TOBACCO PRODUCTS, SMOKELESS (Group 1)

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

In North America and western Europe, case reports indicate an association between tobacco chewing and oral cancer at the site where the quid was placed habitually. In those case-control studies in which an association between tobacco chewing and cancer of the oral cavity, pharynx and larynx has been observed, confounding by tobacco smoking or alcohol consumption could not be excluded. A slight increase in the incidence of oesophageal cancer related to tobacco chewing has been seen in four case-control studies[1].

Case reports indicate an association between oral use of snuff and oral cancer. Four case-control studies imply a causal association between snuff use and oral, and possibly pharyngeal, cancer. That oral use of snuff increases the risk of nasal-sinus cancer was suggested in one case-control study[1].

Three case series also show a high relative frequency of smokeless-tobacco use (chewing tobacco or oral snuff, unspecified) among oral cancer patients. Four case-control studies have shown an association between smokeless-tobacco use and the risk of oral cancer. Two cohort mortality studies provide evidence of a positive association with oesophageal cancer, and one suggests an increased risk for oral and pharyngeal cancer[1].

Two large case-control studies from Pakistan and India reported substantial increases in the risk for oral cancer related to tobacco-lime (*khaini*) chewing[1]. In addition, evidence is available from various studies in which cancer risks were studied in relation to unspecified habits of betel-tobacco-lime chewing[2].

Case series have indicated an association between use of *shammah* and *nass* and oral cancer. Oral cancer was found to develop at the site at which *nass* was placed habitually. Two case-control studies showed substantial increases in the risk of oral cancer associated with *nass* use and one with *naswar* use; however, in these studies positive confounding by smoking and other factors could not be excluded. Oral cancer in users of *mishri* and *gudakhu* was studied in a prevalence survey; no case was found[1]. A study of 64 patients with squamous-cell carcinoma of the head and neck in Saudi Arabia showed that 81% were

alshammah users and 34% were *alqat* users, but only 14% were cigarette smokers; none used alcohol to excess[3].

No association has been seen between nasal use of snuff and oral cancer. In two case-control studies an association between snuff inhaling and nasal-sinus cancer has been reported. One case-control study reported snuff inhaling to be more common among patients with cancers of the oesophagus, hypopharynx or oropharynx than among controls[1].

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

Various chewing tobaccos and unburnt cigarette tobaccos and their extracts were tested for carcinogenicity by oral administration in mice, by topical application to the oral mucosa of mice, rats and hamsters, and by subcutaneous administration, skin application, inhalation, intravesicular implantation and intravaginal application to mice. All of these studies suffered from certain deficiencies[1].

In a two-stage mouse-skin assay, applications of tobacco extract followed by treatment with croton oil induced papillomas and squamous-cell carcinomas of the skin. In further two-stage mouse-skin assays, application of tobacco extracts following initiation by 7,12-dimethylbenz[*a*]anthracene resulted in papillomas[1].

A commercial Swedish snuff was tested for carcinogenicity in rats by topical administration in a surgically-created oral canal, alone or in combination with herpes simplex type 1 infection. Two squamous-cell carcinomas of the oral cavity were observed in the group receiving both treatments, but this result was not statistically significant[1]. A commercial North American snuff was tested in rats by the same route. One squamous-cell carcinoma and two papillomas of the oral cavity were found, but this result was not statistically significant[4].

An aqueous extract of a commercial North American snuff was also tested by topical application to the oral mucosa in rats, alone or enriched with the tobacco-specific nitrosamines, *N'*-nitrosonornicotine and 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone. Some papillomas of the oral cavity were observed in rats treated with the enriched snuff extract, but this result was not statistically significant[4].

Snuff was tested by oral administration in hamsters, alone and in combination with calcium hydroxide, but the data were insufficient for evaluation. Several studies in hamsters in which snuff was administered as single or repeated applications into the cheek pouch or fed in the diet yielded insufficient data for evaluation. Subcutaneous injection of ethanol extracts of snuff to rats did not produce an increase in tumour incidence[1].

Nass was tested for carcinogenicity in hamsters by administration into the cheek pouch or by skin application. No tumour was found at the site of application. Although *nass* administration was associated with an apparent excess of liver tumours in various groups receiving cheek-pouch administration, which may be indicative of carcinogenicity, deficiencies in reporting do not allow an evaluation to be made[1].

C. Other relevant data

An increased incidence of micronuclei was observed in exfoliated epithelial cells from chewers of *khaini* and *nass*. Saliva collected from chewers of Indian tobacco induced chromosomal aberrations in Chinese hamster ovary cells *in vitro*[5].

Ethanol extracts of Indian chewing tobacco induced micronuclei in bone-marrow cells of Swiss mice treated *in vivo* and were mutagenic to Chinese hamster V79 cells *in vitro*, both in the presence and absence of an exogenous metabolic system, and to *Salmonella typhimurium*. Both ethanol and ethyl acetate extracts of Sri Lankan chewing tobacco induced transformation of Syrian hamster embryo cells. Ethyl acetate extracts induced sister chromatid exchanges in cultured human cells, but not mutation in Chinese hamster V79 cells when tested in the absence of an exogenous metabolic system[5].

Aqueous extracts of *nass* and *khaini* induced chromosomal aberrations in Chinese hamster ovary cells. Powdered tobacco fed to larvae of *Drosophila* did not induce sex-linked recessive lethal mutations, autosomal translocations or sex-chromosome loss[5].

Chloroform extracts of *shammah* induced transformation in mouse C3H 10T1/2 cells. The same extracts also induced aberrant colonies and gene conversion in yeast and were mutagenic to *S. typhimurium*, both in the presence and absence of an exogenous metabolic system[5].

Extracts of North American oral snuff (at pH 3.0) and extracts of North American chewing tobacco treated with sodium nitrite under acidic conditions were mutagenic to *S. typhimurium* in the presence and absence of a metabolic system. Organic solvent extracts of snuff induced a dose-related increase in the frequency of sister chromatid exchanges in human peripheral lymphocytes *in vitro* in the absence of a metabolic system[5].

References

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