5-FLUOROURACIL (Group 3)

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

No epidemiological study of 5-fluorouracil as a single agent was available to the Working Group. Occasional case reports of exposure to 5-fluorouracil, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis[1].

No increased risk of second malignancies was found among 276 patients with colorectal cancer randomized to low-dose (20 mg/kg bw) 5-fluoro-2′-deoxyuridine adjuvant therapy, followed for 1774 person-years (14 second noncolorectal cancers observed, 15 expected)[2].

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

5-Fluorouracil was tested by intravenous administration in mice and rats and by oral administration in rats. No evidence of carcinogenicity was found, but the studies suffered from limitations with regard to duration or dose[1]. It was reported that ingestion of 5-fluorouracil prevented or delayed the appearance of spontaneous mammary and pituitary tumours in old female rats; no histopathological evaluation was made of the tumours that developed[3]. A study in which 5-fluorouracil was given intraperitoneally to rats in combination with methotrexate (see p. 241) and cyclophosphamide (see p. 182) resulted in induction of tumours in the nervous system, haematopoietic and lymphatic tissue, the

urinary bladder and the adrenal glands; however, because of the 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[4].

C. Other relevant data

Neither chromosomal aberrations (in two patients) nor sister chromatid exchanges (in three patients) were induced following administration of 5-fluorouracil[5].

5-Fluorouracil induced micronuclei but not specific locus mutations in mice treated *in vivo*. It induced aneuploidy, chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*, but caused genetic crossing-over in fungi. Studies on mutation in bacteria were inconclusive[5].

References

[1]*IARC Monographs, 26*, 217-235, 1981

[2]Boice, J.D., Greene, M.H., Keehn, R.J., Higgins, G.A. & Fraumeni, J.F., Jr (1980) Late effects of low-dose adjuvant chemotherapy in colorectal cancer. *J. natl Cancer Inst., 64*, 501-511

[3]Ferguson, T. (1980) Prevention and delay of spontaneous mammary and pituitary tumors by long- and short-term ingestion of 5-fluorouracil in Wistar-Furth rats. *Oncology, 37*, 353-356

[4]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

[5]*IARC Monographs, Suppl. 6*, 316-318, 1987