

BUSULFAN

Busulfan was considered by previous IARC Working Groups in 1973 and 1987 ([IARC, 1974, 1987a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 55-98-1

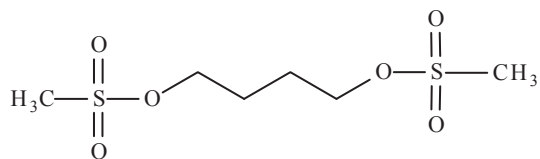
Chem. Abstr. Name: 1,4-Butanediol, 1,4-dimethanesulfonate-

IUPAC Systematic Name: 4-Methylsulfonyloxybutyl methanesulfonate

Synonyms: 1,4-Bis(methanesulfonyloxy)butane; 1,4-bis(methanesulfonyloxy)butane; 1,4-butanediol dimethanesulfonate; 1,4-butanediol dimesylate; busulphan; Busilvex; Busulfex; 1,4-dimethanesulfonyloxybutane; 1,4-dimethylsulfonyloxybutane; Myleran

Description: White, crystalline powder ([Sweetman, 2008](#))

1.1.1 Structural and molecular formulae, and relative molecular mass



Relative molecular mass: 246.3

1.2 Use of the agent

Busulfan is an antineoplastic agent with a cell-cycle nonspecific alkylating action (unlike that of the nitrogen mustards) that has a selective depressant action on the bone marrow. In small doses, it depresses granulocytogenesis and to a lesser extent thrombocytogenesis, but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues. Information for Section 1.2 is taken from [McEvoy \(2007\)](#), [Royal Pharmaceutical Society of Great Britain \(2007\)](#), [Thomson Healthcare \(2008\)](#), and [Sweetman \(2008\)](#).

1.2.1 Indications

Busulfan is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukaemia. It provides symptomatic relief with a reduction in spleen size and a general feeling of well-being. The fall in leukocyte count is usually accompanied by a rise in the haemoglobin concentration. Permanent remission is not induced, and resistance to its beneficial effects gradually develops.

Busulfan has been used in patients with *polycythaemia vera*, and in some patients with myelofibrosis and primary thrombocythaemia.

It has also been used at high doses, orally, and more recently, intravenously, as part of a conditioning regimen to prepare patients for stem-cell transplantation.

1.2.2 Dosage

Busulfan is typically administered orally. The usual adult dose range for remission induction is 4–8 mg, total dose, daily. Dosing on a weight basis is the same for both paediatric and adult patients, approximately 60 µg/kg of body weight or 1.8 mg/m² of body surface, daily. This initial dose is continued until the white blood cell count has fallen to between 15000 and 25000 cells/mm³ (typically 12–20 weeks). Alternatively, the dose of busulfan is halved as the white blood cell count halves. It is stopped earlier if the platelet count falls below 100000 cells/mm³. Higher doses can be given if the response after 3 weeks is inadequate.

In patients with *polycythaemia vera*, the usual dose is 4–6 mg daily orally, continued for 4–6 weeks with careful monitoring of blood counts. Further courses are given when relapse occurs; alternatively, maintenance therapy may be given at half the dose required for induction. Doses of 2–4 mg daily have been given for essential thrombocythaemia or myelofibrosis.

In conditioning regimens for stem-cell transplantation, busulfan has been given in oral doses of 3.5–4 mg/kg daily in divided doses for 4 days (total dose 14–16 mg/kg), with cyclophosphamide or melphalan, for ablation of the recipient's bone marrow; most centres now use intravenous preparations of busulfan as part of the conditioning regimens. When given by intravenous infusion in a regimen with phenytoin, the usual dose is 0.8 mg/kg ideal body weight every 6 hours for 4 days (total dose, 12.8 mg/kg).

Busulfan is available as a tablet containing 2 mg busulfan for oral administration, and as an injection concentrate for intravenous infusion containing 6 mg/mL (60 mg) busulfan for parenteral administration.

