LEARNING TOXICOLOGY
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HEXACHLOROCYCLOHEXANE (HCH)

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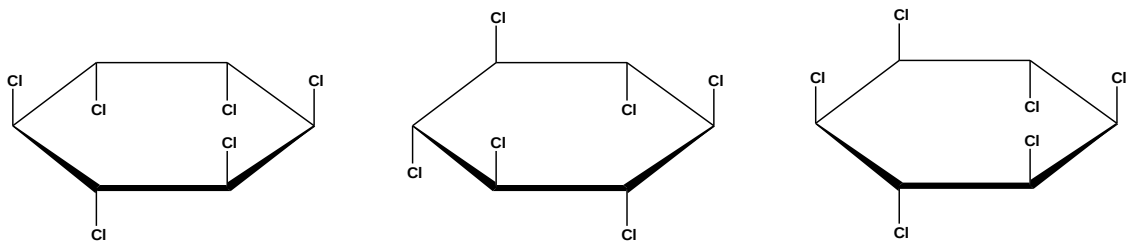
INTRODUCTION

Technical hexachlorocyclohexanes (HCHs) are 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 for fruits and vegetable crops (including greenhouse vegetables and tobacco), for seeds treatment, and in forestry. γ-HCH was also used for medical treatments in humans and animals (1% concentration) and as lotion, cream or shampoo. The application of both Lindane ((γ–HCH isomer (after separation of the waste isomers) and the technical HCHs (containing the whole isomers mixture) during the last six decades determined environmental contamination at global dimensions (Vijgen et. al. 2006). Between 4 and 7 million tonnes wastes of toxic, persistent/bioaccumulative HCHs were produced and used around the globe during 60 years of HCHs production (Vijgen et. al. 2011). The use of gamma-HCH in Europe decreased from about 25 000 tonnes in 1970 to 671 tonnes in 1990**.** Commercial (γ -HCH (Lindane) production in the US ended in 1976 and in EU in 2000. Lindane was restricted to seeds treatment, soil application followed by incorporation into the topsoil, industrial treatment of timber and logs, as insecticide for public health and veterinary use, and indoor industrial and residential applications. Because of its carcinogenic, persistent, bioaccumulative and endocrine disrupting roperties (ATSDR, 2005), the use of Lindane has been banned in 52 countries, and HCHs/Lindane were included in Protocols/Conventions reagarding POPS monitoring (Stockholm Convention, 2007; UNEP New POPS 2010).

STRUCTURE OF HCHs

Synthesised raw HCH contains a total of 8 stereoisomers which are termed α- to θ-HCH depending on the spatial arrangements of the chlorine atoms. Among these, only the α, β, γ, δ, and ε isomers are stable and are formed in the following percentages in reaction mixtures: α, 55–80%; β, 5–14%; γ, 8–15%; δ, 2–16%, and ε, 3–5%. The remaining three isomers are formed in trace. In the Figure 1. are presented the formulas for α- HCH, β-HCH and γ-HCH isomers.



α- HCH **β- HCH** **γ-HCH**

PROPERTIES OF HCHs

The isomer Lindane contains > 99% gama-HCH. It is a white solid with a low vapour pressure, poorly soluble in water but very soluble in organic solvents acetone, aromatic and chlorinated solvents. γ-HCH is relatively stable against acids, and oxidative and hydrolytic degradation.Under alkaline conditions dehydrohalogenation reaction occurs.

Some physical properties of alpha-, beta- and gamma-HCH are listed in Table 1.

The insecticidal activity can be almost exclusively attributed to the γ-isomer. Hence, some companies began in the 1950s to isolate the active ingredient γ-HCH which was used under the name Lindane. The (γ -HCH used in human and veterinary medicinal and pharmaceutical products must be 99% pure. In some countries, the change to Lindane began much later than the 1950s. For example, India used technical HCHs until the late 1990s and then changed to the production/use of Lindane. In China, the use of technical HCHs was banned in 1983, and Lindane use began in 1990 (Li et al. 2005).

