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Volume 37
Tobacco Habits other than Smoking;
Betel-Quid and Areca-Nut Chewing;
and some Related Nitrosamines

Summary of Data Reported and Evaluation

Tobacco habits other than smoking
Betel-quid and areca-nut chewing

Some related nitrosamines

4-(Methylnitrosamino)-4-(3-pyridyl)butanal (NNA)
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
N'-Nitrosoanabasine (NAB)
N'-Nitrosoanatabine (NAT)
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Some *N*-nitrosamines derived from areca-nut alkaloids

3-Methylnitrosaminopropionaldehyde (MNPA)
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Last updated: 21 April 1998

TOBACCO HABITS OTHER THAN SMOKING

VOL.: 37 (1985) (p. 37)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Smokeless-tobacco habits are practised by many millions of people, principally in Africa, Asia, Europe and North America, utilizing several techniques, products and dosage levels. In some countries, average consumption by users is estimated to be about 5 kg per year.

Among the thousands of compounds present in tobacco, the tobacco-specific nitrosamines are the only identified carcinogens that occur in mg/kg concentrations. Low levels ($\mu\text{g}/\text{kg}$) of carcinogenic polynuclear aromatic hydrocarbons and metals and of the α -emitting ^{210}Po (0.1-1.0 pCi/g) have also been detected. Use of smokeless tobacco entails extensive exposure to relatively high levels of tobacco-specific nitrosamines.

5.2 Experimental data

Various chewing tobaccos and unburnt cigarette tobaccos and their extracts were tested 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.

In a two-stage, mouse-skin assay, applications of tobacco extract followed by promotion by 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.

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 virus 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.

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.

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 was associated with an apparent excess of liver tumours in various groups receiving cheek-pouch administrations, which may be indicative of carcinogenic activity, deficiencies in reporting do not allow an evaluation to be made.

Ethanol extracts of chewing tobacco (*Nicotiana tabacum*) induce mutations in *Salmonella typhimurium* and in Chinese hamster V79 cells. They also induce micronuclei in bone-marrow cells of Swiss mice.

Ethyl acetate extracts of a chewing tobacco induce sister chromatid exchanges in cultured human lymphocytes and in a human lymphoblastoid cell line. Ethyl acetate and ethanol extracts of this tobacco induce transformation in Syrian hamster embryo cells.

Aqueous extracts of nass and khaini induce chromosomal aberrations in Chinese hamster ovary cells.

Saliva collected during the chewing of an Indian tobacco induce chromosomal aberrations in Chinese hamster ovary cells.

An increased proportion of micronucleated cells was found in exfoliated oral-mucosa cells from users of khaini and nass.

Sister chromatid exchanges are induced in Chinese hamster ovary cells by anatabine, nicotine and nornicotine.

5.3 Human data

Oral leukoplakia, a precancerous lesion, has been associated with oral-snuff use in a number of studies. One study of shammah users and several studies of nass users showed the same association.

Epidemiological studies of cancer and the oral use of smokeless tobacco in western populations have often not distinguished between tobacco chewing and snuff usage. Studies that have are summarized first.

Chewing tobacco

Reports of series of oral-cancer patients indicate that a high proportion were tobacco chewers and that the cancer often developed at the site at which the quid was placed habitually. However, data on chewing tobacco often came only from medical records; coexistent smoking habits often were not mentioned.

In two of five case-control studies in which data on tobacco use were appropriately obtained, the proportion of tobacco chewers among patients with cancer of the oral cavity, pharynx or larynx was two to three times higher than in control subjects; however, confounding by tobacco smoking or alcohol consumption could not be excluded. A large study of oral, pharyngeal and oesophageal cancer reported no difference in chewing-tobacco use between cases and controls; although the relative risk of having cancer of the oral cavity or pharynx was increased in tobacco chewers, this study is not convincing because of major discrepancies in the tabulated data. Data on dose-response are lacking in all three studies. The other two case-control studies provide no clear evidence that tobacco chewing is associated with oral cancer: one study was very large but did not control for smoking, and one had serious methodological limitations.

