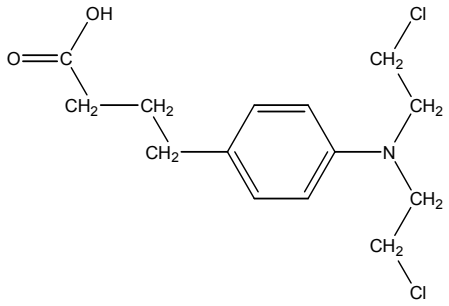
CHLORAMBUCIL
CAS No. 305-03-3
First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

Chlorambucil is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1987). Excesses of leukemia were reported in a number of epidemiological studies in which chlorambucil, either alone or in combination with other therapies, was used in treating nonmalignant and malignant diseases. Other cancers have also been associated when chlorambucil, in combination with other agents, was used for treatment. An excess of leukemia in association with chlorambucil was seen in a further study in which 431 previously untreated patients with polycythemia vera were given phlebotomy alone or chlorambucil with phlebotomy and followed for a mean of 6.5 years. Of the 26 cases of acute leukemia that occurred, 16 were in the group receiving chlorambucil. The risk increased with increasing dose and time of treatment (IARC 1981, 1982, 1987).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of chlorambucil in experimental animals (IARC 1982, 1987). When administered by intraperitoneal injection, chlorambucil increased incidences of lymphosarcomas and lung adenomas and adenocarcinomas in mice of both sexes, ovarian neoplasms in female mice, and lymphosarcomas, myelogenous leukemia and reticulum cell sarcomas in male rats (Weisburger *et al*. 1975, IARC 1981, 1982, 1987). When the compound was administered topically as the initiator in a two-stage study with croton oil, skin papillomas were induced in mice (IARC 1975, 1981, 1982).

PROPERTIES

Chlorambucil is a white crystalline powder with a slight odor. It is insoluble in water, but is soluble in ethanol, chloroform, acetone, benzene, ether, acid, and alkali. The sodium salt is soluble in water. It undergoes hydrolysis in aqueous and alkaline solutions to produce the hydroxyl form (IARC 1975). Chlorambucil is sensitive to light, oxidation, and moisture. When heated to decomposition, it emits toxic fumes of chlorine and nitrogen oxides (NTP 2001). Chlorambucil is available in the United States in tablets containing 2 mg active ingredient (Calabresi and Parks 1985). The USP grade powders used to formulate the tablets contain 98% to 101% active ingredient (IARC 1975).

USE

Chlorambucil is used as an antineoplastic agent to treat chronic lymphocytic leukemia, malignant lymphomas (including lymphosarcoma), giant follicular lymphoma, and Hodgkin's disease. It is also an immunosuppressive agent that has been used to treat systemic lupus erythematosus, Waldenström's macroglobulinemia, glomerular nephritis, nephrotic syndrome, psoriasis, Wegener's granulomatosis, chronic hepatitis, vasculitis associated with rheumatoid arthritis, and autoimmune hemolytic anemia with cold agglutins (Calabresi and Parks 1985, NTP 2001). Chlorambucil has also been investigated for use in chronic hepatitis and as an insect chemosterilant (IARC 1981).

PRODUCTION

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB 2001). Two current U.S. suppliers were identified (Chem Sources 2001). U.S. imports in the early 1970s were approximately 70 to 75 lb/yr. Imports through the principal U.S. customs districts was 106 lb in 1978 (IARC 1981). Estimates of U.S. sales in the mid 1970s were less than 20 kg (44 lb) per year (IARC 1975).

EXPOSURE

The primary routes of potential human exposure to chlorambucil are ingestion, inhalation, and dermal contact. Continuous and intermittent oral treatment schedules are employed for patients treated with chlorambucil. In the former, the initial daily dose is 0.1 to 0.2 mg/kg body weight (total dose of 4 to 10 mg) for three to six weeks. If clinical improvement or bone marrow toxicity occurs, the dosage is reduced. In the latter case, it is common to give intermittent 2-week courses of 10 to 20 mg daily with rest periods of 2 to 4 weeks (IARC 1981).

Potential occupational exposure may occur during the formulation, packaging, and administration of the pharmaceutical. NIOSH reported no indication of potential worker exposure in the National Occupational Hazard Survey conducted from 1972 to 1974 (NIOSH 1976). The National Occupational Exposure Survey, conducted by NIOSH from 1981 to 1983, however, estimated that 3,718 workers, including 2,018 women, were potentially exposed to chlorambucil (HSDB 2001). More recent estimates of worker or patient exposure were not available.

REGULATIONS

EPA regulates chlorambucil under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). EPA's Carcinogen Assessment Group includes chlorambucil on its list of potential carcinogens and regulates it as a hazardous waste under RCRA. In fulfilling the purposes of the Toxic Substances Control Act (TSCA), EPA requires the submission of lists and copies of health and safety studies on chlorambucil or mixtures containing chlorambucil under section 4(a) of TSCA.

Chlorambucil is regulated by the FDA under the Food, Drug, and Cosmetic Act (FD&CA). FDA approved chlorambucil under the FD&CA for use as a prescription drug in 1969, noting restrictive approved clinical use for the treatment of chronic lymphocytic leukemia, malignant

lymphomas, and Hodgkin's disease. Drug labeling requirements under the FD&CA also apply to chlorambucil.

OSHA regulates chlorambucil under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 31.

REFERENCES

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