1,4-BUTANEDIOL DIMETHANESULPHONATE (MYLERAN) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Leukaemia patients who had been treated with Myleran developed many different cytological abnormalities, and some developed carcinomas[1-8]. A follow-up study of patients with bronchial carcinoma who were randomized to chemotherapy after pulmonary resection showed that of 69 who had been given Myleran and had survived five years, four developed acute nonlymphocytic leukaemia (three myelomonocytic leukaemias and one erythroleukaemia) and 15 others developed pancytopenia in the succeeding four years; among 148 other survivors at five years who had not been given Myleran, one case of pancytopenia appeared. Risk was not dose-related, although the cases were confined to those who had received no radiation and no other cytotoxic agent[9].

B. Evidence for carcinogenicity to animals (*limited*)

Myleran was tested for carcinogenicity by intraperitoneal injection and by intravenous injection in mice and rats and by oral administration to rats. Intraperitoneal administration of Myleran to mice did not increase the incidence of tumours in two studies[1,10], but leukaemia[11] and hypoplastic marrow[11,12] were induced in further studies and T-cell lymphoma in another, in which the effect was markedly enhanced by combined administration of chloramphenicol[13]. Leukaemia/lymphosarcoma was also reported in one study[12], but the experiment could not be evaluated due to incomplete reporting. No mammary tumour was seen in rats after intraperitoneal injection, but near-lethal doses were used and the animals were followed for only five months[14]. Intravenous administration of Myleran to mice significantly increased the incidences of thymic and ovarian tumours[1]. Intravenous administration of 7% of the LD_{50} dose to rats for one year was reported to induce a variety of tumours in male rats, but the experiments could not be evaluated due to incomplete reporting[15]. Oral administration to rats of Myleran did not increase the incidence of tumours over that seen in untreated animals[1].

C. Other relevant data

Myleran is a bifunctional alkylating agent. Patients treated with Myleran for chronic myeloid leukaemia were found to have increased frequencies of sister chromatid exchanges and chromosomal aberrations (in a single study) in their peripheral blood lymphocytes[16].

Treatment of rodents *in vivo* with Myleran induced dominant lethal mutations and increased the frequency of chromosomal aberrations and micronuclei in bone-marrow cells; in single studies, it induced DNA damage but not mutation. Evidence for covalent binding to DNA, RNA and protein was obtained in mice treated *in vivo*. Myleran induced chromosomal aberrations and sister chromatid exchanges in human and rodent cells *in vitro*, and mutation in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila* and was mutagenic to bacteria[16].

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