

N'-NITROSONORNICOTINE AND 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE

N'-Nitrosoornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were considered by previous IARC Working Groups in 1984 and 2004 ([IARC, 1985](#), [2007](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1. Chemical and physical data

1.1.1 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone

(a) Synonyms and trade names

Chem. Abstr. Services Reg. No.: 64091-91-4

Chem. Abstr. Name: 1-Butanone,

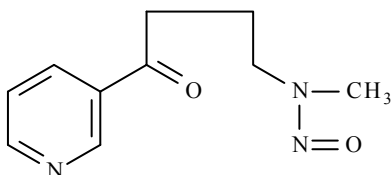
4-(methylnitrosoamino)-1-(3-pyridinyl)-

IUPAC Systematic Name:

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone

Synonym: 4-(N-Methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone

(b) Structural and molecular formulae and relative molecular mass



Rel. mol. mass: 207.2

(c) Chemical and physical properties of the pure substance

From [IARC \(2007\)](#)

Description: Light-yellow crystalline solid

Melting-point: 61–63 °C

Spectroscopy data: Infrared, nuclear magnetic resonance and mass spectra have been reported.

Solubility: Soluble in dichloromethane, dimethyl sulfoxide (DMSO), dimethylformamide, ethyl acetate and methanol

Stability: Sensitive to light

1.1.2 N'-Nitrosoornicotine

(a) Synonyms and trade names

Chem. Abstr. Services Reg. Nos: 80508-23-2; 16543-55-8; 84237-38-7

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

3-(1-nitroso-2-pyrrolidinyl)-, (S)-; pyridine,
3-(1-nitroso-2-pyrrolidinyl)-, (+,-)-

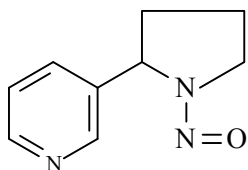
IUPAC Systematic Name:

1'-Demethyl-1'-nitrosonicotine

Synonyms: 1'-Demethyl-1'-nitrosonicotine;
1'-desmethyl-1'-nitrosonicotine; 1'-nitroso-
1'-demethylnicotine; nitrosornicotine;
N-nitrosornicotine; 1'-nitrosornico-
tine; 1-nitroso-2-(3-pyridyl)pyrrolidine;
3-(1-nitroso-2-pyrrolidinyl)pyridine

Note: the chemical abstracts services registry number 16543-55-8 and name refer to the (S) stereoisomer; the chemical abstracts services registry number 84237-38-7 and name refer to the racemic mixture that was synthesized and used in the biological studies reported in this *Monograph*.

(b) *Structural and molecular formulae and relative molecular mass*



$C_9H_{11}N_3O$

Rel. mol. mass: 177.2

(c) *Chemical and physical properties of the pure substance*

From [IARC \(2007\)](#)

Description: Light-yellow oil

Boiling-point: 154 °C at 0.2 mm

Melting-point: 47 °C; 42–45 °C

Spectroscopy data: Mass, ultraviolet, infrared and nuclear magnetic resonance spectra have been reported.

Solubility: Soluble in acetone and chloroform

Stability: Hygroscopic

1.2 Occurrence in tobacco products

Virtually all commercial tobacco products contain NNN and NNK, and they always occur together. They are mainly formed during the curing of tobacco. There is a great variation in levels of these compounds in mainstream smoke and sidestream smoke of cigarettes and in smokeless tobacco products. This is mainly due to differences in tobacco types used for the various products, in agricultural practices, curing methods, and in manufacturing processes. Factors that lead to relatively high levels of NNN and NNK in cured tobacco include the use of Burley tobacco, the use of midribs from air-cured tobacco or lamina from flue-cured tobacco, storage of tobacco leaves under humid conditions or in bales, processes that encourage bacterial growth thus leading to increased nitrite, and heating with propane during curing ([IARC, 2007](#)).

