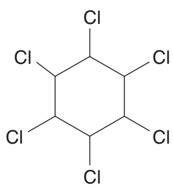
Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers

CAS No. 58-89-9 (Lindane)

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Lindane is also known as γ-hexachlorocyclohexane



Carcinogenicity

Lindane (as γ-hexachlorocyclohexane), hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to technical-grade hexachlorocyclohexane or individual isomers caused tumors in rodents at two different tissue sites. Dietary administration of technical-grade hexachlorocyclohexane (66.5% α isomer, 11.4% β isomer, 15.2% lindane, 6.4% δ isomer, and 0.5% other isomers), lindane, α- or β-hexachlorocyclohexane, or mixtures of various isomers caused liver tumors in both sexes of several strains of mice (IARC 1979). Dietary administration of the α isomer also caused liver tumors in rats (Schulte-Hermann *et al.* 1981, IARC 1987). In addition, dietary exposure to technical-grade hexachlorocyclohexane caused tumors of the lymphoreticular system in mice of both sexes (Kashyap *et al*. 1979, IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to hexachlorocyclohexane or its isomers. Three cases of leukemia (paramyeloblastic and myelomonocytic) were reported in men exposed to lindane with or without co-exposure to other chemicals (IARC 1974, 1979). Many cases of aplastic anemia have also been associated with exposure to hexachlorocyclohexane or lindane, and death from lung cancer was increased among agricultural workers who had used hexachlorocyclohexane (unspecified) and a variety of other pesticides and herbicides.

Properties

Hexachlorocyclohexane isomers, including lindane, are organochlorine pesticide compounds that are brownish to white crystalline powders with a penetrating musty odor (IARC 1974). 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.

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

Use

The only identified uses for hexachlorocyclohexane-containing products are based on the insecticidal activity of the γ isomer (lindane), which is considered to be the only insecticidally effective component (Extoxnet 1996). Lindane or technical-grade hexachlorocyclohexane containing the γ isomer is used primarily as an insecticide in the treatment of wood and wooden structures, seed grains, and livestock (ATSDR 2005, HSDB 2009). Other major uses are as an insecticide for several dozen fruit and vegetable crops, in baits and seed treatments for rodent control, and for treatment of scabies (mites) and lice. It is approved by the U.S. Food and Drug Administration for use in three products for the treatment of lice and scabies (one lotion and two shampoos) (FDA 2009). Agricultural and pesticide uses accounted for about 270,000 kg (594,000 lb) of lindane and 450,000 kg (1 million pounds) of technical-grade hexachlorocyclohexane in 1974; the remaining uses were industrial or pharmaceutical (IARC 1979).

Production

Technical-grade hexachlorocyclohexane is produced as a mixture of isomers (primarily the α, β, γ, δ, and ε isomers) by photochlorination of benzene, a reaction that can be started by free-radical initiators such as visible or ultraviolet light, X-rays, or gamma rays (ATSDR 2005). The active γ-hexachlorocyclohexane (lindane) can be concentrated by treatment with methanol or acetic acid, followed by fractional crystallization, which produces technical grade lindane containing 99.9% γ isomer. Commercial production of lindane in the United States began in 1945 and peaked in the 1950s, when 17.6 million pounds was manufactured (IARC 1974). Lindane is no longer produced commercially in the United States, but it is produced by 13 manufacturers worldwide, including 7 in India and 4 in China (SRI 2009), and is available from 42 suppliers, including 19 U.S. suppliers (ChemSources 2009). U.S. imports of hexachlorocyclohexane increased from 310,000 lb to 1.4 million pounds between 1989 and 1999, declining to zero in 2005 and remaining zero through 2017 except in 2006, when 73,000 lb was imported. U.S. exports of hexachlorocyclohexane increased from zero in 1990 to 1.5 million pounds in 2005, but by 2017 had declined to 882 pounds (USITC 2018).