Results from the four case-control studies of chewing-tobacco use and cancer of the oesophagus tend to show a slight increase in incidence. Nose and nasal-sinus cancers were found to be unrelated to tobacco chewing in one case-control study. No association between chewing tobacco and bladder cancer was observed in five case-control studies.

No cohort study of chewing tobacco alone and cancer has been reported.

Oral snuff

Reports of case series indicate that a high proportion of oral-cancer patients took snuff orally, and that the cancer frequently developed at the site of snuff application.

Four case-control studies, three from the south-eastern USA and one from Scandinavia, have implicated snuff use in the etiology of cancer of the oral cavity and, to a lesser extent, of the pharynx. In three of these studies, relative risks could not be computed; however, the differences in snuff usage between cases and controls were substantial, and confounding by cigarette smoking could be largely excluded. In the fourth study, in the south-eastern USA, the relative risk of oral and pharyngeal cancer for white women who used snuff but did not smoke was four times that for women with no tobacco habit; a strong dose-response relationship was observed; adjustment for other risk factors did not substantially reduce the relative risks.

In a cohort study of snuff users with non-malignant oral lesions, none developed cancer; however, the study was inadequately reported, had methodological limitations, and therefore could not be satisfactorily interpreted.

One case-control study has suggested that oral use of snuff may be associated with certain types of nasal-sinus cancer; in other case-control studies, no association was evident between snuff use and bladder cancer or between snuff use and cancer of the oesophagus.

Smokeless tobacco, unspecified

Studies that have not distinguished snuff from chewing tobacco are informative for four reasons when considered in conjunction with the habit-specific studies summarized above. First, reports of three case series confirm the high relative frequency of smokeless-tobacco use in oral-cancer patients. Four case-control studies have reported smokeless-tobacco use to be moderately to strongly associated with oral cancer, although smoking habits were not controlled for in three of the studies.

Second, a dose-response relationship was found in one large case-control study. The relative risks for oral cancer in men, after adjustment for other risk factors, ranged from four-fold for moderate smokeless-tobacco use to more than six-fold for heavy use.

Third, two cohort mortality studies, in which large numbers of persons with and without unspecified smokeless-tobacco habits were followed, provide evidence of a positive association with cancer. There was a two- to three-fold increased risk of death from oral, pharyngeal and oesophageal cancer in one study and from oesophageal cancer in the second.

Fourth, studies of unspecified smokeless-tobacco use provide some evidence of an increased risk of cancers at sites outside the upper digestive and respiratory tracts.

Whereas the data summarized above all come from studies in North America and western Europe, the data below refer to studies of oral use of tobacco and nasal use of snuff in South-East Asia and in Africa.

Mishri/gudakhu

Oral cancer in users of mishri and gudakhu has been studied only in prevalence surveys; no case was found.

Shammah

Oral cancers were seen in users of shammah.

Tobacco plus lime (khaini)

Two large case control-studies, from Pakistan and India, reported two-fold to 14-fold increases in the risk of oral-cancer occurrence in tobacco (presumably tobacco-lime) users relative to non-users, in smokers and nonsmokers considered separately. Indirect evidence, deducible from various other studies of chewing and oral cancer in which the predominant habit entailed use of tobacco and lime without areca nut, corroborates the existence of this increased cancer risk.

Tobacco plus lime plus other components

In two case series, the majority of oral-cancer patients used nass; in another, the cancers were found to develop at the site at which the quid was placed habitually. Two case-control studies showed five-fold to 20-fold increases in the risk of oral cancer in association with nass use in the USSR; however, adjustment was not made for smoking habits and other potential confounders.

Use of naswar, examined in one case-control study in Pakistan, was associated with a marked increase in oral-cancer risk; however, positive confounding by tobacco smoking and betel-quid chewing could not be eliminated.

Nasal snuff

Two case-control studies among Bantu subpopulations in Africa, among whom nasal and oral use of indigenous snuff (containing tobacco and other ingredients, including aloe) are common, showed a moderately elevated risk of nasal-sinus cancer in relation to this habit; however, the studies had severe methodological limitations.