1.2.3 Trends in use

Randomized trials have shown a small survival advantage with treatment with hydroxyurea compared with busulfan, and a major survival advantage with imatinib mesylate. Hence, treatment with busulfan is now used less frequently for patients with chronic myeloid leukaemia.

2. Cancer in Humans

Case reports of chronic myeloid leukaemia patients treated with busulfan who developed various cytological abnormalities have been described, with a few reporting the development of carcinoma ([Diamond *et al.*, 1960](#); [Waller, 1960](#); [Gureli *et al.*, 1963](#); [Feingold & Koss, 1969](#); [Becher & Prescher, 1988](#); [Storti *et al.*, 1990](#); [Foa *et al.*, 1993](#)). [The Working Group noted that most patients with chronic myeloid leukaemia are older, and therefore might have been at risk of developing solid tumours independently of exposure to busulfan.]

Long-term follow-up of patients with bronchial carcinoma who were randomized to chemotherapy after pulmonary resection showed that of 69 patients who had been given busulfan and had survived 5 years, four developed acute myeloid leukaemia and a further 15 developed pancytopenia in the following 4 years ([Stott *et al.*, 1977](#)). The increase in risk was not related to dose. Among 148 other survivors at 5 years who had not been given busulfan, one case of pancytopenia appeared. No cases of acute myeloid leukaemia developed in patients who received cyclophosphamide. The cases were confined to those who had not received radiation or other cytotoxic agents ([Stott *et al.*, 1977](#)).

Patients with myeloproliferative disorders such as *polycythaemia vera* and essential thrombocytosis can potentially develop acute myeloid leukaemia or myelodysplastic syndromes even without specific treatment. The long natural

history of these diseases and the use of a variety of different therapies during an individual patient's clinical course make it difficult to precisely estimate the frequency of conversion to acute myeloid leukaemia, and the contribution of specific treatments. Randomized trials and long-term follow-up cohort studies have shown that this transformation rate is substantially increased in patients treated with alkylating agents that include busulfan and chlorambucil, and radioactive inorganic phosphate ([Berk et al., 1981](#)).

In the most recent and largest of such studies, acute myeloid leukaemia developed in 1.3% of 1638 patients with *polycythaemia vera*, with multivariable analyses demonstrating that treatment with busulfan was associated with higher rates of acute myeloid leukaemia (hazard ratio, 8.6 compared to no treatment or treatment with phlebotomy-alone or interferon). A total of 86% of these patients had been followed for < 10 years ([Finazzi et al., 2005](#)). A smaller study in 114 patients with essential thrombocytosis showed that three of 14 patients treated with busulfan followed by hydroxyurea developed acute myeloid leukaemia/myelodysplastic syndromes; one additional case was treated with hydroxyurea alone ([Finazzi et al., 2000](#)).

3. Cancer in Experimental Animals

Intraperitoneal administration of busulfan to mice did not increase the incidence of tumours in two studies ([Stoner et al., 1973](#); [IARC, 1974](#)), but induced lymphomas in two others ([Robin et al., 1981](#); [Turton et al., 2006](#)). In a study, intravenous administration of busulfan to mice significantly increased the incidences of thymic and ovarian tumours ([Conklin et al., 1965](#); [IARC, 1974](#)). In another study, busulfan in conjunction with X-rays further increased the incidence of thymic lymphomas ([IARC, 1974](#)). [The Working Group

noted that the increased incidences of thymic lymphomas and ovarian tumours are difficult to interpret in the mouse model.]

Intravenous administration of busulfan to rats for 1 year was reported to induce a variety of tumours in male rats, but the experiments could not be evaluated due to incomplete reporting ([Schmähl, 1975](#); [IARC, 1987a](#)). Maternal exposure to busulfan induced uterine adenocarcinoma in the offspring of rats treated with *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine ([Yoshida et al., 2005](#)).

