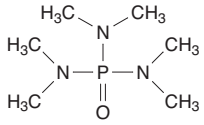
Hexamethylphosphoramide

CAS No. 680-31-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as HMPA or hexamethylphosphoric triamide



Carcinogenicity

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

Cancer Studies in Experimental Animals

Exposure of rats to hexamethylphosphoramide by inhalation caused nasal tumors, which are rare in this species. Inhalation of hexamethylphosphoramide caused benign and malignant nasal tumors (papilloma, epidermoid carcinoma, adenoid squamous carcinoma, transitional-cell carcinoma, and adenocarcinoma) in rats of both sexes (IARC 1977, Lee and Trochimowicz 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to hexamethylphosphoramide.

Properties

Hexamethylphosphoramide is a phosphoric acid amide derivative that exists at room temperature as a colorless to light-amber mobile liquid with a spicy odor. It is miscible with water and most organic liquids but is immiscible with high-boiling-point saturated hydrocarbons. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of hexamethylphosphoramide are listed in the following table.

Property	Information
Molecular weight	179.2[a]
Specific gravity	1.03 at 20°C[a]
Freezing point	5°C to 7°C[a]
Boiling point	233°C at 760 mm Hg[a]
Log K_{ow}	0.28[b]
Water solubility	1,000 g/L[b]
Vapor pressure	0.03 mm Hg at 25°C[c]
Vapor density relative to air	6.18[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009, [c]Akron 2009.

Use

Hexamethylphosphoramide was formerly used by its major U.S. producer only as a processing solvent for aromatic polyamide fiber (Kevlar); however, it now has a number of additional uses (IARC 1977, 1999, HSDB 2009). It is used as a solvent for other polymers, for gases, and for organic and organometallic reactions in research laboratories. It is also used as a polymerization catalyst, a stabilizer against thermal degradation in polystyrene, an additive to polyvinyl and polyolefin resins to protect against degradation by ultraviolet light, and a color-enhancing agent for the thiocyanate-cobalt complex used for cobalt detection. Hexamethylphosphoramide has been used as an antistatic agent and a flame retardant and deicing additive for jet fuels. It also can be used as a flame-retarding additive in lithium-ion batteries; however, it reduces the performance of the battery (Izquierdo-Gonzales *et al.* 2004).

Production

In 2009, hexamethylphosphoramide was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 21 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. production, import, or export volumes were found.

Exposure

The routes of potential human exposure to hexamethylphosphoramide are inhalation, ingestion, and dermal contact (HSDB 2009). The major source of exposure is probably occupational; however, the general population potentially could be exposed through release of hexamethylphosphoramide to the environment. No environmental releases of hexamethylphosphoramide were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009). Hexamethylphosphoramide exists in the air solely in the vapor phase and will be degraded by photochemically produced hydroxyl radicals, with a half-life of 2 hours (HSDB 2009). If released to soil or water, hexamethylphosphoramide may leach rapidly in soil and sediments. It is not expected to bioconcentrate in aquatic organisms.

EPA evaluated the potential for release of of hexamethylphosphoramide into the soil, surface water, and groundwater near a site in Spruance, Virginia, where hexamethylphosphoramide was used and disposed of (EPA 1980, 1999). In 1976, disposal of hexamethylphosphoramide from the facility directly into the James River was documented. Up to 48 lb per month was discharged; however, surface-water concentrations downstream from the discharge point were approximately 0.5 ppb, the lower limit of detection. Solid wastes from the Spruance site containing hexamethylphosphoramide also had been disposed of in Anniston, Alabama; evaluation of the disposal site indicated detectable quantities of hexamethylphosphoramide in a drainage ditch downstream from the disposal site, in an on-site groundwater well, and in a well upgradient from the disposal site, but not in Anniston's drinking water. The waste was removed from the disposal site, and remedial actions were taken at the site to mitigate risks of human exposure (EPA 1980). In 1999, hexamethylphosphoramide was identified as a contaminant in groundwater monitoring wells at the Spruance facility site, in nearby off-site wells at concentrations of up to 480 µg/L, and in surface water downgradient from the facility at a concentration of 0.17 µg/L (EPA 1999). Potential levels of off-site exposure were below levels of concern for human health and the environment.

Occupational exposure may occur among workers involved in the production of hexamethylphosphoramide or in its use as a solvent or chemical additive or in the packaging of consumer products. The National Institute for Occupational Safety and Health estimated that up to 90% of about 5,000 people who worked in U.S. laboratories that used hexamethylphosphoramide might have been exposed (NIOSH 1975). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 700 workers (in the Business Services industry), including 51 women, potentially were exposed to hexamethylphosphoramide (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Potential for dermal absorption.

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

Hexamethylphosphoramide is listed as a potential occupational carcinogen.

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: 4/29/09.

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp and select Registry Number and search on CAS number. Last accessed: 5/11/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on hexamethylphosphoramide. Last accessed: 4/29/09.

EPA. 1980. *Chemical Hazard Information Profiles (CHIPs), August 1976 – August 1978*. EPA 560/11-80-011. Washington, DC: U.S. Environmental Protection Agency. pp. 142-146.

EPA. 1999. *Environmental Indicator (EI) RCRIS code (CA750) – Migration of Contaminated Groundwater Under Control. DuPont Spruance Environmental Indicator Form.* U.S. Environmental Protection Agency. http://www.epa.gov/reg3wcmd/ca/va/gwpdf/gw_vad009305137.pdf.

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: 4/29/09.

IARC. 1977. Hexamethylphosphoramide. In *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 15. Lyon, France: International Agency for Research on Cancer. pp. 211-222.

IARC. 1999. Hexamethylphosphoramide. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. pp. 1465-1481.

Izquierdo-Gonzales S, Li W, Lucht BL. 2004. Hexamethylphosphoramide as a flame retarding additive for lithium-ion battery electrolytes. *J Power Sources* 135(1-2): 291-296.

Lee KP, Trochimowicz HJ. 1982. Induction of nasal tumors in rats exposed to hexamethylphosphoramide by inhalation. *J Natl Cancer Inst* 68(1): 157-171.

NIOSH. 1975. *Current Intelligence Bulletin 6. Hexamethylphosphoric Triamide (HMPA)*. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/78127_6.html.

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/x4066sic.html.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 4/29/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select Hexamethylphosphoramide. Last accessed: 4/29/09.