CYCLOPHOSPHAMIDE (Group 1)

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

Many cases of cancer have been reported following therapy with cyclophosphamide[1].

Excess frequencies of bladder cancer following therapy with cyclophosphamide for nonmalignant diseases have been clearly demonstrated in two epidemiological studies[1,2]. Three recent studies confirmed that cyclophosphamide is also a leukaemogen. Among 602 patients treated predominantly with cyclophosphamide for non-Hodgkin's lymphoma in Denmark, nine cases of acute nonlymphocytic leukaemia (ANLL) or preleukaemia were observed, compared to 0.12 expected on the basis of incidence rates in the general population[3]. In the USA, three cases of ANLL or preleukaemia were observed among 333 women treated only with cyclophosphamide for ovarian cancer; 1.2 were expected[4]. In the German Democratic Republic, a case-control study was carried out of leukaemia arising as a second primary malignancy following breast or ovarian cancer. Relative risks of 1.5, 3.3 and 7.3 were estimated in association with cumulative doses of <10 g, 10-29 g and >30 g of cyclophosphamide, respectively[5].

Cyclophosphamide is a far less potent leukaemogen than 1,4-butanediol dimethanesulphonate (Myleran; see p. 137) when used following surgery for lung cancer[6]. Similarly, melphalan (see p. 239) produces a much higher incidence of leukaemia than cyclophosphamide when used in the therapy of multiple myeloma[7] and of ovarian cancer[4].

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

Cyclophosphamide has been tested for carcinogenicity by oral administration and by intravenous and intraperitoneal injection in rats and by subcutaneous and intraperitoneal injection in mice. It produced benign and malignant tumours at various sites, including the bladder, in rats after its oral or intravenous administration, and benign and malignant tumours at the site of injection and at distant sites in mice following its subcutaneous

injection. There was some evidence of its carcinogenicity to mice and rats following intraperitoneal injection[1]. A study in which cyclophosphamide was given intraperitoneally to rats in combination with methotrexate (see p. 241) and 5-fluorouracil (see p. 210) resulted in induction of tumours in the nervous system, haematopoietic and lymphatic tissues, the urinary bladder and adrenal glands; however, because of lack of matched controls, it could not be concluded whether tumour induction was due to a combined effect of the three chemicals or of any one of them[8].

C. Other relevant data

Cyclophosphamide is metabolized to an alkylating intermediate. Increased incidences of chromosomal aberrations and sister chromatid exchanges were observed in peripheral blood lymphocytes and, in one study, in bone-marrow cells of patients treated with cyclophosphamide for a variety of malignant and nonmalignant diseases[9].

Cyclophosphamide has been tested extensively for genetic effects in a wide variety of tests *in vivo* and *in vitro*, giving consistently positive results. It bound to DNA in kidney, lung and liver of mice and induced dominant lethal mutations, chromosomal aberrations, micronuclei, sister chromatid exchanges, mutation and DNA damage in rodents treated *in vivo*. In human cells *in vitro*, it induced chromosomal aberrations, sister chromatid exchanges and DNA damage. In rodent cells *in vitro*, it induced transformation, chromosomal aberrations, sister chromatid exchanges, mutation and unscheduled DNA synthesis. In *Drosophila*, it induced aneuploidy, heritable translocations and somatic and sex-linked recessive lethal mutations. In fungi, it induced aneuploidy, mutation, recombination, gene conversion and DNA damage. In bacteria, it induced mutation and DNA damage. In bacteria, it induced mutation and DNA damage. In host-mediated assays, it induced chromosomal aberrations and sister chromatid exchanges in human lymphoid cells, mutation and sister chromatid exchanges in Chinese hamster cells, gene conversion in yeast, and mutation in bacteria. It was active in body-fluid assays of urine from humans and rodents exposed *in vivo*, and in one study using serum from rats[9].

References

[1]*IARC Monographs*, *26*, 165-202, 1981

[2]Kinlen, L.J. (1985) Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am. J. Med.*, *78* (*Suppl. 1A*), 44-49

[3]Pedersen-Bjergaard, J., Ersbøll, J., Sørensen, H.M., Keiding, N., Larsen, S.O., Philip, P., Larsen, M.S., Schultz, H. & Nissen, N.I. (1985) Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. *Ann. int. Med.*, *103*, 195-200

[4]Greene, M.H., Harris, E.L., Gershenson, D.M., Malkasian, G.D., Jr, Melton, L.J., III, Dembo, A.J., Bennett, J.M., Moloney, W.C. & Boice, J.D., Jr (1986) Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann. int. Med.*, *105*, 360-367

[5]Haas, J.F., Kittelmann, B., Mehnert, W.H., Staneczek, W., Möhner, M., Kaldor, J.M. & Day, N.E. (1987) Risk of leukaemia in ovarian tumour and breast cancer patients following treatment by cyclophosphamide. *Br. J. Cancer, 55*, 213-218

[6]Stott, H., Fox, W., Girling, D.J., Stephens, R.J. & Galton, D.A.G. (1977) Acute leukaemia after busulphan. *Br. med. J., ii*, 1513-1517

[7]Cuzick, J., Erskine, S., Edelman, D. & Galton, D.A.G. (1987) A comparison of the incidence of myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's Working Party on leukaemia in adults. *Br. J. Cancer, 55*, 523-529

[8]Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. *Int. J. Cancer, 28*, 91-96

[9]*IARC Monographs, Suppl. 6*, 196-205, 1987