See [Table 3.1](#).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, upon oral administration, busulfan is readily absorbed from the gastrointestinal tract, binds rapidly to plasma proteins (e.g. albumin) and red blood cells, and rapidly disappears from the blood ([GlaxoSmithKline, 2004](#); [Sweetman, 2005](#); [Thomson Healthcare, 2008](#)). Busulfan is reported to have a half-life of 2–3 hours ([Sweetman, 2005](#); [Thomson Healthcare, 2008](#)). In the liver, it rapidly undergoes both enzymatic and non-enzymatic transformations, primarily through glutathione-mediated processes, to less active, sulfur-containing metabolites ([Thomson Healthcare, 2008](#)). Twelve metabolites have been isolated including methanesulfonic acid and 3-hydroxytetrahydrothiophene-1,1-dioxide, two major urinary metabolites ([Bishop & Wassom, 1986](#); [GlaxoSmithKline, 2004](#)). In spite of its rapid clearance from the blood and its extensive metabolism, radiolabelled busulfan is excreted relatively slowly, with 25–60% of the radioactivity being excreted, primarily as metabolites, within 48 hours after dosing ([McEvoy, 1987](#); [GlaxoSmithKline, 2004](#)).

Table 3.1 Studies of cancer in experimental animals exposed to busulfan (intraperitoneal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/He (M, F) 24 wk Stoner et al. (1973)	0, 1.2, 3.0, 6.0 g/kg bw (total dose) 24 times for 8 wk 30/30, 10/10, 10/10, 10/10	Lung: 14/58, 4/18, 1/16, 3/17	NS	85–99% pure
Mouse, BALB/c, XAF1 (M) 50 wk Robin et al. (1981)	0, 0.5 mg 4 times over 6 wk 45, 45	Lymphomas: 0/41, 4/35	[<i>P</i> = 0.0408]	
Mouse, BALB/c (F) 127 d Turton et al. (2006)	0, 8.25, 9.0, 9.75 mg/kg bw 10 times over 21 d 65, 64, 65, 65	Lymphomas: 0/15, 4/14, 1/16, 0/11 (at Day 127 post-dosing)	<i>P</i> < 0.05 (8.25 mg/kg)	Mortality: 0/65, 2/64, 3/65, 8/65 [Study not designed as a carcinogenicity study]
Rat, Donryu (F) 15 mo Yoshida et al. (2005)	0, 2.5, 5.0 mg/kg bw single oral dose to pregnant females on Day 14 of gestation; 20 mg/kg bw single dose ENNG in uterine horn to offspring at 11 wk Pregnant females: 10, 10, 10; offspring: 27, 24, 24	Uterine adenocarcinomas: 4/16, 6/18, 14/26	<i>P</i> < 0.05 (5.0 mg/kg)	

bw, body weight; d, day or days; ENNG, *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine; F, female; M, male; mo, month or months; NS, not significant; wk, week or weeks

4.2 Genotoxic effects

Busulfan is a direct-acting bifunctional alkylating agent that binds to cellular macromolecules including DNA, RNA, and proteins. Consequently, it is capable of producing monoadducts, intrastrand cross-links, and DNA-protein cross-links ([Iwamoto et al., 2004](#); [Morales-Ramírez et al., 2006](#)) that are believed to play an important role in its toxic and carcinogenic effects ([Bishop & Wassom, 1986](#); [Sanderson & Shield, 1996](#)). Busulfan exhibits an interesting, but poorly understood, selective toxicity for early myeloid precursor cells ([Guest & Uetrecht, 2000](#); [Kufe et al., 2003](#)).

