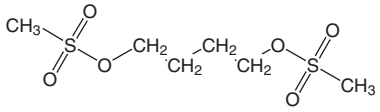
1,4-Butanediol Dimethanesulfonate (Myleran®) CAS No. 55-98-1

Known to be a human carcinogen
First Listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

1,4-Butanediol dimethanesulfonate (Myleran®; busulfan) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Cases of cytological abnormalities (e.g., giant nuclei, cytomegaly and dysplasia) and cancer at different tissue sites, including cancer of the breast and female genital organs and leukemia, have been reported among leukemia patients receiving 1,4-butanediol dimethanesulfonate. Leukemia was observed in a follow-up study of bronchial cancer patients treated with 1,4-butanediol dimethanesulfonate. In this study, the patients had been randomized to treatment with Myleran, cyclosphosamide, or placebo after surgical removal of the tumor. Leukemia only developed in patients who had not received radiation or other cytotoxic agents, but the risk of leukemia was not dose-related (IARC 1987).

Evidence of the carcinogenicity of 1,4-butanediol dimethanesulfonate in experimental animals is limited. This chemical has been tested by oral administration and intraperitoneal and intravenous injection in rats and by intraperitoneal and intravenous injection in mice. Oral administration did not increase tumor incidence in rats. Mice administered 1,4-butanediol dimethanesulfonate by intraperitoneal injection had increased incidences of leukemia in one study and T-cell lymphomas in another; however, tumors were not increased in two other studies. When administered by intravenous injection, 1,4-butanediol dimethanesulfonate increased the incidence of thymic lymphomas and ovarian tumors in female mice. One study reported that pulmonary lesions developed in mice treated with 1,4-butanediol dimethanesulfonate, but the route of administration was not specified. Although 1,4-butanediol dimethanesulfonate administered intravenously induced a variety of tumors in male rats, this experiment could not be evaluated because of incomplete reporting (IARC 1982, 1987).

Properties

1,4-Butanediol dimethanesulfonate is a symmetrical bis-substituted methanesulfonic acid ester belonging to a general class of drugs known as alkylating agents. It is a white crystalline powder with a molecular weight of 246.3 and a melting point of 114°C to 118°C. This compound is insoluble but decomposes by hydrolysis in water. It is soluble in acetone and slightly soluble in ethanol. When burned, it emits toxic fumes of sulfur oxides, carbon monoxide, and carbon dioxide (IARC 1974, AldrichChemCo 1997).

Use

1,4-Butanediol dimethanesulfonate is used as a chemotherapeutic agent to treat some forms of leukemia, particularly chronic myelocytic leukemia (IARC 1974, 1982). It also may be used in combination with cyclophosphamide as a conditioning regimen prior to bone marrow transplants for chronic myelogenous leukemia. 1,4-Butanediol dimethanesulfonate is given in tablets or by intravenous injection (MEDLINEplus 2001, RxList 2001).

Production

One U.S. company has produced 1,4-butanediol dimethanesulfonate since 1954 (IARC 1974, SRI 1992). Total annual production was believed to be less than 500 kg (1,100 lb) (IARC 1974). Ten U.S. suppliers were listed by Chem Sources (2003), and two U.S. pharmaceutical companies with drug products approved by the U.S. Food and Drug Administration (FDA) containing 1,4-butanediol dimethanesulfonate as the active ingredient were identified (FDA 2003). No data on imports or exports were available.

Exposure

Patients may be exposed to 1,4-butanediol dimethanesulfonate during its use in chemotherapeutic treatment by ingestion or intravenous administration. It is available as 2-mg oral tablets or in injectable form (6 mg/mL) (FDA 2003). The typical dosage level (tablet form) is 4 to 8 mg daily (IARC 1974). The recommended intravenous dose given prior to a bone marrow transplant is 0.8 mg/kg body weight given as a two-hour infusion every six hours for four days (RxList 2001).

Potential occupational exposure may occur for workers formulating or packaging the tablets and for health care professionals administering the drug. The National Occupational Exposure Survey (1981-1983) estimated that a total of 1,764 workers, including 892 women, potentially were exposed to 1,4-butanediol dimethanesulfonate (NIOSH 1984).

Regulations

FDA

1,4-Butanediol dimethanesulfonate is a prescription drug subject to labeling and other requirements

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