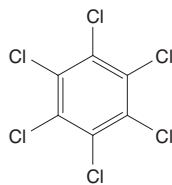


Hexachlorobenzene

CAS No. 118-74-1

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Hexachlorobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to hexachlorobenzene caused tumors in several rodent species and at two different tissue sites. Dietary administration of hexachlorobenzene caused liver tumors (hepatocellular tumors) in female rats and mice and in hamsters of both sexes. In hamsters of both sexes, it also caused blood-vessel tumors in the liver (hemangioendothelioma) and benign thyroid-gland tumors (follicular-cell adenoma) (IARC 1979, Smith and Cabral 1980).

Since hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, additional studies in rats have been identified. Dietary exposure caused benign and malignant liver tumors (bile-duct adenoma and hepatocellular carcinoma) and benign blood-vessel tumors in the liver (hemangioma) in females and benign kidney tumors (adenoma) in both sexes. Perinatal exposure to hexachlorobenzene followed by dietary exposure for up to 130 weeks caused benign liver tumors (hepatocellular adenoma) in females, benign parathyroid-gland tumors (adenoma) in males, and benign adrenal-gland tumors (pheochromocytoma) in both sexes (IARC 1987, 2001).

Cancer Studies in Humans

At the time hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, no epidemiological studies had evaluated the relationship between human cancer and exposure specifically to hexachlorobenzene. Since then, several case-control studies, mostly of breast cancer, have been published. The International Agency for Research on Cancer concluded that there was inadequate evidence in humans for the carcinogenicity of hexachlorobenzene (IARC 2001). No association between exposure to hexachlorobenzene and breast cancer risk was found in five small case-control studies or three larger studies that assessed hexachlorobenzene exposure by measuring it in biological samples obtained close to the time of breast-cancer diagnosis. In a fourth large study, which assessed exposure from banked serum samples collected prior to diagnosis, breast-cancer risk was higher among women with higher serum concentrations of hexachlorobenzene than among women with the lowest serum concentrations, based on sampling close to the time of diagnosis; however, no dose-response relationship was observed. No significant associations between serum hexachlorobenzene concentration and risk of cancer at other tissue sites were found; however, only one study was available for each tissue site.

Since the IARC (2001) review, a number of additional studies have been conducted, mainly of breast cancer and non-Hodgkin lymphoma (NHL). Two studies reported significantly higher serum hexachlorobenzene levels in women with breast cancer than in control

subjects (Charlier *et al.* 2003, 2004), but four other studies found no significant association between serum hexachlorobenzene level and breast cancer (Lopez-Carrillo *et al.* 2002, Pavuk *et al.* 2003, Iwasaki *et al.* 2008, Itoh *et al.* 2009). One study of NHL found a significant dose-related risk associated with serum hexachlorobenzene (Spinelli *et al.* 2007), and two studies found a significantly increased risk among patients with high Epstein-Barr virus antibody titers (also associated with NHL) (Hardell *et al.* 2001, 2009). However, no association with NHL was observed in a study using banked serum samples collected up to 20 years prior to diagnosis and analyzed for hexachlorobenzene (Cantor *et al.* 2003) or in a multicenter study of lymphoma patients using blood levels of hexachlorobenzene measured close to the time of diagnosis (Cocco *et al.* 2008).

Properties

Hexachlorobenzene is a chlorinated aromatic hydrocarbon that exists as a white needle-like crystalline solid at room temperature (HSDB 2010). It is practically insoluble in water, sparingly soluble in cold alcohol and carbon tetrachloride, and soluble in benzene, chloroform, ether, and carbon disulfide. It is stable under normal temperatures and pressures (Akron 2010). It is combustible but it does not ignite readily. When hexachlorobenzene decomposes, it emits highly toxic fumes of hydrochloric acid, other chlorinated compounds, carbon monoxide, and carbon dioxide. Physical and chemical properties of hexachlorobenzene are listed in the following table.

Property	Information
Molecular weight	284.8
Density	2.044 g/cm ³ at 23°C
Melting point	231.8°C
Boiling point	325°C
Log <i>K</i> _{ow}	5.73
Water solubility	4.7 × 10 ⁻⁶ g/L at 25°C
Vapor density relative to air	9.83

Source: HSDB 2010.

Use

No commercial uses of hexachlorobenzene as an end product in the United States were identified (ATSDR 2002). Previously, it was used as a seed-treatment fungicide for onions, sorghum, wheat, and other grains (IARC 1979). All registered pesticide uses in the United States were voluntarily cancelled in 1984 (ATSDR 2002). Hexachlorobenzene was also used as a chemical intermediate in dye manufacturing, in the synthesis of other organic chemicals, and in the production of pyrotechnic compositions for the military. It was used as a raw material for synthetic rubber, as a plasticizer for polyvinyl chloride, as a porosity controller in the manufacture of electrodes, and as a wood preservative (IARC 1979, ATSDR 2002).

Production

Commercial production of hexachlorobenzene in the United States was first reported in 1933 (IARC 1979). In 1975, 3,200 lb of hexachlorobenzene was produced, but it has not been produced commercially in the United States since the late 1970s. In 1972, an estimated 2.5 million to 4.9 million pounds of hexachlorobenzene was produced in the United States as a by-product of production of other chlorinated solvents and pesticides such as tetrachloroethylene, trichloroethylene, carbon tetrachloride, vinyl chloride, atrazine, propazine, simazine, pentachlorophenol, chlorothalonil, and pentachloronitrobenzene. In addition, hexachlorobenzene may be formed during combustion of municipal waste or in waste streams from chlor-alkali and wood-preserving plants (IARC 1979, ATSDR 2002).