Table 1. Physical properties of alfa-, beta- and gama-HCH

Property	alfa-HCH	beta-HCH	gamma-HCH
Molecular weight	290.83	290.83	290.83
Solubility in water	10 ppm; 69.5 mg/L at 28 °C	5 ppm	17 ppm
Log Kow	3.46–3.85	4.50; 3.78; 3.98	3.3–3.61
Log Koc	3.57	3.57	3.0–3.57
Vapour pressure	0.02 mmHg at 20 °C	0.005 mmHg at 20 °C	9.4×10^{-6} mmHg at 20^{0}C
Henry's law constant at 25 °C	4.8×10^{-6} atm·m^3/mol 6.0×10^{-6} atm·^{m3}/mol	4.5×10^{-7} atm·m^3/mol	7.8×10^{-6} atm·m^3/mol l3.2×10^{-6} atm·m^3/mol

Source: ATSDR 2000.

PERSISTENCE OF HCHs

HCHs/Lindane are very persistent in the environment, bioaccumulative in sediments, plants and animals and toxic. HCHs/Lindane present in soil are slowly degraded and accumulated or can leach to groundwater, sorb to soil particulates and volatilize to the atmosphere. Gamma-HCH (Lindane) sorbed to the soil can partition to the atmosphere by wind erosion of surface soil particulates and via volatilization from treated agricultural soils and plants. Persistence is dependent on climate, properties of the soils, microbial environment, diffusion and method of application, i.e. foliar or soil incorporation (EPA, 2003). Extensive studies in temperate countries with aerobic soils have

shown that HCHs persist in the soil for several years. 41% of applied Lindane was recovered 11years after application to soil (Padhi et al. 2016). Beta-HCH is the most persistent isomer. Biodegradation and the abiotic degradation by UV rays occur in the environment and produce pentachlorocyclohexane at a slower rate than in the case of gamma-HCH. Lindane have been found in environmental samples all over the world, as well as in human blood, human breast milk and human adipose tissue in different studied populations (EPA, 2003), especially in Arctic communities that depend on marine foods for nutrition (AMAP, 2014). HCHs have been in used across the world to control agricultural pests and vector- borne diseases and also have been identified in hazardous waste sites. The HCHs by-products generally became hazardous waste causing considerable concern because for each tonne of Lindane produced, 8–12 t of other HCH isomers are generated as waste Viigen et. *al.* 2011). Although nowadays HCHs use is restricted or completely banned in the most countries, it continues posing serious environmental and health concerns, being imperative to develop methods to remove HCHs from the environment (Alvarez et.al. 2012).

BIOACCUMULATION. BIOCONCENTRATION OF HCHs

Because of the lipophilic properties and persistence in the environment, β-HCH followed by α-HCH and to a less extent γ-HCH may generate bioaccumulation/biomagnification through the food chain (FDA, 2015). The octanol-water partition coefficient (log Kow = 3.8) for alpha-HCH indicates a potential for bioaccumulation. Due to the persistence of beta-HCH (with reduced water solubility) rapid bioconcentration mentioned as BCF are determined in invertebrates (125 days), in fish (250–1500 days) and in birds and humans 525 days). The bioconcentration is higher and the elimination slower for beta-HCH than for the other HCHs isomers (ATSDR, 2005). Alpha- and gamma-HCH are relatively water-soluble and have little bioconcentration potential.Gamma-HCH is prevalent in the marine environment and soils, but low

levels are found in biota. Residues of HCHs are found in water and air samples all over the world, higher concentrations being found in the waters of northern regions comparing with regions in the mid-latitudes. The LRTAP of gamma-HCH far away from the source has been demonstrated, especially or the European Region (AMAP, 2014). The presence of large quantities of gamma-HCH in oceans or lakes delay the response of atmospheric concentrations to reduction emissions Viigen et.al. 2011).

MONITORING

A study of global distribution and LRTAP of chlorinated hydrocarbons in the Western Pacific, Eastern Indian and Antarctic Oceans confirmed the widespread distribution of HCHs isomers in air and water samples. Gamma-HCH/Lindane was found in the lower troposphere, in the snow and in the ice samples collected in the Canadian islands and oceans which represent a major reservoir of gamma-HCH / Lindane (Stockholm Convention, 2007). In the Arctic Ocean, during 20 years of monitoring, α- and γ-HCHs declined in air at all monitoring stations. The half-live of α-HCH range from 4.8 to 5.7 years; and half-live of γ-HCH was about 4 years for all sites. While the use of technical HCHs decreased significantly since the 1980s, Lindane continued to be used in Canada until 2004 and in the US until 2009.The atmospheric declined rates of Lindane have accelerated in the Arctic after its use has been restricted in North America (AMAP, 2014). Alpha-HCH have a long residence time in the atmosphere and is controlled primarily by transport (ATSDR, 2005). According to EMEP UE, 2008, less than 1% of Lindane in air is bound to particles, and dry deposition is superior to wet deposition and depends on the season. Lindane concentrations in air are correlated with ambient air temperature and removal by rainfall and dry deposition, the maximum concentrations being observed in the summer period, suggesting that more volatile POPs may be revolatilised from soil or other surface media during warmer periods. According to the official / inofficial emission data, the total emissions of Lindane the EU

