AZATHIOPRINE (Group 1)

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

Two large prospective epidemiological studies have shown that renal transplant patients, who usually receive azathioprine as an immunosuppressant, become at high risk for non-Hodgkin's lymphoma, squamous-cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumours. While this is true for each of the various etiological entities resulting in the need for a transplant, these patients also have in common heavy exposure to foreign antigens[1]. Other patients who have received azathioprine as an immunosuppressant, including those with rheumatoid arthritis, systemic lupus and other 'collagen' disorders, inflammatory bowel disease and certain skin and renal diseases, have also been studied: the same array of malignancies was found to be in excess, although to a lesser extent[1,2]. For these patients, however, the picture is still not completely clear, because patients with rheumatoid arthritis constituted the largest category in the latter study[2], and some[3], but not all studies[4], have found that this disease conveys a risk for non-Hodgkin's lymphoma in the absence of treatment.

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

Suggestive evidence was obtained that lymphomas were induced in mice after intraperitoneal, subcutaneous or intramuscular injection of azathioprine, and that thymic lymphomas and squamous-cell carcinomas of the ear duct were induced in rats after oral administration, but there were limitations in the design and reporting of these studies[1,5].

C. Other relevant data

There are conflicting reports of effects on the incidence of chromosomal aberrations in lymphocytes and bone-marrow cells of patients treated with azathioprine. In one study, the incidence of sister chromatid exchanges in lymphocytes of treated patients was not increased[6].

In animals treated *in vivo*, azathioprine induced dominant lethal mutations in mice, chromosomal aberrations in rabbit lymphocytes and Chinese hamster bone-marrow cells, and micronuclei in mice, rats and hamsters; it did not induce sister chromatid exchanges in

Chinese hamster bone-marrow cells. Azathioprine induced chromosomal aberrations but not sister chromatid exchanges in human lymphocytes *in vitro*. It induced chromosomal aberrations in *Drosophila*, was weakly mutagenic to fungi and was mutagenic to bacteria[6].

References

[1]*IARC Monographs, 26*, 47-78, 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]Isomäki, H.A., Hakulinen, T. & Joutsenlahti, U. (1978) Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J. chron. Dis., 31*, 691-696

[4]Fries, J.F., Bloch, D., Spitz, P. & Mitchell, D.M. (1985) Cancer in rheumatoid arthritis: a prospective long-term study of mortality. *Am. J. Med., 78 (Suppl. 1A)*, 56-59

[5]Cohen, S.M., Erturk, E., Skibba, J.L. & Bryan, G.T. (1983) Azathioprine induction of lymphomas and squamous cell carcinomas in rats. *Cancer Res., 43*, 2768-2772

[6]*IARC Monographs, Suppl. 6*, 86-88, 1987