BLEOMYCINS (Group 2B)

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

No epidemiological study of bleomycins alone was available to the Working Group. Occasional case reports of exposure to bleomycins, 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].

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including bleomycins (plus adriamycin [see p. 82], vinblastine [see p. 371] and dacarbazine [see p. 184]) but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy[2].

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

Bleomycin has been tested in mice by subcutaneous and intramuscular injection and in rats transplacentally. These studies could not be evaluated because of incomplete

reporting[1]. A study in rats by repeated subcutaneous injections showed that bleomycin produced renal tumours (adenomas, adenocarcinomas, sarcomas) and fibrosarcomas at the site of application at significantly dose-related incidences[3].

C. Other relevant data

Bleomycins induced chromosomal aberrations in lymphocytes of treated patients in one study[4].

In mice treated *in vivo*, bleomycin induced chromosomal aberrations (including heritable translocations) and sister chromatid exchanges but gave conflicting results in tests for micronuclei. It induced chromosomal aberrations and DNA strand breaks in human cells *in vitro* but gave conflicting results in tests for unscheduled DNA synthesis and sister chromatid exchange. It induced transformation of mouse C3H 10T1/2 cells, and induced aneuploidy, chromosomal aberrations, mutation and DNA damage in rodent cells *in vitro*; a weakly positive response was observed for the induction of sister chromatid exchanges. In *Drosophila*, bleomycin induced aneuploidy, chromosomal aberrations, sex-linked recessive lethal mutations, somatic mutations, genetic crossing-over and recombination, but not heritable translocations. It induced chromosomal aberrations but not sister chromatid exchanges in plants. Bleomycin was mutagenic to fungi and induced gene conversion, recombination and genetic crossing-over. It was mutagenic and caused DNA damage in bacteria[4].

References

[1]*IARC Monographs, 26*, 97-113, 1981

[2]Santoro, A., Viviani, S., Villarreal, C.J.R., Bonfante, V., Delfino, A., Valagussa, P. & Bonadonna, G. (1986) Salvage chemotherapy in Hodgkin's disease irradiation failures: superiority of doxorubicin-containing regimens over MOPP. *Cancer Treat. Rep., 70*, 343-348

[3]Habs, M. & Schmähl, D. (1984) Carcinogenicity of bleomycin sulfate and peplomycin sulfate after repeated subcutaneous application to rats. *Oncology, 41*, 114-119

[4]*IARC Monographs, Suppl. 6*, 121-125, 1987