Busulfan has been tested for genotoxicity in a variety of assays, both *in vitro* and *in vivo* ([Bishop & Wassom, 1986](#); [IARC, 1987b](#)). *In vivo* treatment

of rodents with busulfan induced dominant lethal mutations, and increased the frequency of chromosomal aberrations or micronuclei in bone marrow, intestine, embryonic liver, and germ cells ([Bishop & Wassom, 1986](#); [IARC, 1987b](#)). In the mouse-specific locus test, increases in mutations were seen in postspermatogonial germ cells (spermatozoa and spermatids), but not in spermatogonia ([Ehling & Neuhäuser-Klaus, 1991](#)). Evidence of covalent binding to DNA, RNA, and proteins was also obtained in mice treated *in vivo*. Busulfan induced chromosomal aberrations, sister chromatid exchange, and mutations in human and rodent cells treated *in vitro*. It also induced sex-linked recessive lethal mutations in *Drosophila*, and was mutagenic to bacteria ([Bishop & Wassom, 1986](#); [IARC, 1987b](#)).

Patients treated with busulfan for chronic myeloid leukaemia were found to have increased frequencies of sister chromatid exchange and chromosomal aberrations in their peripheral blood lymphocytes ([Honeycombe, 1981](#); [Bishop & Wassom, 1986](#)). Haematotoxicity and immunosuppression have also been reported in patients treated with this agent ([Bishop & Wassom, 1986](#)).

4.3 Mechanisms of carcinogenesis

Acute myeloid leukaemia that develops in patients who have previously been treated with alkylating agents, such as busulfan, frequently exhibits distinctive characteristics that allow it to be distinguished from acute myeloid leukaemia induced by other agents (such as DNA-topoisomerase II inhibitors) or acute myeloid leukaemia that occurs spontaneously ([Pedersen-Bjergaard & Rowley, 1994](#); [Jaffe *et al.*, 2001](#); [Mauritzson *et al.*, 2002](#); [Pedersen-Bjergaard *et al.*, 2006](#)). One of the hallmarks of leukaemias induced by alkylating agents is that they frequently exhibit a clonal loss of either chromosome 5 or 7 (–5, –7) or a loss of part of the long arm of one of these chromosomes (5q–, 7q–). For example, a deletion within the long arm of chromosome 5 involving the bands q23 to q32 is often seen ([Jaffe *et al.*, 2001](#)). Leukaemias that have developed in patients treated with busulfan (often in combination with other agents) frequently exhibit these clonal chromosomal changes ([Mauritzson *et al.*, 2002](#)).

In addition, mutations in *TP53* are frequently seen in leukaemias with the –5/5q– karyotype, and mutations involving the *AML1* gene as well as mutations in *TP53* and *RAS* are often seen in a subset of leukaemias that exhibit the –7/7q– karyotype ([Christiansen *et al.*, 2001, 2005](#); [Pedersen-Bjergaard *et al.*, 2006](#)). These treatment-related acute myeloid leukaemias also frequently exhibit increased methylation of the *p15* promoter ([Pedersen-Bjergaard *et al.*, 2006](#)). Although the evidence that busulfan directly

induces losses or deletions affecting chromosomes 5 or 7 is limited, this drug has been reported to induce similar types of chromosomal alterations and deletions in a variety of experimental models (see description above), and in the lymphocytes of treated patients ([Honeycombe, 1981](#); [Bishop & Wassom, 1986](#)). The detection of elevated levels of chromosomal aberrations in the peripheral blood lymphocytes of patients treated with busulfan is of particular note, as multiple prospective studies have now shown that individuals with increased levels of chromosomal aberrations in these cells are at increased risk of developing cancer ([Hagmar *et al.*, 1998, 2004](#); [Liou *et al.*, 1999](#); [Smerhovsky *et al.*, 2001](#); [Boffetta *et al.*, 2007](#)).

4.4 Synthesis

Busulfan is a direct-acting alkylating agent that is carcinogenic via a genotoxic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of busulfan. Busulfan causes acute myeloid leukaemia.

There is *limited evidence* in experimental animals for the carcinogenicity of busulfan.

Busulfan is *carcinogenic to humans* (Group 1).

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