Exposure

Evidence that the general population in the United States has been exposed to at least one of the isomers of hexachlorocyclohexane is provided by the 2009–2010 National Health and Examination Survey (CDC 2018), which measured the β isomer in serum. In all race and ethnicity groups, the mean serum levels (reported as nanograms per gram of lipid) increased with increasing age and were consistently higher in women than in men. Levels were also higher in Hispanic than non-Hispanic individuals, regardless of race or gender. The highest levels were detected in minority women over the age of 60

(31.6 ng/g in non-Hispanic black women and 45.4 ng/g in Hispanic women). Among adolescents (aged 12 to 19), the proportion of results below the limit of detection (2.19 ng/g) was too high to allow means to be calculated for any race or ethnicity group or by gender. Similarly, in the 20-to-39 age group, means could not be calculated for non-Hispanic men or non-Hispanic black women. Overall, measureable mean levels in men ranged from 3 ng/g in non-Hispanic white men aged 40 to 59 to 17.8 ng/g in Hispanic men over the age of 60. Among women, the lowest reported mean levels were in the 20-to-39 age group (2.19 ng/g in non-Hispanic white women and 5.24 ng/g in Hispanic women). Because β-hexachlorocyclohexane has a longer half-life than the other isomers, it is likely to be detected in a higher percentage of the general population.

The routes of potential human exposure to lindane and other hexachlorocyclohexane isomers are ingestion, inhalation, and dermal contact (HSDB 2009). The general population potentially is exposed through consumption of foodstuffs contaminated with pesticide residues. According to U.S. Food and Drug Administration's Total Diet Survey, lindane was detected in 279 of 2,168 samples and in at least one sample of all 54 different food items analyzed (FDA 2006). Most of the food items in which lindane was detected had significant fat content; however, the highest lindane concentrations were in pickles and raw mushrooms, which have low fat content. Daily dietary intake of hexachlorocyclohexane isomers by the adult U.S. population was estimated at 0.010 μg/kg (10 ng/kg) of body weight for all isomers and 0.002 μg/kg (2 ng/kg) for lindane. For 1982 to 1984, the estimated dietary intake of lindane was 1.9 ng/kg of body weight for infants aged 6 to 11 months and 7.9 ng/kg for toddlers aged two years, who had the highest average daily intake. By 1986 to 1991, daily intake had fallen to 0.8 ng/kg for infants and 3.2 ng/kg for toddlers (ATSDR 2005).

Dermal exposure occurs when shampoos and lotions containing lindane are used for the treatment of lice and scabies (FDA 2009). The highest average blood concentration of lindane measured in children after scabies treatment with one of these products was 0.028 μg/mL (ATSDR 2005).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of lindane ranged from 314 and 2,118 lb between 1988 and 1997. In 1998, over 25,000 lb was sent to a hazardous-waste landfill. By 2006, releases had declined to 10 lb. In 2007, five facilities released a total of 1,555 lb of lindane, mostly off site for unspecified management (TRI 2009). Lindane was found in at least 189 hazardous-waste sites currently or formerly on the National Priorities List; it occurred in air at 9 sites, surface water at 33 sites, sediment at 36 sites, and soil at 90 sites. The Non-Occupational Pesticide Exposure Study, published in 1990, collected personal air samples at one U.S. location with high pesticide usage and one with low to medium usage. The range of mean γ-hexachlorocyclohexane concentration was 7 to 22 ng/m^3 at the high-usage site and 0.7 to 5 ng/m^3 at the low- to medium-usage site (ATSDR 2005).

Hexachlorocyclohexane isomers have been detected in human fatty tissue, blood, and breast milk. The National Human Adipose Tissue Survey (NHATS), conducted in 1982, found β-hexachlorocyclohexane in 87% of composite post-mortem samples of fatty tissue. According to NHATS data, the mean concentration of β-hexachlorocyclohexane in fat decreased from 0.45 ppm in 1970 to 0.16 ppm in 1981. The levels were highest in the southern United States. β-Hexachlorocyclohexane was measured in breast milk at a concentration of 0.6 ng/g in Canadian populations living near the Great Lakes. In the Netherlands, concentrations of γ-hexachlorocyclohexane in breast-milk fat in 1988 ranged from 0.01 to 0.24 mg/kg (HSDB 2009). Many other studies in populations throughout the world, especially Arctic populations, have found hexachlorocyclohexane isomers in blood, fat, and breast-milk samples. Hexachlorocyclohexane isomers have been measured at higher concentrations in all types of samples in areas of the world where lindane is still extensively used for pest control, such as India and Africa.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 15,036 workers, including 5,153 women, potentially were exposed to lindane (NIOSH 1990). No occupational exposure data were found for other hexachlorocyclohexane isomers.

