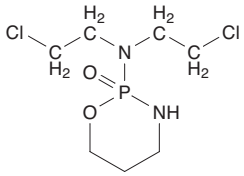
Cyclophosphamide

CAS No. 50-18-0

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Cyclophosphamide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Several epidemiological studies consistently found excesses of urinary-bladder cancer and leukemia among people treated with cyclophosphamide for various medical conditions. A case-control study in Germany found that the risk of leukemia increased with increasing dose of cyclophosphamide (IARC 1981, 1987). More recently, a nested case-control study of non-Hodgkin lymphoma patients reported that the risk of urinary-bladder cancer increased with increasing cumulative dose of cyclophosphamide (Travis *et al.* 1995).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of cyclophosphamide from studies in experimental animals. Exposure to cyclophosphamide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure (IARC 1981). In rats, exposure to cyclophosphamide in drinking water or by intravenous injection caused benign and malignant tumors at various tissue sites, including the urinary bladder. Cyclophosphamide administered by intraperitoneal injection to female rats caused benign and malignant mammary-gland tumors. In mice, cyclophosphamide administered by subcutaneous or intraperitoneal injection caused leukemia, lymphoma, and benign and malignant tumors at various sites, including the lung, liver, mammary gland, and injection site (IARC 1981, 1987).

Properties

Cyclophosphamide is an antineoplastic and immunosuppressant agent that is usually a fine white crystalline powder at room temperature. The substance liquefies and becomes an oily semisolid mass when water is removed under high vacuum. It is soluble in water, alcohol, chloroform, dioxane, and glycols, slightly soluble in benzene and carbon tetrachloride, very slightly soluble in ether and acetone, and insoluble in carbon disulfide. Cyclophosphamide is sensitive to oxidation, moisture, and light (Akron 2009). Physical and chemical properties of cyclophosphamide are listed in the following table.

Property	Information
Molecular weight	261.1[a]
Density	1.479 g/cm^3[b]
Melting point	49.5°C to 53°C[a]
Boiling point	336°C[b]
Log K_{ow}	0.63[a]
Water solubility	40 g/L at 20°C[a]
Vapor pressure	4.45×10^{-5} mm Hg at 25°C[c]
Dissociation constant (pK_b)	9.91[b]

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

Use

Cyclophosphamide is used as a drug to treat cancer and other medical conditions. In chemotherapy, it may be used alone, but more frequently is used concurrently or sequentially with other anticancer drugs. Cyclophosphamide is available in the United States as 25- or 50-mg tablets, as an oral solution, or in a crystalline hydrate form for injection in strengths of 100 to 2,000 mg. It is used to treat malignant lymphoma, multiple myeloma, leukemia, breast and ovarian cancer, neuroblastoma, retinoblastoma, and mycosis fungoides (MedlinePlus 2009, RxList 2010). Cyclophosphamide is also used as an immunosuppressive agent following organ transplants or to treat autoimmune disorders such as rheumatoid arthritis, Wegener granulomatosis, and nephrotic syndrome in children (Chabner *et al.* 2001). Researchers have tested cyclophosphamide for use as an insect chemosterilant and in the chemical shearing of sheep (IARC 1975).

Production

Cyclophosphamide is not produced in the United States, and no data on U.S. imports were found. Total U.S. sales were 600 kg (1,300 lb) annually in the mid 1970s (IARC 1975); more recent data were not found. In 2009, cyclophosphamide was available from seven U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing cyclophosphamide as the active ingredient were produced by eleven U.S. pharmaceutical companies (FDA 2009).

Exposure

The general population is not expected to be exposed to cyclophosphamide, because its use is limited to medical treatment. An estimated 500,000 patients worldwide are treated with cyclophosphamide annually (Travis *et al.* 1995). Doses used in medical treatment depend on the patient and the specific disease. Cyclophosphamide may be given orally (in 25- or 50-mg tablet form) or by intravenous injection (from 100-, 200-, or 500-mg or 1- or 2-g vials) (FDA 2009). The initial treatment for cancer patients with no hematologic deficiency may be 40 to 50 mg/kg of body weight in divided intravenous doses over two to five days; other regimens are 10 to 15 mg/kg every seven to ten days or 3 to 5 mg/kg twice a week. The adult dosage for tablets typically is 1 to 5 mg/kg per day for both initial and maintenance treatment of cancer. For nonmalignant diseases, an oral dose of 2.5 to 3 mg/kg per day is administered for 60 to 90 days (RxList 2010). In 2009, 1,564 clinical trials using cyclophosphamide were in progress or recently completed (ClinicalTrials 2009).

Occupational exposure may occur from skin contact or inhalation of dust during drug formulation or packaging. Health professionals who handle cyclophosphamide, such as pharmacists, nurses, and physicians, could potentially be exposed during drug preparation, administration, or cleanup; however, exposure can be avoided through the use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981). In a cross-sectional study of hospital workers, handling of cyclophosphamide was clearly related to its detection in the urine (Evelo *et al.* 1986). Of 62 urine samples collected from 17 nurses and pharmacy technicians who prepared or administered antineoplastic drugs, including cyclophosphamide, 18 contained cyclophosphamide, at concentrations ranging from 50 ng/L (the limit of detection) to 10,030 ng/L. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 30,026 workers, including 20,745 women, potentially were exposed to cyclophosphamide (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of cyclophosphamide = U058.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Cyclophosphamide is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

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

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