PHENOBARBITAL (Group 2B)

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

Phenobarbital has been associated with increased frequencies of several cancers[1]. Excesses of brain tumours have been reported in studies of epileptics, most of whom were treated with phenobarbital, often in combination with other drugs[2,3]. The role of anticonvulsant therapy in the origin of these brain tumours is not clear, however, since the tumours may have been the precipitating cause or secondary to the cause of the epilepsy. In the largest study[2,4], there was an almost 12-fold excess of brain tumours in the first ten years of follow-up (45 observed, 3.8 expected), but this decreased with duration of follow-up to 1.3 (2 observed, 1.5 expected) 30 or more years following admission. A case-control study involving 84 children with brain tumours[5] showed a two-fold increase in the incidence of these tumours associated with prenatal or childhood exposure to barbiturates (mostly phenobarbital[6]). In a study of 11 169 matched case-control pairs of childhood cancers and controls, epilepsy was reported by 39 mothers of cases and 22 mothers of controls (20 and 12, respectively, having used phenobarbital). The number of brain tumours among the 39 cancers was not reported[7].

Lung cancer was reported in excess in 5834 members of a prepaid health plan prescribed phenobarbital during 1969-1973 and followed to 1976. The standardized mortality ratio (SMR) was 1.5 [95% confidence interval, 1.1-1.9]. Excesses were also found in users of pentobarbital sodium and secobarbital sodium. When users of the three drugs were considered together, the excess of lung cancer was found in both men and women, appeared to be accounted for only partly by cigarette smoking and persisted when cases diagnosed during the first two years of follow-up were excluded. There was no apparent relation with duration of use[8]. Small increases in lung cancer incidence were also observed in two cohort

studies of epileptics[3,4], 'largely ascribable to tobacco' in one study[4], although the effects of smoking were not studied. In the larger of the two[4], the SMR was 1.3 [1.0-1.6]; in the other[3], it was 1.4 (0.9-2.1).

Liver cancer occurred in excess in the larger cohort study of epileptics[4] (SMR, 3.8 [2.7-4.9]). However, ten of the 13 observed cancers occurred in individuals exposed to thorotrast. Histology was available for nine of these: two were reported to be haemangiosarcomas, four, cholangiocarcinomas, one, a hepatocellular carcinoma, and two, adenocarcinomas[2]. In the other cohort study with data available[3], no primary liver tumour was observed although 0.6 cases of cancer of the liver and gall-bladder were expected.

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

Phenobarbital produced benign and malignant hepatocellular tumours in mice and hepatocellular tumours in rats after its oral administration[1,9,10]. Experiments with mice and rats in which phenobarbital was studied for its promoting activity included comparison groups given phenobarbital alone. Oral administration of phenobarbital enhanced the incidences of liver tumours induced in mice by *N*-nitrosodimethylamine[11] or *N*-ethyl-*N*-nitrosourea[12] and of benign and malignant liver tumours induced in rats by 2-acetylaminofluorene[13-16], *N*-nitrosodiethylamine[17,18], 2-methyl-*N*,*N*-dimethyl-4-aminoazobenzene[19], benzo[*a*]pyrene[20], cycasin[21], *N*-hydroxy-*N*-formyl- or -acetylaminobiphenyl[22], *N*-nitroso-*N*-(4-hydroxybutyl)butylamine[16] or *N*-nitrosomorpholine[23]. In rats, oral administration of phenobarbital in combination with DDT resulted in a high incidence of liver tumours[24]. Phenobarbital enhanced the development of thyroid tumours[25,26] and of liver foci[26] induced in rats by *N*-nitrosodi(2-hydroxypropyl)amine and enhanced the incidences of liver foci, thyroid adenocarcinomas and forestomach carcinomas induced in rats by *N*-methyl-*N*-nitrosourea[27].

C. Other relevant data

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

Neither phenobarbital nor its sodium salt induced sister chromatid exchanges, chromosomal aberrations, micronuclei or sperm abnormalities in mice treated *in vivo*. Phenobarbital induced chromosomal aberrations and mutation but not sister chromatid exchanges in cultured human cells. Both positive and negative results were obtained for transformation in rodent cells *in vitro*. Phenobarbital enhanced transformation of virus-infected rat embryo cells initiated with 3-methylcholanthrene in a two-stage transformation assay. It induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells, but not in cultured rat liver cells; micronuclei and aneuploidy were not induced in Chinese hamster cells. Phenobarbital induced mutation in Chinese hamster cells, but conflicting or negative results were obtained in other rodent cells. Phenobarbital and its sodium salt did not induce DNA strand breaks, and phenobarbital did not induce unscheduled DNA synthesis, in cultured rodent cells. Phenobarbital inhibited intercellular communication in human hepatoma cells and both phenobarbital and its sodium salt did so in rodent systems. Phenobarbital induced neither somatic mutation nor recombination in *Drosophila*; the sodium salt did not induce sex-linked recessive lethal mutations.

Phenobarbital induced aneuploidy but not mutation or gene conversion in fungi. Conflicting results were obtained concerning the mutagenicity of these compounds in bacteria[28].

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