In India, two studies (one cross-sectional, one prospective) of oral cancer found no association between oral cancer and snuff inhaling. A case-control study reported snuff inhaling to be more common among patients with cancers of the oesophagus, hypopharynx or oropharynx than among controls; however, adjustment was not made for other risk factors for these cancers.

No study was available that specifically addressed the possible carcinogenicity of nasal use of snuff formulated in North America or western Europe.

5.4 Evaluation

There is *sufficient evidence* that oral use of snuffs of the types commonly used in North America and western Europe is carcinogenic to humans. There is *limited evidence* that chewing tobacco of the types commonly used in these areas is carcinogenic.

Epidemiological studies that did not distinguish between chewing tobacco and snuff provide *sufficient evidence* for the carcinogenicity of oral use of smokeless-tobacco products, as reported in these studies.

In aggregate, there is *sufficient evidence* that oral use of smokeless tobacco of the above types is carcinogenic to humans.

There is *sufficient evidence* that oral use of tobacco mixed with lime (khaini) is carcinogenic to humans.

There is *inadequate evidence* that oral use of the other smokeless-tobacco preparations considered (nass, naswar, mishri, gudakhu and shammah) is carcinogenic to humans.

There is *inadequate evidence* that nasal use of snuff is carcinogenic to humans.

There is *inadequate evidence* to evaluate the carcinogenicity of chewing tobacco, snuff or nass to experimental animals.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

BETEL-QUID AND ARECA-NUT CHEWING

VOL.: 37 (1985) (p. 141)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The habit of chewing betel quid is widespread in South-East Asia and the South Pacific islands and in people of Indian origin elsewhere in the world. Betel quid usually contains areca nut, lime and catechu wrapped in a betel leaf. Tobacco is often added.

These habits result in exposure *inter alia* to areca-nut alkaloids, *N*-nitroso compounds derived from these alkaloids, polyphenols, and, when the habit includes tobacco, tobacco-specific nitrosamines.

5.2 Experimental data

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 a wax pellet containing powdered betel quid with tobacco into the cheek pouch; carcinomas occurred in the cheek pouch following implantation of the wax pellets.

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 the wax pellets.

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.

Areca nut or 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 tested by oral administration, and aqueous extracts were tested by subcutaneous injection. Studies involving dietary administration were inadequate, but local mesenchymal tumours occurred after subcutaneous injection. 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.

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

Arecoline (an alkaloid of areca nut) was tested in mice by oral intubation and by intraperitoneal and subcutaneous injection, and in hamsters by feeding or application to the cheek-pouch mucosa in combination with lime. The data are inadequate for evaluation.

Aqueous extracts of betel quid without tobacco induce mutations in *Salmonella typhimurium* but not in Chinese hamster V79 cells. They do not induce micronuclei in bone-marrow cells of Swiss mice.

Aqueous extracts of betel quid with tobacco induce mutations in *Salmonella typhimurium* and in Chinese hamster V79 cells. They also induce micronuclei in bone-marrow cells of Swiss mice.

Aqueous extracts of areca nut induce mutations in *Salmonella typhimurium* and in Chinese hamster V79 cells, gene conversion in *Saccharomyces cerevisiae*, as well as chromosomal aberrations in Chinese hamster ovary cells. They induce micronuclei in bone-marrow cells of Swiss mice. A tannin fraction of areca nut induces gene conversion in *Saccharomyces cerevisiae*.

Ethyl acetate and *n*-butanol extracts of areca nut induce chromosomal aberrations in Chinese hamster ovary cells. Ethyl acetate extracts do not induce mutations in Chinese hamster V79 cells, sister chromatid exchanges in human lymphoblastoid cells or transformation in Syrian hamster embryo cells.

Aqueous extracts of betel leaf are not mutagenic to *Salmonella typhimurium*. They induce chromosomal aberrations in human lymphocytes and in Chinese hamster ovary cells.

n-Butanol and ethyl acetate extracts of betel leaf induce chromosomal aberrations in Chinese hamster ovary cells. Ethyl acetate extracts of betel leaf do not induce mutations in Chinese hamster V79 cells, sister chromatid exchanges in human lymphoblastoid cells or transformation in Syrian hamster embryo cells.

