TOBACCO SMOKE (Group 1)

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

Cigarette smoking has been shown to cause lung cancer, bladder cancer, cancer of the renal pelvis (and possibly renal adenocarcinoma), cancer of the lip, and oropharyngeal, hypopharyngeal, laryngeal, oesophageal and pancreatic cancers. In some studies, increased

risks of cancers of the stomach, liver and cervix have been noted, but the data were inadequate to decide whether the association is causal or not. The risk for lung cancer due to cigarette smoking is substantially increased in conjunction with exposure to radon daughters or asbestos (see p. 106). An increase in the incidence of lung cancer also results from smoking other forms of tobacco, i.e., pipe, cigars and *bidis*. Pipe and cigar smoking probably increase the risk of bladder cancer, but at lower levels than that caused by cigarette smoking. They also increase the risks of oral, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers to approximately the same extent as cigarette smoking, and, as with cigarette smoking, the risk is substantially augmented in conjunction with high-dose exposure to alcohol[1].

Tobacco smoke affects not only people who smoke but also those who are exposed to the combustion products of other people's tobacco (passive smokers). The most numerous observations hitherto available concern lung cancer, and the results of most of the 13 main epidemiological studies[2] carried out so far are compatible with either an increased risk from passive smoking or an absence of risk. However, the aggregate evidence from these studies, taken together with knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during passive smoking and of the quantitative relationships between dose and effect that are commonly observed after exposure to carcinogens, leads to the conclusion that passive smoking does carry some risk for lung cancer.

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

Cigarette smoke has been tested for carcinogenicity by inhalation in mice, rats, hamsters and dogs. Exposure of hamsters and rats to whole smoke produced malignant respiratory-tract tumours[1]. In mice, inhalation of whole tobacco smoke resulted in a slightly increased incidence of alveologenic lung tumours, but this was not statistically significant in some of the studies[1,3]. An increased incidence of lung tumours has also been reported in dogs exposed to cigarette smoke, but the data were insufficient for evaluation. More tumours of the respiratory tract occurred in rodents exposed to both cigarette smoke and 7,12-dimethylbenz[*a*]anthracene than to either one alone; the same is true for concomitant exposure to benzo[*a*]pyrene or radon daughters[1].

Cigarette-smoke condensate induced benign and malignant skin tumours in mice and rabbits after application to the skin. Following its topical administration to oral mucosa, it resulted in an increased incidence of lung tumours and tumours of other organs, primarily lymphomas, in one strain of mice. In rats, cigarette-smoke condensate produced lung cancer after intrapulmonary injection. In two-stage mouse-skin assays, a single topical administration of cigarette-smoke condensate induced changes resulting in benign and malignant skin tumours after additional application of croton oil. Skin tumours were also produced when cigarette-smoke condensate was applied chronically subsequent to a single treatment with other agents, such as 7,12-dimethylbenz[*a*]anthracene[1].

C. Other relevant data

Structural chromosomal aberrations, sister chromatid exchanges and micronuclei have been observed in peripheral blood lymphocytes of tobacco smokers. Although in some

studies there was no increase in the incidence of sister chromatid exchanges, in several others a dose-response relationship was reported between the amount and duration of cigarette smoking and the frequency of sister chromatid exchange. Long-term heavy smokers generally also had higher frequencies of chromosomal aberrations in peripheral blood lymphocytes. In a large study, a significant dose-response relationship was found between the frequency of structural chromosomal aberrations and the estimated daily uptake of condensate. In a single study, it was reported that DNA adducts associated with cigarette smoke were detected in the bronchus of one smoker and in the larynx of another, but not in the bronchus of a nonsmoker. In another study, one of several DNA adducts detected in 16/17 placentas from smokers and 3/14 placentas from nonsmokers was claimed to be related to maternal smoking. Antigenicity against polycyclic aromatic hydrocarbon-DNA adducts has been demonstrated in peripheral lymphocytes and lung samples from cigarette smokers, although the occurrence of these adducts could not be correlated with cigarette smoking[4].

Extracts of urine from smokers induced chromosomal aberrations in Chinese hamster ovary cells and were mutagenic to bacteria in the presence of an exogenous metabolic system. Passive exposure to tobacco smoke has also been reported to increase urinary mutagenicity. In studies of amniotic fluid samples from smoking and nonsmoking mothers, more mutagenicity to *Salmonella typhimurium* was reported in samples taken at term from heavy smokers as compared to nonsmokers, but not in samples taken at 16 weeks by amniocentesis. One study of the mutagenicity of cervical mucus from smoking and non-smoking women was difficult to interpret due to inadequate reporting[4].

Tobacco smoke inhibited DNA repair capacity in mice and increased the frequency of sister chromatid exchanges in bone-marrow cells of mice exposed *in vivo* and in human lymphocytes *in vitro*; it also induced single-strand breaks in cultured human cells. It induced sex-linked recessive lethal mutations in *Drosophila* and mitotic recombination, gene conversion and mutation in yeast. The urine of rats and baboons exposed to cigarette smoke was mutagenic to bacteria[4].

Tobacco smoke and extracts of particulate matter collected on filters in rooms containing cigarette smoke were mutagenic to bacteria. The extracts also induced sister chromatid exchanges in cultured Chinese hamster ovary cells[4].

Tobacco condensates induced mutation, sister chromatid exchanges and transformation in rodent cells in culture, sex-linked recessive lethal mutations in *Drosophila* and mutation and gene conversion in fungi. Tobacco-smoke condensate inhibited intercellular communication of Chinese hamster V79 cells. All tobacco-smoke condensates tested were mutagenic to bacteria[4].

References

[1]*IARC Monographs, 38*, 1986

[2]Wald, N.J., Nanchahal, K., Thompson, S.G. & Cuckle, H.S. (1986) Does breathing other people's tobacco smoke cause lung cancer? *Br. med. J., 293*, 1217-1222

[3]Henry, C.J. & Kouri, R.E. (1986) Chronic inhalation studies in mice. II. Effects of long-term exposure to 2R1 cigarette smoke on (C57BL/Cum × C3H/AnfCum)F_1 mice. *J. natl Cancer Inst.*, *77*, 203-212

[4]*IARC Monographs, Suppl. 6*, 519-520, 1987