

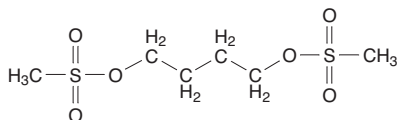
1,4-Butanediol Dimethanesulfonate

CAS No. 55-98-1

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as busulfan; trimethylene methanesulfonate; Busulfex, a registered trademark of Otsuka Pharmaceutical Co., Ltd.; or Myleran, a registered trademark of GlaxoSmithKline, LLC



Carcinogenicity

1,4-Butanediol dimethanesulfonate is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Cases of cytological abnormalities (e.g., giant nuclei, cytomegaly, and dysplasia) and cancer at several different tissue sites, including the breast and female genital organs, were reported among leukemia patients who had been treated with 1,4-butanediol dimethanesulfonate. In a follow-up study of bronchial-cancer patients randomly assigned to treatment with Myleran, cyclophosphamide, or placebo after surgical removal of the tumor, leukemia developed in patients who had received Myleran only, without radiation or other cytotoxic agents; however, the risk of leukemia was not dose-related (IARC 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of 1,4-butanediol dimethanesulfonate in experimental animals is limited. 1,4-Butanediol dimethanesulfonate administered to mice by intraperitoneal injection caused leukemia in one study and T-cell lymphoma in another, but did not increase the incidences of tumors in two other studies. When administered by intravenous injection to female mice, 1,4-butanediol dimethanesulfonate caused thymic lymphoma and ovarian tumors. One study reported that pulmonary lesions (including benign tumors) developed in mice exposed to 1,4-butanediol dimethanesulfonate, but the route of administration was not specified. In rats, 1,4-butanediol dimethanesulfonate did not cause tumors when administered orally. When administered intravenously, it was reported to cause a variety of tumors in male rats, but this study could not be evaluated because of incomplete reporting (IARC 1982, 1987).

Properties

1,4-Butanediol dimethanesulfonate is an alkylsulfonate alkylating agent that exists at room temperature as an off-white granular powder with a slight odor. It has a molecular weight of 246.3 and a melting point of 119°C. It is almost insoluble in water, sparingly soluble in acetone, and slightly soluble in ethanol, and it hydrolyzes in aqueous solution (IARC 1974, Akron, 2009).

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. It is given in tablets or by intravenous injection (FDA 2009, MedlinePlus 2009).

Production

Total annual production of 1,4-butanediol dimethanesulfonate was believed to be less than 500 kg (1,100 lb) in 1974 (IARC 1974). In 2009, no producer of 1,4-butanediol dimethanesulfonate was identified worldwide (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing 1,4-butanediol dimethanesulfonate as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of 1,4-butanediol dimethanesulfonate were found.

Exposure

Patients may be exposed to 1,4-butanediol dimethanesulfonate by ingestion or intravenous administration during chemotherapeutic treatment. 1,4-Butanediol dimethanesulfonate is available as 2-mg oral tablets or in injectable form (6 mg/mL) (FDA 2009). The typical dosage in tablet form is 4 to 8 mg daily (IARC 1974). The recommended intravenous dose prior to a bone-marrow transplant is 0.8 mg/kg of body weight given as a two-hour infusion every six hours for four days (RxList 2010). Occupational exposure could occur among workers formulating or packaging the tablets or health-care professionals administering the drug. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,764 workers, including 892 women, potentially were exposed to 1,4-butanediol dimethanesulfonate (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

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

Food and Drug Administration (FDA)

Regulated as 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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