Arecoline induces mutations in *Salmonella typhimurium* and Chinese hamster V79 cells, and chromosomal aberrations in Chinese hamster ovary cells. It also induces micronuclei, chromosomal aberrations and sister chromatid exchanges in bone-marrow cells of Swiss mice.

Arecaidine induces mutations in *Salmonella typhimurium* and Chinese hamster V79 cells. It induces sister chromatid exchanges but not micronuclei in bone-marrow cells of Swiss mice.

5.3 Human data

Chewers of betel quid in India and the Philippines had elevated frequencies of micronucleated cells in their buccal mucosa. The proportion of micronucleated exfoliated cells is related to the site within the oral cavity where the betel quid is kept habitually and to the number of betel quids chewed per day. The proportion can be reduced by administration for two to three months of vitamin A or β -carotene or a mixture of the two.

Oral leukoplakia shows a strong association with habits of betel-quid chewing in India. Some follow-up studies have shown malignant transformation of a proportion of leukoplakias. Oral submucous fibrosis and lichen planus, which are generally accepted to be precancerous conditions, appear to be related to the habit of chewing betel quid.

Many descriptive studies and reports of case series have identified an association between the habit of chewing betel quid with tobacco and oral cancer. The association has been consistent across many countries [Bangladesh, China (Taiwan), India, Malaysia, Pakistan, the Philippines, Singapore, Sri Lanka and Thailand]. Further, in case-control studies of oral cancer, whether smoking was controlled for (five studies) or not (five studies), the relative risks were high and statistically significant. However, the results are not directly comparable owing to the inclusion of different anatomical sites; most of these studies did not clearly describe the chewing habits of subjects, and some probably included a large proportion of users of tobacco-lime with or without areca nut. A significant association between the chewing of betel quid with tobacco and oesophageal cancer was reported from a case-control study in Sri Lanka.

Two case-control studies of oral cancer and one of oral and oropharyngeal cancer distinguished between different types of chewing and smoking habits. Controls were age-matched, and relative risks were statistically significant, in the range of 4 to 14, for chewing of betel quid with tobacco.

A positive dose-response relationship was found in two case-control studies.

In a population-based case-control study from Bombay, controls selected from the population were matched for age, sex and religion. Chewing habits were not precisely defined. After controlling for smoking habits, the relative risks were statistically significant for cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, but not for cancer of the nasopharynx. When habits were categorized into chewing with and without tobacco, but smoking habits were not taken into account, the relative risks remained statistically significant for all sites except the nasopharynx.

In a case-control study from Thailand, relative risks associated with chewing of betel quid with tobacco were statistically significant for oral and oropharyngeal cancers for men and women, and for laryngeal and hypopharyngeal cancer for men, after adjusting for several possible confounding variables, including smoking.

In cross-sectional surveys from India, although the number of oral cancer cases was generally small, samples were large (10 000 to 100 000). Oral cancer was consistently found much more frequently among chewers and/or smokers than among those who did not chew or smoke. Two of these cross-sectional samples were subsequently followed up for two and 10 years. New oral-cancer cases were seen only among those who chewed and/or smoked.

In a large-scale prospective study, two types of chewing habit were distinguished: of Mainpuri tobacco (which contains tobacco, lime and areca nut) and 'other' tobacco usages (which very often included lime and, frequently, areca nut). After controlling for smoking and alcohol drinking (although not for age), prevalence rates of oral cancer were highest for Mainpuri-tobacco usage and generally in second rank for the 'other'-tobacco usage category, in comparison to no chewing habit. The association with oral cancer for both types combined was examined in many different ways and was found to be positive.

Several descriptive studies from Papua New Guinea indicated an association between the habit of chewing betel quid without tobacco and oral cancer. The association is consistent for different areas and different communities (without controlling for smoking); however, analysis of time trends of incidence, chewing and smoking, by sex, suggests that smoking is an important risk determinant.

