ADRIAMYCIN (Group 2A)

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

No epidemiological study of adriamycin as a single agent was available to the Working Group. Occasional case reports, 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.

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including adriamycin [plus vinblastine (see p. 371), bleomycin (see p. 134) and dacarbazine (see p. 184)] but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy[1].

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

Adriamycin was tested for carcinogenicity in rats by a single intravenous injection, producing mammary tumours[2-5], and by single or repeated subcutaneous injections, producing local sarcomas and mammary tumours[6,7]. Intravesicular instillation of adriamycin in rats resulted in a low incidence of bladder papillomas and enhanced the incidence of bladder tumours induced by *N*-nitroso-*N*-(4-hydroxybutyl)-*N*-butylamine[8].

C. Other relevant data

Adriamycin induced chromosomal aberrations in treated patients in one of two studies and sister chromatid exchanges in both studies. In another study, cisplatin-adriamycin combination chemotherapy induced sister chromatid exchanges in peripheral blood lymphocytes of treated patients. DNA strand breaks were induced in the cells of treated patients in one study[9].

Adriamycin has been tested extensively for genetic effects in a wide variety of tests *in vivo* and *in vitro*, giving consistently positive results. It induced chromosomal aberrations, micronuclei, sister chromatid exchanges and DNA damage in rodents *in vivo* and

chromosomal aberrations, micronuclei, sister chromatid exchanges and DNA damage in human cells *in vitro*. It transformed virus-infected Fischer rat embryo cells and induced chromosomal aberrations, sister chromatid exchanges, mutation and DNA damage in cultured rodent cells. Adriamycin induced sex-linked recessive lethal mutations in *Drosophila*, chromosomal aberrations in plants and mutation in fungi. It was mutagenic to bacteria and induced DNA damage[9].

References

[1]Valagussa, P., Santoro, A., Kenda, R., Fossati Bellani, F., Franchi, F., Banfi, A., Rilke, F. & Bonadonna, G. (1980) Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. *Br. med. J., i*, 216-219

[2]*IARC Monographs, 10*, 43-49, 1976

[3]Marquardt, H., Philips, F.S. & Sternberg, S.S. (1976) Tumorigenicity *in vivo* and induction of malignant transformation and mutagenesis in cell cultures by adriamycin and daunomycin. *Cancer Res., 36*, 2065-2069

[4]Solcia, E., Ballerini, L., Bellini, O., Sala, L. & Bertazolli, C. (1978) Mammary tumors induced in rats by adriamycin and daunomycin. *Cancer Res., 38*, 1444-1446

[5]Bucciarelli, E. (1981) Mammary tumor induction in male and female Sprague-Dawley rats by adriamycin and daunomycin. *J. natl Cancer Inst., 66*, 81-84

[6]Maltoni, C. & Chieco, P. (1975) Adriamycin: a new potent carcinogen (Ital.). *Osp. Vita, 2*, 107-109

[7]Casazza, A.M., Bellini, O., Formelli, F., Giuliani, F., Lenaz, L. & Magrini, U. (1977) Tumors and dental and ocular abnormalities after treatment of infant rats with adriamycin. *Tumori, 63*, 331-338

[8]Ohtani, M., Fukushima, S., Okamura, T., Sakata, T., Ito, N., Koiso, K. & Niijima, T. (1984) Effects of intravesical instillation of antitumor chemotherapeutic agents on bladder carcinogenesis in rats treated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. *Cancer, 54*, 1525-1529

[9]*IARC Monographs, Suppl. 6*, 35-39, 1987