PHENYLBUTAZONE (Group 3)

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

Cases of leukaemia have been reported in patients following phenylbutazone therapy[1,2], but their significance cannot be evaluated, given the widespread use of phenylbutazone[1]. No significant excess of leukaemia or other malignancy was observed during 1969-1976 among 3660 members of a prepaid health plan prescribed phenylbutazone during 1969-1973[3]. In a case-control study of 409 patients with leukaemia or lymphoma and a subset of 127 patients with myelocytic leukaemia, who were compared with equal numbers of hospital controls and with a second control series of members of a prepaid health plan, prior use of

phenylbutazone was more frequent in cases than in members of the health plan (relative risk, 1.26; 95% confidence interval, 0.86-1.86). This appeared to be explained by an association of musculo-skeletal disease with these cancers. There was no clear association between the amount or duration of phenylbutazone therapy and risk of leukaemia[4]. In a cohort study of 489 patients with rheumatoid arthritis, followed for an average of 12.2 years, seven patients developed non-Hodgkin's lymphoma compared to 0.29 expected from regional rates (relative risk, 24.1 [20.4-27.9]), two developed Hodgkin's disease, one, a chronic lymphatic leukaemia and one, an acute myeloid leukaemia. A study of hospital charts indicated that 60% of those with malignancies had received phenylbutazone compared to 3% of the whole cohort; however, the author considered it likely that far more than 3% of the whole cohort had received phenylbutazone. Those patients with malignancies had also received other drugs: 40% had received gold, 20%, steroids and 10%, chloroquine, but none had received cytotoxic agents or radiotherapy. Further, 30% were believed not to have received any of these agents (including phenylbutazone)[5]. Lymphoproliferative malignancies have been recognized as a complication of other immune disorders, and it is possible that phenylbutazone therapy did not play a causal role in this study.

B. Evidence for carcinogenicity to animals

No data were available to the Working Group.

C. Other relevant data

In one study of patients given high doses of phenylbutazone, no chromosomal aberration was found in bone-marrow cells[6].

Phenylbutazone did not induce dominant lethality, micronuclei or chromosomal anomalies in bone-marrow cells of mice treated *in vivo*. It induced chromosomal aberrations in cultured Chinese hamster fibroblasts, but did not induce sister chromatid exchanges or chromosomal aberrations in cultured human cells. Phenylbutazone was not mutagenic to bacteria[6].

References

[1]*IARC Monographs, 13*, 183-199, 1977

[2]Mitarnun, W. & Peerabool, R. (1983) Blood dyscrasia evolving into acute lymphoblastic leukemia following ingestion of phenylbutazone, indomethacin, dexamethasone and prednisolone. *J. med. Assoc. Thailand, 66*, 649-654

[3]Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. *J. natl Cancer Inst., 65*, 723-733

[4]Friedman, G.D. (1982) Phenylbutazone, musculoskeletal disease, and leukemia. *J. chron. Dis., 35*, 233-243

[5]Symmons, D.P.M. (1985) Neoplasms of the immune system in rheumatoid arthritis. *Am. J. Med., 78 (Suppl. 1A)*, 22-28

[6]*IARC Monographs, Suppl. 6*, 459-460, 1987