One case-control study from Pakistan suggests that chewing of betel without tobacco increases the risk of oral cancer when practised alone or in combination with smoking. Another case-control study from India and Sri Lanka provides different results, showing a clear effect of chewing betel with tobacco but not of chewing betel without tobacco, taking into account smoking. A case-control study from Bombay which categorized chewing habits (presumably betel) without tobacco, but did not control for smoking, showed statistically significantly increased relative risks for cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, in the range of 3 to 5.

Cross-sectional surveys in India show that the percentage of people who chew betel quid without tobacco is small. In one case-control study from India and Sri Lanka, after controlling for smoking, the relative risk for oropharyngeal cancer of the habit of chewing betel quid without tobacco was increased but not significantly so.

5.4 Evaluation

There is *sufficient evidence* that the habit of chewing betel quid containing tobacco is carcinogenic to humans.

There is *inadequate evidence* that the habit of chewing betel quid without tobacco is carcinogenic to humans.

The Working Group also concluded that, while there is *sufficient evidence* that the combined habits of smoking tobacco and chewing betel quid without tobacco cause oral and pharyngeal cancer, the evidence considered here does not allow an assessment of the possible contribution of betel quid without tobacco to this carcinogenic risk.

There is *limited evidence* that aqueous extracts of betel quid with and without tobacco are carcinogenic to

experimental animals.

There is *limited evidence* that areca nut with and without tobacco is carcinogenic to experimental animals.

The data are inadequate to allow an evaluation of the carcinogenicity of betel leaf or arecoline to experimental animals.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#); [Vol. 85 \(2004\)](#)

Last updated: 21 April 1998

4-(METHYLNITROSAMINO)-4-(3-PYRIDYL)BUTANAL (NNA)

VOL.: 37 (1985) (p. 205)

CAS No.: 64091-90-3

Chem. Abstr. Name: 3-Pyridinebutanal, γ -(methylnitrosoamino)-

5. Summary of Data Reported and Evaluation

5.1 Exposures

No analytical evidence was found that 4-(methylnitrosamino)-4-(3-pyridyl)butanal (NNA) occurs in tobacco or in the saliva of snuff users, although, under certain laboratory conditions, its formation from nicotine has been observed.

5.2 Experimental data

NNA was tested by intraperitoneal injection in female mice of one strain at one dose level only. Although the incidence of lung adenomas in treated mice exceeded those in controls, the experiment does not allow an evaluation of the carcinogenicity of NNA.

No data were available on mutagenic or related effects of NNA.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of NNA to humans was available to the Working Group.

5.4 Evaluation

The available data are *inadequate* to evaluate the carcinogenicity of 4-(methylnitrosamino)-4-(3-pyridyl)butanol to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 68: **Group 3**)

Synonym

- γ -(Methylnitrosamino)-3-pyridinebutyraldehyde

4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE (NNK)

VOL.: 37 (1985) (p. 209)

CAS No.: 64091-91-4

Chem. Abstr. Name: 1-Butanone, 4-(methylnitrosoamino)-1-(3-pyridinyl)-

5. Summary of Data Reported and Evaluation

5.1 Exposures

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) has been found in a variety of tobacco products (chewing tobacco, snuff, cigarettes and cigars), in mainstream and sidestream smoke from cigars and cigarettes, in saliva of chewers of betel quid with tobacco, and in saliva of oral-snuff users. Some of the NNK in saliva appears to be formed endogenously from salivary nitrite and nicotine. Thus, there is widespread exposure to NNK among users of tobacco products and those exposed to sidestream smoke.

5.2 Experimental data

NNK was tested for carcinogenicity in several studies by subcutaneous injection in rats and hamsters and by intraperitoneal injection in mice. In rats, it induced carcinomas of the nasal cavity, lung and liver, with a clear dose-response relationship. In hamsters, it induced benign and malignant tumours of the nasal cavity, trachea and lung, even after a single administration. In mice, NNK and its metabolites 4-(methylnitrosamino)-1-(3-pyridyl-*N*-oxide)-1-butanone and 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol induced benign and malignant tumours of the lung.

NNK and its metabolites can cross the placental barrier in mice. NNK can be metabolically activated by mouse foetal tissues.

