TRIS(1-AZIRIDINYL)PHOSPHINE SULPHIDE (THIOTEPA) (Group 2A)

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

Occasional case reports of exposure to Thiotepa, 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 470 patients with colorectal cancer randomized to low-dose (four doses of 0.2 mg/kg bw) adjuvant therapy with Thiotepa, followed for 3102 person-years (30 second noncolorectal malignancies observed, 31.4 expected)[1]. No increased risk of second malignancies was found among 90 patients with breast cancer randomized to adjuvant therapy with Thiotepa for one year (0.8 mg/kg bw in divided doses followed by 0.2 mg/kg bw weekly maintenance); after an average follow-up of approximately five years, five nonskin, nonbreast cancers had occurred in 5819 person-years among 90 treated subjects compared with six in 4746 person-years among the 77 nonexposed patients[2].

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

Thiotepa was tested for carcinogenicity in mice by intraperitoneal injection and in rats by intraperitoneal and intravenous injection, producing a variety of malignant tumours[3,4,5].

C. Other relevant data

Thiotepa is an alkylating agent. An increased frequency of chromosomal aberrations was observed in one study of cancer patients receiving therapeutic doses of this compound[6].

Thiotepa induced dominant lethal mutations, chromosomal aberrations, micronuclei and sister chromatid exchanges in rodents treated *in vivo*. It induced sister chromatid exchanges and chromosomal aberrations in human and rodent cells *in vitro* and transformation of C3H 10T1/2 mouse cells. It was mutagenic to Chinese hamster cells *in vitro* and to mouse lymphoma cells in a host-mediated assay. Thiotepa induced sex-linked recessive lethal mutations in *Drosophila*, caused sister chromatid exchanges and chromosomal aberrations in plant cells and was mutagenic to fungi and to bacteria *in vitro* and in host-mediated assays[6].

References

[1]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

[2]Kardinal, C.G. & Donegan, W.L. (1980) Second cancers after prolonged adjuvant Thiotepa for operable carcinoma of the breast. *Cancer*, *45*, 2042-2046

[3]*IARC Monographs*, *9*, 85-94, 1975

[4]National Cancer Institute (1978) *Bioassay of Thio-tepa for Possible Carcinogenicity* (*Tech. Rep. Ser. No. 58; DHEW Publ. No. (NIH) 78-1308*), Washington DC, US Government Printing Office

[5]Schmähl, D. (1975) *Experimental investigations with anti-cancer drugs for carcinogenicity with special reference to immunodepression.* In: Grundmann, E. & Gross, R., eds, *The Ambivalence of Cytostatic Therapy*, New York, Springer, pp. 18-28

[6]*IARC Monographs, Suppl. 6*, 549-553, 1987