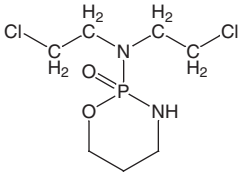
Cyclophosphamide
CAS No. 50-18-0

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 in humans. Several epidemiological studies have consistently found excesses of 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). Since cyclophosphamide was reviewed for listing in the *First Annual Report on Carcinogens*, a nested case-control study of non-Hodgkin's lymphoma patients treated with cyclophosphamide reported that the risk of bladder cancer increased with increasing cumulative dose of cyclophosphamide (Travis *et al.* 1995).

There is sufficient evidence for the carcinogenicity of cyclophosphamide in experimental animals. Cyclophosphamide caused benign and malignant tumors at multiple sites in rats and mice exposed by multiple routes (IARC 1981). Rats administered cyclophosphamide in their drinking water or by intravenous (i.v.) injection developed benign and malignant tumors at various tissue sites, including the bladder. Female rats administered cyclophosphamide by intraperitoneal (i.p.) injection developed benign and malignant mammary-gland tumors. Mice administered cyclophosphamide by subcutaneous or i.p. injection developed 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 alkylating agent and a derivative of nitrogen mustard. It is an odorless, fine white crystalline powder with a molecular weight of 261.1 and a melting point of 49.5°C to 53°C. Cyclophosphamide is soluble in water and ethanol; slightly soluble in benzene, ethylene glycol, carbon tetrachloride, and dioxane; and sparingly soluble in diethyl ether and acetone. Its log octanol-water partition coefficient is 0.63. Cyclophosphamide reacts with strong oxidizing agents, is sensitive to moisture and light, and is hydrolyzed in aqueous solutions above 30°C (IARC 1981, HSDB 2003).

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- to 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 (bone-marrow cancer), leukemia, breast and ovarian cancer, neuroblastoma (childhood nerve-cell cancer), retinoblastoma (childhood cancer of the retina), and mycosis fungoides (lymphoma of the skin) (IARC 1975, 1981, MEDLINEplus 2001, RxList 2001). Cyclophosphamide also is used as an immunosuppressive agent following organ transplants or to treat autoimmune disorders such as rheumatoid arthritis, Wegener's granulomatosis (an inflammation of the blood vessels), and nephrotic syndrome (a kidney disorder) 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 imports were found (IARC 1981). Total U.S. sales were reported to be about 600 kg (1,300 lb) annually in the mid 1970s (IARC 1975); more recent data were not found. In 2003, four U.S. suppliers of cyclophosphamide (ChemSources 2003) and four U.S. pharmaceutical companies with drug products approved by the U.S. Food and Drug Administration (FDA) containing cyclophosphamide as the active ingredient were identified (FDA 2003).

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 this drug 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 i.v. injection (100-mg, 200-mg, 500-mg, 1-g, or 2-g vials) (FDA 2003). The initial treatment for cancer patients with no hematologic deficiency may be 40 to 50 mg/kg of body weight in divided i.v. doses over two to five days, 10 to 15 mg/kg every seven to ten days, or 3 to 5 mg twice a week. The adult dosage for tablets typically is 1 to 5 mg/kg of body weight per day for both initial and maintenance treatment. For nonmalignant diseases, an oral dose of 2.5 to 3 mg/kg per day is administered for 60 to 90 days (RxList 2001).

Occupational exposure may occur from skin contact or inhalation of dust during drug formulation or packaging. Health professionals, such as pharmacists, nurses, and physicians, who handle cyclophosphamide 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). The National Occupational Exposure Survey (1981–1983) estimated that 30,026 workers, including 20,745 women, potentially were exposed to cyclophosphamide (NIOSH 1984).

Regulations

CPSC

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

EPA

Comprehensive Environmental Response, Compensation, and Liability Act
- Reportable Quantity (RQ) = 10 lb

Resource Conservation and Recovery Act
- Listed as a Hazardous Constituent of Waste
- Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U058

FDA

Cyclophosphamide is a prescription drug subject to labeling and other requirements

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