CLOFIBRATE (Group 3)

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

Results of a further four years of follow-up to the clofibrate trial of the World Health Organization[1] have become available[2]. On average, the total follow-up period was 13.2 years, 5.3 of which were during the actual treatment phase (range, four to eight years) and 7.9 thereafter. Three groups of men, divided according to their cholesterol levels, were studied, comprising 208 000 man-years of observation. The first two groups included subjects in the upper third of the serum cholesterol distribution, randomly allocated either to treatment by clofibrate (1.6 g daily) or an olive-oil placebo. The third group was composed of half of the men in the lowest third of the distribution, who received an olive-oil placebo. At the conclusion of follow-up, the age-standardized death rates from malignant neoplasms per 1000 per annum were 2.4, 2.4 and 2.3, respectively (based on 206, 197 and 173 deaths from neoplasms). However, the age-standardized death rates for malignant neoplasms during the treatment phase had been 1.9 (42 deaths), 1.2 (25 deaths) and 1.7 (30 deaths), respectively.

Reports of two of four other clofibrate trials did not include information on the occurrence of cancer[1]. Of those which did, one showed no excess of cancer in treated groups over the six-year period of the trial (eight cancer deaths in all)[3], and, in the other, covering a follow-up period of five to 8.5 years, the death rates for all cancers were 0.9% for the group receiving clofibrate, 0.8% for a group receiving niacin and 0.9% for the placebo group[4]. Two further trials of clofibrate showed no excess of cancer in treated groups[2].

In a single case report, a man who received clofibrate (among other drugs) for 15 years developed a jejunal adenocarcinoma[2].

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

Clofibrate was tested in two studies by oral administration to male rats; it produced hepatocellular carcinomas, and a few pancreatic exocrine acinar adenomas and carcinomas were observed[1]. Clofibrate decreased the incidence of 7,12-dimethylbenz[*a*]anthracene-induced mammary carcinomas in rats, but did not affect the carcinogenic action of

N-methyl-*N*-nitrosourea[5] or of dimethylhydrazine (isomer unspecified)[6]. In two studies, it enhanced *N*-nitrosodiethylamine-induced liver tumorigenesis[7,8], but, in a limited bioassay, when fed after the induction of liver foci by 2-acetylaminofluorene, it did not enhance liver carcinogenesis[9].

C. Other relevant data

No data were available on the genetic and related effects of clofibrate in humans. It did not induce chromosomal aberrations in Chinese hamster fibroblasts *in vitro* and was not mutagenic to bacteria[10].

References

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