developmental delays, alterations in GABAergic neuro-transmission, and neuro-behavioural changes, including cognitive deficits at all doses. It also appears that the dopaminergic system is particularly sensitive to heptachlor, which increases dopamine uptake, attributed to dopamine transporter induction (WHO-IPCS, 2006).

Immunotoxicity
Immunological studies in rats indicate the suppression of the primary IgM and secondary IgG anti-sheep red blood cell responses following perinatal exposure to all tested doses (0.03, 0.3, or 3 mg/kg bw per day) of heptachlor. Studies on peripheral mononuclear blood cells from monkeys showed immunomodulatory effects of heptachlor (WHO-IPCS, 2006).

Establishment of Health Based Reference Values
A tolerable daily intake (TDI) of 0.0001 mg/kg bw was derived based on histopathological changes in the liver in dog studies with a NOAEL of 0.025 mg/kg bw/day. An uncertainty factor of 200 was used (10 for intra- and 10 for inter species variation and an extra factor of 2 for inadequacy of the data base (WHO-IPCS, 2006).

Occurrence in food

During the period when these compounds were being used as pesticides, a number of studies were carried out to determine the concentrations of chlordane, heptachlor and related compounds in foods. Most foods were found to contain low or undetectable concentrations of these chemicals, with the exception of meat, poultry and dairy products, in which significant concentrations were found.

Concentrations in organochlorine pesticides measured is fish in Belgium in 2005-2006 were generally under the reporting limit (Vromman et al., 2008).

The level of heptachlor epoxide isomer B measured in smoked fish products available in Szczecin, Poland ranged from 0.06 ± 0.01 (smoked eel) to 0.27 ± 0.07 ng/g ww (smoked sprat). The content of heptachlor was 0.48-1.99 ng/g ww (Witczak &Tomza-Marciniak, 2010).

The most significant source of exposure of infants to chlordane, heptachlor and their metabolites appears to be breast milk, in which the concentrations can be much higher than those in dairy milk. In a large international survey carried out in the 1970s, the mean concentrations of heptachlor and heptachlor epoxide in human breast milk ranged from 2 to 720 ng/g of fat; 2560 ng of heptachlor per gram of fat was found in a rural area in Spain (WHO-IPCS, 1984). The median concentration of heptachlor epoxide in breast milk of women in the USA reported in 1991 was 10 ng/g of fat, with a 90th percentile value of 100 ng/g of fat.
Concentration of heptachlor were found under the quantification limit of 10 ng/g in Belgian human milk collected in 2006 during the fourth World Health Organization survey (Colles et al., 2008).

Dietary exposure assessment

Dietary exposure of the Belgian adult population to heptachlor has been estimated to 0.21 ng/kg bw/day (mean) and 1.3 ng/kg bw/day (P97.5) on basis on data from the Belgian control plan 2010 and 2011. Estimations of the dietary intake of total heptachlor in Poland during the period 1970 – 1996 were less than 10 ng/kg bw (Falandysz, 2003). The main sources were thought to be meat, meat products, and animal fats (WHO-IPCS, 2006). More recent data were not available. In breast adipose tissue sampled in the period 1997 – 2001, the concentration was usually about at or below the limit of quantification of 2.5 - 6 µg/kg of fat (Struciński *et al.,* 2002).
Dietary exposure of the Belgian adult population to heptachlor epoxide has been estimated to 0.4 ng/kg bw/day (mean) and 2.91 ng/kg bw/day (P97.5) on basis on data from the Belgian control plan 2010 and 2011. In the Czech Republic, heptachlor epoxide was determined in the period 2004/2005 in 220 composite food samples (consumption market baskets) representing 205 food types and in the form of 3696 individual samples. Samples with the highest values were: liver sausage, marinated fish, butter and cheese. The estimated daily dietary intake for adults was less than 4 ng/kg bw (Ruprich, 2006).
In Germany, heptachlor epoxide is routinely found in human milk. Since 1980 almost 40,000 human milk samples were analyzed in Germany for organochlorine pesticides, including cis(exo)-heptachlor epoxide. While the mean levels in 1979 - 1981 still amounted to 33 µg/kg milk fat, they decreased to 7 µg/kg milk fat in 1990 and 6 µg/kg milk fat in 1997. In the last 10 years the levels of cis (exo)-heptachlor epoxide are in the range or lower than the analytical limit of detection (BGVV, 2001).

Risk characterization

The available data indicate that the average daily intake of total heptachlor in the EU is well below the tolerable daily intake of 100 ng/kg bw (EFSA, 2007) (table 2)

Table 2: Heptachlor dietary exposure for adult and children and percentage of the PTDI

Population	Dietary exposure (ng/kg bw/day)	%PTDI (= 100 ng/kg bw/day) (WHO, 2006)
Heptachlor		
Belgian, adults - Mean	0.21	0.21
Belgian, adults - P97,5	1.3	1.3
Belgian consumer, adults - Mean	2.39	2.39
Poland (Falandysz, 2003)	4.88	4.88
Heptachlor epoxyde		
Belgian, adults - Mean	0.4	0.4
Belgian, adults - P97,5	2.91	2.91
Belgian consumer, adults - Mean	4.08	4.08
Belgian consumer, adults - P97,5	10.01	10.01
Adult Czech Republic (Ruprich, 2006)	4	10

Nougadère et al. (2011) have calculated an estimated daily intake (EDI) (mean % of TDI) between

9.8 and 182.2% for the French children and between 4.6 and 141.8% for the French adult on basis of monitoring result of 2005 and 2006. The higher percentage are explained by high concentration of heptachlor in some food.

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 heptachlor in feed (EFSA, 2007):

- Besides heptachlor and heptachlor epoxide, the analyses of feed samples, especially of marine origin, should also include the determination of photoheptachlor.
- In the clean-up of samples, treatment with sulfuric acid must be avoided in order to prevent the decomposition of the analytes.
- Inter-comparisons performed on biological samples revealed large discrepancies in the performance of laboratories, indicating scope for improvement of the analytical methods.
- Toxicity and kinetic studies in fish exposed to heptachlor and heptachlor epoxide via the diet are lacking and should be conducted.

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