PROCARBAZINE HYDROCHLORIDE (Group 2A)

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

No epidemiological study of procarbazine as a single agent was available to the Working Group. In various combinations with other chemotherapeutic agents, given for Hodgkin's disease, procarbazine use has repeatedly been shown to lead to the appearance of acute nonlymphocytic leukaemia. These combinations usually also include nitrogen mustard (see p. 269), an alkylating agent which is also a potent animal carcinogen, and these many observations do not permit conclusions about the independent effect of either drug[1].

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

Procarbazine hydrochloride administered by repeated intraperitoneal injections produced malignant tumours of the nervous system and haematopoietic system in mice and rats of each sex and adenocarcinomas of the mammary gland in rats only[1]. Repeated

intravenous injections induced malignant tumours in different organs of rats[1]. Oral administration produced pulmonary tumours and leukaemias in mice[1,2] and mammary tumours in rats[1,3]. Leukaemias, haemangioendothelial sarcomas and osteogenic sarcomas were induced in rhesus, cynomolgus and African green monkeys of each sex by intraperitoneal, subcutaneous, intravenous or oral administration of procarbazine hydrochloride[1,4].

C. Other relevant data

Procarbazine generates an alkylating species[1].

No data were available on the genetic and related effects of procarbazine hydrochloride in humans.

Procarbazine gave positive results for germinal mutation in the mouse specific-locus test and caused mutation in the mouse spot test. It induced micronuclei and structural chromosomal aberrations in mice treated *in vivo*, but conflicting results were obtained in tests for dominant lethal mutations and negative results in the heritable-translocation test. It induced sister chromatid exchanges in mice and Chinese hamsters and caused DNA damage in rodents treated *in vivo*. Procarbazine did not transform Syrian hamster embryo cells. It induced mutation but not sister chromatid exchanges in rodent cells *in vitro*. It induced aneuploidy, dominant lethal mutations, sex-linked recessive lethal mutations and somatic mutation and recombination in *Drosophila*, but did not cause heritable translocations. It induced mutation, gene conversion and mitotic recombination in fungi. Conflicting results were obtained for mutation in bacteria, both *in vitro* and in host-mediated assays; it induced DNA damage in bacteria[5].

References

[1]*IARC Monographs, 26*, 311-339, 1981

[2]Bacci, M., Cavaliere, A. & Fratini, D. (1982) Lung carcinogenesis by procarbazine chlorate in BALB/c mice. *Carcinogenesis, 3*, 71-73

[3]Bacci, M., Cavaliere, A. & Amorosi, A. (1984) Procarbazine hydrochlorate carcinogenesis in Osborne-Mendel rats. *Oncology, 41*, 106-108

[4]Adamson, R.H. & Sieber, S.M. (1982) *Studies on the oncogenicity of procarbazine and other compounds in nonhuman primates.* In: Rosenberg, S. & Kaplan, H., eds, *Malignant Lymphomas: Etiology, Immunology, Pathology, Treatment (Bristol-Myers Cancer Symposia Series Vol. 3)*, Orlando, FL, Academic Press, pp. 239-257

[5]*IARC Monographs, Suppl. 6*, 474-478, 1987