In 2002, nine U.S. chemical companies produced hexachlorobenzene for on-site use and processing, as a by-product, or as an impurity (ATSDR 2002). In 2009, hexachlorobenzene was available from 19 suppliers worldwide, including 13 U.S. suppliers (ChemSources 2010). U.S. imports of hexachlorobenzene totaled about 5,400 lb in 1977 and 38,000 lb in 1982 (ATSDR 2002, HSDB 2010).

Exposure

Although hexachlorobenzene is no longer used in the United States, it is highly persistent in the environment and highly resistant to degradation; therefore, the general population may be exposed at low concentrations (ATSDR 2002). When hexachlorobenzene is released to the environment, it may be taken up by plants and animals and can bioaccumulate through the food chain. Hexachlorobenzene has been detected in terrestrial, freshwater, and marine food chains in the Great Lakes and Arctic regions. Populations with the greatest potential for exposure include those who ingest fish caught from contaminated water bodies or who reside near former manufacturing or waste-disposal sites.

Evidence that people living in the United States, as well as other countries, still are exposed to hexachlorobenzene comes from studies that have detected it in the blood of numerous groups of people, especially indigenous populations of Arctic regions, in the blood and breast milk of pregnant and lactating women, and in the placenta and cord blood. The 2009–2010 National Health and Nutrition Examination Survey found mean lipid-adjusted serum hexachlorobenzene levels ranging from about 7 to 13 ng/g of lipid in men across different age, race, and ethnic groups and about 6 to 23 ng/g in women; the highest level (23 ng/g) was found among Hispanic women over the age of 60 (CDC 2018).

Organochlorine compounds were found in maternal blood in circumpolar populations in Greenland, Canada, Alaska, Norway, Sweden, Iceland, Finland, and Russia (Van Oostdam *et al.* 2004). In Arctic Canada, hexachlorobenzene was detected in all samples of maternal blood, and at higher concentrations in blood from Inuit women than from Caucasian women in the region. Cord-blood plasma concentrations showed a similar trend (Butler Walker *et al.* 2003). Breast-milk concentrations of hexachlorobenzene were elevated in populations of women who ate contaminated local fish in New York State and Finland (Greizerstein *et al.* 1999, Kostyniak *et al.* 1999, Fitzgerald *et al.* 2001, Damgaard *et al.* 2006). Hexachlorobenzene was found in all blood samples from pregnant women in an agricultural community in California (Fenster *et al.* 2006). The diet of the Inuit population in Greenland was studied to determine the source of the high and increasing concentration of hexachlorobenzene. The blood levels of hexachlorobenzene in Greenland Arctic populations appeared to correlate with consumption of meals containing seal and whale (Deutch *et al.* 2004, 2006). Hexachlorobenzene was detected in all adipose tissue samples collected at autopsy from Greenlanders (Dewailly *et al.* 1999). Hexachlorobenzene was detected in 98% of the blood samples collected from Akwesasne Mohawk youth living along the St. Lawrence River in New York State and Quebec; levels were somewhat higher in youths who had been breastfed as infants (Schell *et al.* 2003). In a study of consumers of sport fish in New York State, the mean blood hexachlorobenzene concentration was not significantly greater than that of nonconsumers of sport fish (Bloom *et al.* 2005).

In dietary surveys conducted by the U.S. Food and Drug Administration (FDA), the frequency at which hexachlorobenzene was detected in foods declined from 9% in the early 1980s to less than 2% in 1994 (ATSDR 2002). Consequently, the U.S. average daily intake of hexachlorobenzene through foods declined by a factor of 5 over this period. In the FDA Total Diet Study, hexachlorobenzene was de-

tected in 229 of 1,748 samples (13%) of 42 different foods; the highest concentration was found in butter (FDA 2006).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of hexachlorobenzene ranged from over 1 million pounds in 1989 and 1991 to a low of about 12,600 lb in 1997. In 2008, 49 facilities released at total of 50,636 lb of hexachlorobenzene, mostly to on-site and off-site landfills. The majority of releases came from 5 facilities, and 12 facilities reported releases of more than 100 lb (TRI 2010). When hexachlorobenzene is released to air, it tends to remain mainly in the vapor phase and can therefore be transported great distances (for example, from temperate to polar regions). When released to water, hexachlorobenzene is strongly adsorbed to particles and sediment and is not degraded or hydrolyzed (ATSDR 2002). In the Great Lakes region, hexachlorobenzene was found in drinking and surface water and, at higher levels, in soil and sediment. In 1972, it was detected in agricultural soils where it had been used as a pesticide, at lower levels in urban soils, and at higher levels in soils near uncontrolled hazardous-waste sites. It was found at high concentrations in sediments near industrial sites at Galveston Bay, Texas (ATSDR 2002).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,038 workers at 10 facilities, including 26 women, potentially were exposed to hexachlorobenzene (NIOSH 1990). The largest numbers of exposed workers were chemical technicians (467 workers) and their supervisors (187 workers). Occupations with the highest potential for past exposure included fungicide application, organic-chemical synthesis, synthetic-rubber production, seed disinfection, pesticide production, and wood preservation.

Regulations

Department of Transportation (DOT)

Hexachlorobenzene is considered a hazardous material, 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: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of hexachlorobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Chlorinated benzenes are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.000079 µg/L; based on fish or shellfish consumption only = 0.000079 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxic characteristic leaching procedure threshold = 0.13 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of hexachlorobenzene = U127, F024, F025, K016, K018, K030, K042, K085, K149, K150, K151.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.001 mg/L.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level in bottled water = 0.001 mg/L.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.002 mg/m³.

Potential for dermal absorption.

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