BENZIDINE (Group 1)

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

Case reports and follow-up studies of workers in many countries have demonstrated that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer. In one extreme instance, all five of a group of workers continuously employed in the manufacture of benzidine for 15 years or more developed bladder cancer[1]. Earlier data suggesting that the incidence of this cancer in workers decreased after a reduction in industrial exposure[1] have been supported by a study of a cohort of workers at a US benzidine-manufacturing facility, in which major preventive measures were instituted in 1950 to minimize worker exposure. The study period covered 1945-1979, and, overall, there was a clearly significant excess of bladder cancer incidence, which, however, declined in those first employed after 1950[2]. Although a longer follow-up is required to evaluate fully the effect of preventive measures on cancer risks, the causal association is strengthened by these two independent observations. Few other epidemiological studies have examined the cancer risk associated with exposure to benzidine alone. In a study at a dyestuffs factory in Italy, it was possible to distinguish a very high bladder cancer risk (5 deaths observed, 0.06 expected) associated with benzidine production[3]. The study was extended and updated, but the role of exposure to benzidine alone in the dramatically increased bladder cancer risk could not be examined further[4]. Of 25 benzidine 'operators' at a plant in the USA, 13 developed bladder cancer; all cases had been exposed for six years or more[5]. A surveillance programme of 179 active and 65 retired workers in a dyestuffs manufacturing plant in Japan revealed nine cases of bladder cancer that occurred between 1968 and 1981; all of the cases had been engaged in benzidine production[6].

Other investigations have shown high incidences of cancer of the bladder and urinary tract after concomitant exposure to benzidine and 2-naphthylamine (see p. 261) [7,8]. Exposure to these two compounds was also associated with an increase in the occurrence of second primary cancers at sites other than the bladder, including the liver[9].

Among 1601 workers in the chemical-dye industry in China who were exposed to benzidine, methylnaphthylamine and dianisidine (see p. 198), 21 cases of bladder carcinoma were found. All had a history of exposure to benzidine, while no carcinoma was found among workers exposed to methylnaphthylamine or dianisidine. Suggestions of a dose-response relationship were provided by analysis according to length of exposure[10].

Bladder cancer was also found to be increased in ecological studies of areas where benzidine (as well as 2-naphthylamine and other compounds) was used, manufactured or stored[11,12].

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

Benzidine and/or its salts were tested for carcinogenicity by oral administration in mice, rats, hamsters and dogs and by subcutaneous and intraperitoneal injection and inhalation in rats. Following oral administration of benzidine and its hydrochloride, significant increases in the incidences of benign and malignant liver neoplasms were observed in mice and

hamsters[1,13-17] and of mammary cancer in rats; benzidine induced bladder carcinomas in dogs. Following subcutaneous administration of benzidine and its sulphate to rats, a high incidence of Zymbal-gland tumours was observed. After intraperitoneal administration of benzidine to rats, a marked increase in the incidence of mammary-gland and Zymbal-gland neoplasms was observed. The results of one study in rats by inhalation could not be evaluated[1].

Two metabolites of benzidine, *N,N'*-diacetylbenzidine and *N*-hydroxy-*N,N'*-diacetylbenzidine, produced mammary-gland and Zymbal-gland tumours in rats following their intraperitoneal injection[1].

C. Other relevant data

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

Covalent binding products of benzidine with DNA have been described in the liver of mice and rats treated *in vivo*. Benzidine induced micronuclei, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis in cells of rodents treated *in vivo*. It induced unscheduled DNA synthesis in humans cells *in vitro*. It caused transformation of Syrian hamster embryo and BALB/c 3T3 cells and induced chromosomal aberrations, sister chromatid exchanges, unscheduled DNA synthesis and DNA strand breaks in rodent cells *in vitro*; conflicting results were obtained for mutation. Benzidine induced aneuploidy, gene conversion and DNA damage in yeast, but not mutation. It was mutagenic to plants and bacteria[18].

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