Regulations

Department of Transportation (DOT)

Lindane is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Lindane (all isomers) is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Hexachlorocyclohexane is listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 4.2 μg/L for lindane; = 0.0066 μg/L for hexachlorocyclohexane (technical grade); = 0.00036 μg/L for the α isomer; = 0.0080 μg/L for the β isomer; based on fish or shellfish consumption only = 4.4 μg/L for lindane; = 0.010 μg/L for hexachlorocyclohexane (technical grade); = 0.00039 μg/L for the α isomer; = 0.014 μg/L for the β isomer.
Lindane is designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for lindane, all isomers.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Lindane and α-hexachlorocyclohexane are listed substances subject to reporting requirements.
Reportable quantity (RQ) = 1 lb for lindane.
Threshold planning quantity (TPQ) = 1,000 lb for lindane solid in powder form with particle size < 100 μm or solution or molten form; = 10,000 lb for lindane in all other forms.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.4 mg/L for lindane.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of lindane or hexachlorocyclohexane = U129, F024.
Lindane is listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0002 mg/L for lindane.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level in bottled water = 0.0002 mg/L for lindane.
Action levels for lindane in food and in animal feed range from 0.1 to 0.5 ppm.
Lindane is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 0.5 mg/m^3 for lindane.
Potential for dermal absorption for lindane.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m^3 for lindane.
Potential for dermal absorption for lindane.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) = 0.5 mg/m^3 for lindane.
Immediately dangerous to life and health (IDLH) limit = 50 mg/m^3 for lindane.
Potential for dermal absorption for lindane.
A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 12/18/09.

ATSDR. 2005. *Toxicological Profile for Alpha-, Beta-, Gamma-, and Delta-Hexachlorocyclohexane*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp43.html.

CDC. 2018. beta-Hexachlorocyclohexane. In F*ourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018,* vol. 2. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. pp. 53-60.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on lindane. Last accessed: 12/18/09.

Extoxnet. 1996. *Lindane*. Extension Toxicology Network Pesticide Information Profiles. http://extoxnet.orst.edu/pips/lindane.htm.

FDA. 2006. *Total Diet Study Market Baskets 1991-3 through 2003-4.* U.S. Food and Drug Administration. http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/UCM184304.pdf.

FDA. 2009. *The Electronic Orange Book. U.S. Food and Drug Administration.* http://www.fda.gov/cder/ob/default.htm and select Search by Active Ingredient and search on lindane. Last accessed: 12/09.

HSDB. 2009. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 12/18/09.

IARC. 1974. BHC (technical grades) and lindane. In *Some Organochlorine Pesticides*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 5. Lyon, France: International Agency for Research on Cancer. pp. 47-74.

IARC. 1979. Hexachlorocyclohexane (technical HCH and lindane). In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 195-239.

IARC. 1982. Hexachlorocyclohexane. In *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 4. Lyon, France: International Agency for Research on Cancer. pp. 133-135.

IARC. 1987. Hexachlorocyclohexanes. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 220-222.

Kashyap SK, Nigam SK, Gupta RC, Karnik AB, Chatterjee SK. 1979. Carcinogenicity of hexachlorocyclohexane (BHC) in pure inbred Swiss mice. *J Environ Sci Health B* 14(3): 305-318.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. http://www.cdc.gov/noes/noes1/09318sic.html.

Schulte-Hermann R, Parzefall W. 1981. Failure to discriminate initiation from promotion of liver tumors in a long-term study with the phenobarbital-type inducer alpha-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. *Cancer Res* 41(10): 4140-4146.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 5/09.

TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select Lindane.

USITC. 2018. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2903810000.