PHENACETIN (Group 2A) and ANALGESIC MIXTURES CONTAINING PHENACETIN (Group 1)

A. Evidence for carcinogenicity to humans (*limited* for phenacetin; *sufficient* for analgesic mixtures containing phenacetin)

There have been many case reports of renal pelvic and other urothelial tumours in patients who had used large amounts of phenacetin-containing analgesics[1-13]. Case-control studies have been consistent in showing a positive association between cancer of the renal pelvis and cancer of the bladder and use of phenacetin-containing analgesics, with relative risks varying from 2.4 to over 6; these associations have not been explained by confounding with other causes of urothelial cancer, and, where looked for, a positive dose-response relationship has been evident[14-19]. In one study[14], use of nonphenacetin-containing analgesics appeared to increase the risk of cancer of the renal pelvis to the same extent as did phenacetin-containing analgesics. This result was not obtained in other studies[15,17,18].

B. Evidence for carcinogenicity to animals (*sufficient* for phenacetin; *limited* for analgesic mixtures containing phenacetin)

Phenacetin given orally induced benign and malignant tumours of the urinary tract in mice[20] and rats[1,21] and of the nasal cavity in rats[1]. When given in combination with aspirin and caffeine to rats or mice, no significant association was found with the incidence of tumours[1]. In rats, phenacetin alone or in combination with phenazone slightly increased the incidences of renal-cell and renal-pelvic tumours; rats treated with phenacetin, phenazone and caffeine in combination developed hepatomas[22]. Also in rats, phenacetin enhanced the incidence of urinary bladder tumours induced by *N*-nitrosobutyl-*N*-(4-hydroxybutyl)-amine[1], and prevented the induction of hepatocellular carcinomas by 2-acetylaminofluorene[23].

C. Other relevant data

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

The results of studies on the induction of chromosomal aberrations, sister chromatid exchanges and micronuclei in rodents treated with phenacetin *in vivo* were equivocal. Phenacetin induced chromosomal aberrations in Chinese hamster cells *in vitro* but not DNA strand breaks in rat hepatocytes. It did not induce sex-linked recessive lethal mutations in *Drosophila*. Phenacetin was mutagenic to bacteria when tested in the presence

of a metabolic system derived from hamster but not mouse or rat liver. The urine from phenacetin-treated Chinese hamsters, but not that from rats, was mutagenic to bacteria[24].

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