BETEL QUID WITH TOBACCO (Group 1) and BETEL QUID WITHOUT TOBACCO (Group 3)

A. Evidence for carcinogenicity to humans (*sufficient* for betel quid with tobacco; *inadequate* for betel quid without tobacco)

Many descriptive studies and case reports have shown an association between the habit of chewing betel quid with tobacco and oral cancer. A significant increase in the risk of oral cancer has been observed in chewers of betel quid with tobacco in several case-control studies and in one large-scale cohort study. In chewers of betel quid with tobacco, a statistically significant increase in risk was also observed for cancers of the oropharynx, hypopharynx, larynx and oesophagus[1].

Several descriptive studies from Papua-New Guinea and a number of case-control studies have suggested an association between the habit of chewing betel quid without tobacco and oral cancer. In one of the case-control studies, in which smoking was not

controlled for, a statistically significant increase in risk was also observed for cancers of the oropharynx, hypopharynx, larynx and oesophagus. In another case-control study of oral cancer, in which a clear effect of chewing betel with tobacco was found, no such effect was found for chewing betel without tobacco[1].

B. Evidence for carcinogenicity to animals (*limited* for betel quid with and without tobacco)

Aqueous extracts of betel quid containing tobacco were tested for carcinogenicity in mice by gastric intubation, skin painting and subcutaneous injection; some malignant tumours occurred at the site of skin or subcutaneous administration. In hamsters, forestomach carcinomas occurred after painting of the cheek-pouch mucosa with aqueous extracts or implantation of wax pellets containing powdered betel quid with tobacco in the cheek pouch; carcinomas occurred in the cheek pouch following implantation of wax pellets[1].

Aqueous extracts of betel quid without tobacco were tested in mice by gastric intubation and by subcutaneous administration; an increased incidence of local tumours was observed after subcutaneous injection. In hamsters, painting of the cheek-pouch mucosa or implantation of wax pellets into the cheek pouch resulted in the induction of forestomach carcinomas; carcinomas occurred in the cheek pouch following implantation of wax pellets[1].

Aqueous or dimethyl sulphoxide extracts of areca nut with tobacco were tested in mice by skin application; a low incidence of skin tumours was reported in a study lacking controls. In hamsters, applications of such extracts to cheek-pouch mucosa produced squamous-cell carcinomas of the cheek pouch and forestomach carcinomas[1].

Areca nut and aqueous extracts of areca nut were tested in mice by oral intubation, dietary administration, skin application and intraperitoneal and subcutaneous injection. Local tumours were produced following subcutaneous injection. In rats, areca nut was inadequately tested by oral administration; aqueous extracts tested by subcutaneous injection produced local mesenchymal tumours. In hamsters, administration of areca nut and application of aqueous or dimethyl sulphoxide extracts to the cheek-pouch mucosa resulted in squamous-cell carcinomas of the cheek pouch and carcinomas of the forestomach[1]. Oral administration of a diet containing 20% betel-nut powder enhanced the incidences of preneoplastic and neoplastic lesions of the tongue in rats pretreated with 4-nitroquinoline-1-oxide and of preneoplastic liver lesions in rats pretreated with 2-acetylaminofluorene[2].

Aqueous extracts of betel leaf were tested in mice by oral intubation and by intraperitoneal injection, in hamsters by application to the cheek-pouch mucosa[1] and in rats by oral administration[3]. Betel leaf was tested in rats by dietary administration and in hamsters by implantation in beeswax pellets into the cheek pouch[1]. All of these studies were inadequate for evaluation.

C. Other relevant data

Chewing of betel quid with or without tobacco increased the frequencies of micronucleated cells in the buccal mucosa of chewers; dose-dependence was observed in relation to the number of betel quids chewed per day. Chewing of betel quid with or without tobacco increased the frequency of sister chromatid exchanges in peripheral blood lymphocytes of chewers. Increased frequencies of sister chromatid exchanges were observed in peripheral blood lymphocytes of chewers of areca nut with slaked lime and tobacco, either alone or wrapped in betel leaf, particularly among chewers who had developed oral submucous fibrosis. Extracts of urine from chewers of betel quid with tobacco were mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system[4].

An aqueous extract of betel quid (containing tobacco) induced micronuclei in bone-marrow cells of mice treated *in vivo* and was mutagenic to Chinese hamster V79 cells. No such effect was observed with extracts of betel quids not containing tobacco. Aqueous extracts of betel quids (both with and without tobacco) were mutagenic to *S. typhimurium*[4].

References

[1]*IARC Monographs, 37,* 141-200, 1985

[2]Tanaka, T., Kuniyasu, T., Shima, H., Sugie, S., Mori, H., Takahashi, M. & Hirono, I. (1986) Carcinogenicity of betel quid. III. Enhancement of 4-nitroquinoline-1-oxide and *N*-2-fluorenylacetamide-induced carcinogenesis in rats by subsequent administration of betel nut. *J. natl Cancer Inst., 77,* 777-781

[3]Rao, A.R., Sinha, A. & Selvan, R.S. (1985) Inhibitory action of *Piper betle* on the initiation of 7,12-dimethylbenz[*a*]anthracene-induced mammary carcinogenesis in rats. *Cancer Lett., 26,* 207-214

[4]*IARC Monographs, Suppl. 6,* 113, 1987