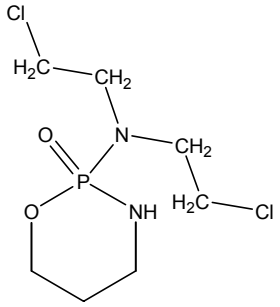
CYCLOPHOSPHAMIDE
CAS No. 50-18-0
First Listed in the *First Annual Report on Carcinogens*



CARCINOGENICITY

Cyclophosphamide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1981). Five epidemiological studies are available in which persons treated with cyclophosphamide for a variety of medical conditions were compared with similarly afflicted controls. These studies consistently demonstrate an excess of various neoplasms, especially of bladder cancer and leukemia, in the treated groups (IARC 1981, 1982, 1987).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of cyclophosphamide in experimental animals (IARC 1975, 1981, 1982, 1987). When administered in drinking water, cyclophosphamide induced transitional cell carcinomas, papillomas of the urinary bladder, and neurogenic sarcomas arising from the peripheral nerves in rats of both sexes. When administered by subcutaneous injection, cyclophosphamide induced mammary carcinomas, lymphomas and lymphoreticular neoplasms, pulmonary adenomas and sarcomas, squamous cell carcinomas (at the site of injection), and ovarian carcinomas in mice. When administered by intravenous injection, cyclophosphamide induced sarcomas of the peritoneal cavity, reticulum cell sarcomas, and hemangioendotheliomas in various organs in male rats (IARC 1981, 1987).

PROPERTIES

Cyclophosphamide is an odorless or almost odorless, fine, white, crystalline powder. It is soluble in water and ethanol, slightly soluble in benzene, ethylene glycol, carbon tetrachloride, and dioxane, and sparingly soluble in diethyl ether and acetone (IARC 1981, HSDB 2000). This chemical reacts with strong oxidizing agents, acids, and bases and is sensitive to moisture and light. Hydrolysis occurs in aqueous solutions above 30°C and polymerization can occur above 49°C. When heated to decomposition, it emits very toxic fumes of hydrogen chloride gas, phosphine, carbon monoxide, carbon dioxide, nitrogen oxides and phosphorus oxides (NTP 2001a, b).

USE

Cyclophosphamide belongs to a group of drugs called alkylating agents and is used to treat a variety of malignant and nonmalignant diseases. In chemotherapy, it may be used alone, but it is more frequently used concurrently or sequentially with other antineoplastic drugs. Cyclophosphamide is available in the U.S. in 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. This drug is used to treat malignant lymphoma, multiple myeloma, leukemias, breast and ovarian cancer, neuroblastoma, retinoblastoma, and mycosis fungoides (IARC 1975, 1981, NTP 2001a, b, MEDLINEplus 2001, RxList 2001). Cyclophosphamide is also used as an immunosuppressive agent following organ transplants or to treat rheumatoid arthritis, systemic lupus erythematosus, scleroderma, glomerulonephritis, chronic hepatitis, and other diseases (NTP 2001b). Researchers have tested cyclophosphamide as an insect chemosterilant and for use in the chemical shearing of sheep (IARC 1981).

PRODUCTION

Cyclophosphamide is not produced in the U.S., and no data were available on the quantities imported (IARC 1981). The *1998 Chemical Buyers Directory* (Tilton 1997) listed three suppliers, *Chemcyclopedia 98* named two suppliers (Rodnan 1997) and Chemical Sources International (Chem Sources 2001) identified six current U.S. suppliers. Total U.S. sales were reported to be approximately 1,300 lb annually (IARC 1975).

EXPOSURE

Cyclophosphamide is rapidly absorbed and distributed following oral or intravenous (i.v.) injection. Other routes of potential human exposure include inhalation and dermal contact. The FDA estimated that 200,000 to 300,000 patients were treated with cyclophosphamide in 1979. No recent estimates were found. Dosing depends on the patient and the specific disease. The initial treatment for cancer patients with no hematologic deficiency may be 40 to 50 mg/kg given i.v. in divided doses over two to five days, 10 to 15 mg/kg given every 7 to 10 days, or 3 to 5 mg given twice per week. The adult dosage for tablets is typically 1 to 5 mg/kg per day for both initial and maintenance dosing. 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 during packaging or drug formulation. Health professionals such as pharmacists, nurses, and physicians who handle this drug may be exposed during drug preparation, administration, or cleanup; however, the risks 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, a clear relationship between cyclophosphamide handling and urinary detection was established (Evelo *et al.* 1986). The National Occupational Exposure Survey (1981-1983) estimated that a total of 27,171 workers, including 18,623 women, potentially were exposed to cyclophosphamide (NIOSH 1984).

REGULATIONS

EPA regulates cyclophosphamide under the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation, and Liability Act

(CERCLA). The CERCLA reportable quantity (RQ) for cyclophosphamide is 10 lb (4.54 kg). Cyclophosphamide is considered a hazardous constituent of waste and is subjected to reporting requirements under RCRA.

FDA regulates cyclophosphamide under the Food, Drug, and Cosmetic Act (FD&CA), subjecting it to drug labeling requirements for human prescription drugs. FDA also regulates the packaging of drugs containing cyclophosphamide; compatibility studies must be submitted when the chemical is packed in a plastic immediate container.

OSHA regulates cyclophosphamide under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 52.

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