Administration of NNK to rats results in abnormal DNA methylation in liver and lung. NNK is mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. It induces unscheduled DNA synthesis in primary cultures of rat hepatocytes.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of NNK to humans was available to the Working Group.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 68: **Group 2B**)

Synonym

- 4-(*N*-Methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone

Last updated: 21 April 1998

N'-NITROSOANABASINE (NAB)

VOL.: 37 (1985) (p. 225)

CAS Nos: 37620-20-5; 1133-64-8; 84237-39-8

Chem. Abstr. Name: Pyridine, 3-(1-nitroso-2-piperidinyl)-; pyridine, 3-(1-nitroso-2-piperidinyl)-(S)-; pyridine, 3-(1-nitroso-2-piperidinyl), (+,-)-

5. Summary of Data Reported and Evaluation

5.1 Exposures

N'-Nitrosoanabasine (NAB) has been found in tobacco products (chewing tobacco and snuff) and in mainstream smoke from cigarettes. Thus, there is widespread exposure to NAB among users of tobacco products.

5.2 Experimental data

NAB was tested for carcinogenicity by oral administration in two strains of rats and by subcutaneous injection in hamsters. In rats, it induced oesophageal carcinomas and/or papillomas. The study in hamsters was inadequate for evaluation.

No data were available on mutagenic or related effects of NAB.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of NAB to humans was available to the Working Group.

5.4 Evaluation

There is *limited evidence* for the carcinogenicity of N'-nitrosoanabasine to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 67: **Group 3**)

Synonym

- 4N-Nitrosoanabasine

N'-NITROSOANATABINE (NAT)

VOL.: 37 (1985) (p. 233)

CAS No.: 71267-22-6

Chem. Abstr. Name: 2,3'-Bipyridine, 1,2,3,6-tetrahydro-1-nitroso-

5. Summary of Data Reported and Evaluation

5.1 Exposures

N'-Nitrosoanatabine (NAT) has been found in a variety of tobacco products (snuff, chewing tobacco, cigarettes and cigars), in mainstream and sidestream smoke from cigars and cigarettes, in saliva of chewers of betel quid with tobacco and in saliva of users of chewing tobacco and oral snuff. Some of the NAT in saliva appears to be formed endogenously from nitrite in saliva and tobacco alkaloids. Thus, there is widespread exposure to NAT among users of tobacco products and those exposed to sidestream smoke.

5.2 Experimental data

NAT was tested for carcinogenicity by subcutaneous injection in rats of one strain at three dose levels. There was no increase in tumour incidence.

No data were available on mutagenic or related effects of NAT.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of NAT was available to the Working Group.

5.4 Evaluation

The available data are *inadequate* to evaluate the carcinogenicity of N'-nitrosoanatabine to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 67: **Group 3**)

Synonym

- NAtB

N'-NITROSONORNICOTINE (NNN)

VOL.: 37 (1985) (p. 241)

CAS Nos: 80508-23-2; 16543-55-8; 84237-38-7

Chem. Abstr. Name: Pyridine, 3-(1-nitroso-2-pyrrolidinyl)-; pyridine, 3-(1-nitroso-2-pyrrolidinyl)-,(S)-; pyridine,3-(1-nitroso-2-pyrrolidinyl)-, (+,-)-

5. Summary of Data Reported and Evaluation

5.1 Exposures

N'-Nitrosonornicotine (NNN) has been found in a variety of tobacco products (chewing tobacco, snuff, cigarettes and cigars), in mainstream and sidestream smoke from cigars and cigarettes, in saliva of chewers of betel quid with tobacco and in saliva of oral-snuff users. Some of the NNN in saliva appears to be formed endogenously from nitrite in saliva and tobacco alkaloids. Thus, there is widespread exposure to NNN among users of tobacco products and those exposed to sidestream smoke.

5.2 Experimental data

NNN was tested for carcinogenicity in rats, mice and hamsters by different routes of administration in multiple experiments. Following its oral administration, NNN produced carcinomas of the upper digestive tract, mainly the oesophagus, and of the nasal cavity in rats and nasal-cavity tumours in hamsters. Following its subcutaneous administration, NNN produced primarily tumours of the nasal cavity in rats and tumours of the trachea in hamsters. Intraperitoneal injection produced lung tumours in mice and tumours of the nasal cavity and trachea in hamsters. There was evidence of a dose-response relationship after subcutaneous administration of NNN to rats.

