DIAZEPAM (Group 3)

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

A short-term screening study of 12 961 users of diazepam showed no evidence of excess of any cancer, and one negative association (lower risks of lymphoma and leukaemia than expected) was found over a four-year period. The morbidity ratio for all cancers was 1.0[1]. Subsequent studies have tended to concentrate on the suggestion that diazepam acts as a promoter in cancer[2], and most relate to breast cancer. No evidence of increased risk of breast cancer with diazepam use was found in a breast cancer screening study. The relative risk for 'ever' use of diazepam was 0.87 (95% confidence interval, 0.7-1.1). For use of diazepam 15 or more years earlier, the relative risk was 1.1 (0.5-2.4); for three or more years since last use of diazepam, the relative risk was 0.94 (0.7-1.3)[3]. Subsequent evaluation of the data from this study showed a negative association between diazepam use and extent of breast cancer and lymph node involvement[4]. These data suggest that diazepam does not act during the late stages of induction of breast cancer. The hypothesis was further evaluated in two case-control studies of breast cancer[5,6]. In one, 1236 cases of breast cancer and 728 controls with other malignancies were evaluated. The relative risk for women who had used diazepam four days a week for at least six months was 0.9 (0.5-1.6)[5]. In the second study, no increased

risk from diazepam use was found in 151 breast cancer cases in comparison with 151 hospital controls (relative risk, 0.95)[6]. In a further study of women newly diagnosed with breast cancer, the age-adjusted risk ratio for diazepam use six months prior to diagnosis was 0.9 (0.7-1.3)[7]. Diazepam use was also studied in relation to malignant melanoma in a case-control study of 166 cases and 498 controls, using both medical records and questionnaires. Although 35% of the cases and 33% of the controls did not return questionnaires, neither data source suggested excess use of diazepam by the cases[8].

The evidence that diazepam is not a breast carcinogen could not be described as 'suggesting lack of carcinogenicity' for breast cancer, because of (1) the restricted statistical power to detect increases after long latent periods or to detect small increases (i.e., relative risks under 2.0), even though these might be expected under reasonable hypotheses, and (2) the special problems of studying a human cancer closely tied to life events in relation to usage of a drug given for poorly defined indications.

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

Oral administration of diazepam to mice resulted in an elevated incidence of liver tumours in males[9]. In rats, a study reported in detail[9] and one reported briefly[10] showed no increase in the incidence of tumours of any type compared to controls. In limited bioassays, oral administration of diazepam enhanced the occurrence of liver preneoplastic lesions and neoplasms induced in mice by *N*-nitrosodiethylamine[11], but not that induced in rats by 3'-methyl-4-(dimethylamino)azobenzene or 2-acetylaminofluorene[12,13].

C. Other relevant data

A metabolite of diazepam, oxazepam, produced liver tumours in mice after its oral administration[14].

Neither chromosomal aberrations nor sister chromatid exchanges (one study) were observed in the lymphocytes of patients receiving treatment with diazepam[15].

Diazepam did not induce chromosomal aberrations in bone-marrow cells of Chinese hamsters treated *in vivo*, or in human or Chinese hamster cells *in vitro*. It did not inhibit intercellular communication in cultured rat hepatocytes. It was not mutagenic to bacteria, but urine from mice treated with diazepam showed increased mutagenicity as compared to controls[15].

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