decreased in period 1990-2006 by 98%. Temporal variations of γ-HCH emission in individual countries during 1990-2006 can be characterized on the example of official emissions of the UK, Spain, and Germany. Lindane emission in the UK during this period decreased by 87% and in Spain increased by 26%. In Germany annual emissions of Lindane have been ceased in 1990-1998 (from 60 tonnes in 1990 down to 14.5 tonnes in 1998) (EMEP, 2008). It can be estimated that during a 28-years period about 60% of the emissions will be transported outside the EU Region (EMEP, 2014).

SOURCES OF HUMAN EXPOSURE AT HCHs

HCHs /Lindane can be found worldwide in all environmental compartments and levels in air, water, soil sediment, aquatic and terrestrial organisms and food (Stockholm Convention, 2007), although the concentrations in different sites are generally low and gradually decreased. Lindane can bio-accumulate easily in the food chain due to its high lipid solubility and can bio-concentrate rapidly in microorganisms, invertebrates, fish, birds and mammals. HCH isomers, including Lindane, accumulate in colder climates of the world. General population exposure to gamma-HCH can result from food intake (FDA, 2015), particularly from animal origin, products like milk and meat, as well as water polluted with HCHs / Lindane (EPA, 2003) There is potential dietary exposure particularly to people in Alaska and the Arctic area who depend on traditional subsistence foods such as fish and marine mammals (AMAP, 2014). The largest source of Lindane released to the air was the agricultural use of this pesticide. All applications of Lindane are now forbidden in the EU and the US. Some air releases also occur during the production of the pesticides and as a result of other uses or disposal of wastes from former production of HCHs, and of HCHs retained in contaminated soils and construction and demolition waste (Stockholm Convention, 2007).

Humans are exposed daily through food, Lindane being found in blood, adipose tissue and breast milk The determined mean concentrations in human adipose

tissue in various countries ranged from < 0.01 to 0.2 mg/kg on a fat basis. Concentrations of lindane in human milk are generally low (< 0.001 to 0.1 mg/kg on a fat basis) representing a reduction over time. Food is the main source of exposure to β-HCH for the general population (FDA, 2015). Reported concentrations in fat-containing food products ranged up to 0.03 mg/kg (on a fat basis), but in milk products levels up to 4 mg/kg (on a fat basis were found. (ATSDR, 2005).

HEALTH HAZARD

Evidence exists that humans absorb HCHs/ Lindane vapour or dust via inhalation followed by the rapid absorption of gamma -HCH from the gastrointestinal tract. The distribution of HCH isomers in humans and animals is primarily in the adipose tissue but also HCHs are found most often in the hundreds of tests of human body tissue: blood, adipose tissue, brain, kidney, muscle, lungs, heart, spleen, liver, blood and breast-milk (WHO, 2016). Because of their chemical structure, HCHs break down slowly, build up in fatty tissue and remain in living organisms for long time. HCHs /Lindane have a wide range of both acute and chronic health effects, including cancer, neurological damage, and birth defects. At high doses Lindane has been shown to be neurotoxic, hepatotoxic, immunotoxic and to have reproductive effects in laboratory animals (EPA, 2003). Human acute intoxication data show that Lindane can cause severe neurological effects, and possible haematological effects. Adverse health effects associated with pharmaceutical use of Lindane include seizures, dizziness, headaches, and paresthesia. Seizures and deaths have been reported following Lindane shampoo use with repeat or prolonged application. (FDA, 2015). The International Agency for Research on Cancer (IARC) classified Lindane as possibly carcinogenic to humans (ATSDR, 2005).

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