Several metabolites of NNN were tested in mice by intraperitoneal injection, producing lung tumours. NNN-1-N-oxide was also tested in rats and hamsters by oral administration; it produced nasal-cavity and oesophageal tumours in rats.

NNN is mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. It induces unscheduled DNA synthesis in primary cultures of rat hepatocytes.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of NNN was available to the Working Group.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of N'-nitrosonornicotine to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Vol. 17 \(1978\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\) \(p. 68: Group 2B\)](#)

Synonyms

- 1'-Demethyl-1'-nitrosonicotine
- 1'-Desmethyl-1'-nitrosonicotine
- 1'-Nitroso-1'-demethylnicotine
- *N*-Nitrosonornicotine
- 1'-Nitrosonornicotine
- Nitrosonornicotine
- 1-Nitroso-2-(3-pyridyl)pyrrolidine
- 3-(1-Nitroso-2-pyrrolidinyl)pyridine

Last updated: 21 April 1998

SOME N-NITROSAMINES DERIVED FROM ARECA-NUT ALKALOIDS

VOL.: 37 (1985) (p. 263)

CAS No.: 85502-23-4

Chem. Abstr. Name: 3-Methylnitrosaminopropionaldehyde (MNPA)

CAS No.: 60153-49-3

Chem. Abstr. Name: 3-Methylnitrosaminopropionitrile (MNPN)

CAS No.: 55557-01-2

Chem. Abstr. Name: *N*-Nitrosoguvacine (NGC)

CAS No.: 55557-02-3

Chem. Abstr. Name: *N*-Nitrosoguvacoline (NGL)

5. Summary of Data Reported and Evaluation

5.1 Exposures

N-Nitrosoguvacoline and *N*-nitrosoguvacine have been found in the saliva of betel-quid chewers. Thus, there is some evidence that chewers are exposed to these compounds.

5.2 Experimental data

N-Nitrosoguvacoline was tested in one experiment in rats by administration in drinking-water. Although no increase in the incidence of tumours was detected, the experiment was not adequate to allow an evaluation of its carcinogenicity.

3-Methylnitrosaminopropionitrile was tested in one 24-week experiment in rats by subcutaneous injection. Within this short period, it produced multiple papillomas and carcinomas of the oesophagus and tongue, and papillomas of the nasal cavity.

No data were available to evaluate the carcinogenicity of *N*-nitrosoguvacine or 3-methylnitrosaminopropionaldehyde to experimental animals.

The one available study was inadequate to evaluate the mutagenicity of *N*-nitrosoguvacine to *Salmonella typhimurium*.

N-Nitrosoguvacoline was mutagenic to *Salmonella typhimurium* in the presence of a metabolic system. It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*.

No data were available to assess the mutagenic or related effects of 3-methylnitrosaminopropionitrile or 3-methylnitrosaminopropionaldehyde.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of these compounds to humans was available to the Working Group.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of 3-methylnitrosaminopropionitrile to experimental animals. There is *inadequate evidence* to evaluate the carcinogenicity of *N*-nitrosoguvacoline to experimental animals. No data were available to assess the carcinogenicity of *N*-nitrosoguvacine or 3-methylnitrosaminopropionaldehyde to experimental animals.

No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 68: 3-methylnitrosaminopropionaldehyde (MNPA) - **Group 3**; 3-methylnitrosaminopropionitrile (MNPN) - **Group 2B**; *N*-nitrosoguvacine (NGC) - **Group 3**; *N*-nitrosoguvacoline (NGL) - **Group 3**); [Vol. 85 \(2004\)](#)

Synonyms

- NGC
- 3-Pyridinecarboxylic acid,1,2,5,6-tetrahydro-1-nitroso-
- NGL
- Methyl 1,2,5,6-tetrahydro-1-nitroso-nicotinate
- 1,2,5,6-Tetrahydro-1-nitroso-nicotinic acid

Last updated: 21 April 1998