METHOTREXATE (Group 3)

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

The relationship between methotrexate treatment and subsequent malignancy has been investigated in one cohort of 457 patients (3522 person-years) treated for trophoblastic tumours (2 observed, 3.5 expected)[1] and in a cohort of 248 patients treated for psoriasis (10 observed, 22 expected)[2]. A case-control study of treatment for psoriasis has also been performed, in which 26 cases of noncutaneous cancer (104 matched controls) and 80 cases of nonmelanoma skin cancer (297 matched controls) were studied; relative risks were 1.0 and 1.2, respectively[3]. In each comparison, no excess (significant or otherwise) or subsequent malignancy was observed.

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

Methotrexate was tested by oral administration in mice and hamsters, by intraperitoneal injection in mice and rats, and by intravenous injection in rats. One study in mice by oral administration showed a high incidence of lung carcinomas, but the study design did not include matched controls. No other study revealed a carcinogenic effect, but the significance of several was limited because of deficiencies in experimental design or reporting of data[4]. A study in which methotrexate was given intraperitoneally in combination with cyclophosphamide (see p. 182) and 5-fluorouracil (see p. 210) to rats 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 to any one of them[5].

C. Other relevant data

In patients treated with methotrexate, chromosomal aberrations were observed in bone-marrow cells, and, in one of two studies, sister chromatid exchanges were induced in lymphocytes[6].

Methotrexate induced micronuclei in mice, but neither aneuploidy in mouse oocytes nor DNA strand breaks in granuloma cells of rats treated *in vivo*. It induced chromosomal aberrations in human and rodent cells *in vitro* and sister chromatid exchanges in rodent but

not in human cells *in vitro*. It did not induce unscheduled DNA synthesis in human cells *in vitro*. It caused transformation of C3H 10T1/2 cells but not of Syrian hamster embryo cells and was mutagenic to mouse lymphoma cells but not to Chinese hamster cells *in vitro*. Methotrexate induced genetic crossing-over but not sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to *Salmonella typhimurium* but gave conflicting results in *Escherichia coli* and was mutagenic to *Bacillus subtilis*. It did not induce DNA damage in bacteria[6].

References

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[2]Nyfors, A. & Jensen, H. (1983) Frequency of malignant neoplasms in 248 long-term methotrexate-treated psoriatics. A preliminary study. *Dermatologica*, *167*, 260-261

[3]Stern, R.S., Zierler, S. & Parrish, J.A. (1982) Methotrexate used for psoriasis and the risk of noncutaneous or cutaneous malignancy. *Cancer*, *50*, 869-872

[4]*IARC Monographs*, *26*, 267-292, 1981

[5]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

[6]*IARC Monographs*, *Suppl. 6*, 372-374, 1987