ISONICOTINIC ACID HYDRAZIDE (ISONIAZID) (Group 3)

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

Several early studies showed no significant excess of cancer among patients treated with isoniazid[1]. A study of 3842 tuberculosis patients followed for 16-24 years showed slight excesses of deaths from malignant neoplasms of the bronchus, lung and pleura in 2041 patients treated with isoniazid during 1953-1957 and followed through to 1973 (relative risk, 1.6; 95% confidence interval, 1.2-2.1), but none in 655 treated for tuberculosis in 1950-1952 when isoniazid was not generally available (0.7; 0.1-1.5). An excess of all malignant neoplasms was seen in patients treated in 1953-1957 (1.4; 1.2-1.7), but also in 145 patients not treated with isoniazid over the same period (1.8; 0.7-2.9). Again, no excess was observed in those treated for tuberculosis in 1950-1952. No dose-response effect was seen either for total consumption or for maximum daily dose of isoniazid[2]. Additional studies of cancer incidence and mortality among patients treated with isoniazid have shown no excess of lung cancer, or of cancer as a whole, that could be attributed to treatment[3-6]. A cancer incidence study in patients with tuberculosis, involving heavy smokers, showed an excess of lung cancer among men exposed to isoniazid (3.4, based on 88 cases observed, 26.2 expected) but also among those not exposed (2.6, based on 18 cases observed, 7.0 expected). The difference between the two ratios was not statistically significant. The corresponding figures for women were 4.6, based on 14 cases exposed, and 0.5, based on one case not exposed[7]. In a preliminary analysis of one-year case records, 72 (4.9%) cancer patients had healed tuberculosis compared with 26 (2%) noncancer patients[8]. Four case-control studies concerning bladder and kidney cancers[9], bladder cancer[10,11] and cancer in children[12] have provided no conclusive evidence of a risk associated with isoniazid therapy. A single case of mesothelioma has been reported in a nine-year-old child whose mother was treated with isoniazid for a positive tuberculin skin test in the second and third trimesters of pregnancy[13].

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

Isoniazid produced lung tumours in mice after its oral, intraperitoneal or subcutaneous administration[1,8,14-16]. Studies in rats were considered inadequate for evaluation. No tumour was produced in hamsters after oral administration of isoniazid[1].

C. Other relevant data

In the one available study, isoniazid did not induce chromosomal aberrations in lymphocytes of treated patients[17].

Isoniazid did not induce dominant lethal mutations in mice, or chromosomal aberrations, sister chromatid exchanges or DNA damage in rodents treated *in vivo*. Results for chromosomal aberrations and sister chromatid exchanges in human cells *in vitro* were inconclusive; it did not induce unscheduled DNA synthesis. In cultured rodent cells, it induced chromosomal aberrations and sister chromatid exchanges, but not DNA damage. It did not induce transformation of Syrian hamster embryo cells. It did not induce gene

conversion in yeast. Isoniazid was mutagenic to *Salmonella typhimurium* but not, in a single study, to *Escherichia coli*[17].

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