Since the first reports of NNN and NNK in tobacco ([Hoffmann et al., 1974](#); [Hecht et al., 1978](#)), many studies have quantified their levels in various tobacco products. Extensive compilations of data may be found in previous *IARC Monographs* ([IARC, 2004, 2007](#)). Levels of NNN ranged from 20 to 58000 ng per cigarette and NNK from 19 to 10745 ng per cigarette in tobacco from commercial cigarettes sold in different parts of the world; and from 4 to 2830 ng per cigarette (NNN) and 3 to 1749 ng per cigarette (NNK) in mainstream smoke of internationally available commercial cigarettes. Levels of NNN ranged from 19 to 3080000 ng per gram tobacco and NNK from 10 to 7870000 ng per gram tobacco in smokeless tobacco products worldwide.

Several recent studies have examined levels of NNN and NNK in cigarette tobacco and mainstream smoke, and in smokeless tobacco. [Hammond & O'Connor \(2008\)](#) reported data for 247 brands sold in Canada, and tested in 2004. Mean (\pm standard deviation (SD)). levels of NNN

were significantly higher in the tobacco of imported (1776.2 ± 817.2 ng/cigarette) than domestic Canadian brands (286.9 ± 118.3 ng/cigarette) while those of NNK were similar (437.2 ± 376.1 ng/cigarette imported and 448.5 ± 237.4 ng/cigarette domestic). Using the Canadian Intense smoking conditions, levels of NNN (353.3 ± 91.3 ng/cigarette) were significantly higher in mainstream smoke of imported cigarettes than if Canadian brands (53.1 ± 12.6 ng/cigarette), as were levels of NNK (212.1 ± 90.8 ng/cigarette imported; 110.3 ± 33.2 domestic Canadian). These differences are caused by the exclusive use of Virginia flue-cured tobacco in Canadian brands while imported brands – mainly from the USA – use a blend of tobacco types.

The impact of curing using indirect-fired barns instead of direct-fired methods on levels of NNK and NNN in cigarette tobacco and mainstream smoke was examined in a study of Canadian brands. Reductions of 65–78% in tobacco NNN levels and 60–85% in NNK levels were observed while the corresponding reductions in mainstream smoke levels (under ISO conditions) were 57–69% for NNN and 59–72% for NNK (Rickert *et al.*, 2008).

Levels of NNN and NNK were quantified in the smoke of research cigarettes made from different tobacco varieties, using the ISO method (Ding *et al.*, 2008). Levels of NNN and NNK were greatest in Burley tobacco smoke, with substantially lower amounts in the smoke of Oriental and Bright cigarettes. Nitrate content of the tobacco was significantly related to levels of smoke NNK (but not NNN), and was inversely proportional to PAH levels. These results are completely consistent with earlier studies (IARC, 1986; IARC, 2004).

Based on currently available data, NNN and NNK in smokeless tobacco products, expressed per g dry weight, can be divided arbitrarily into three levels:

Level I: less than 2 µg per g NNN plus NNK;

Level II: 2–10 µg per g NNN plus NNK;

Level III: greater than 10 µg per g NNN plus NNK.

The “new” products Taboka, Marlboro Snus, and Camel Snus were introduced in test markets in the USA and probably use pasteurization-like processing parameters designed to reduce levels of NNN and NNK, similar to those used by Swedish Match for products sold in Sweden. The NNN plus NNK levels in these products mostly fall into Level I, while “traditional” smokeless tobacco products manufactured in the USA fall into Level II (Stepanov *et al.*, 2008a).

Another study reported tobacco-specific nitrosamine levels in 40 top selling brands of USA moist snuff manufactured by four different companies, which collectively held over 97% of the US market in the year in which they were purchased (Richter *et al.*, 2008). The results for NNN plus NNK demonstrate that 12 brands were in Level II while 27 were in Level III. None were in Level I. In this study, amounts of NNN ranged from 2.2–42.5 µg/g wet weight while those of NNK ranged from 0.38–9.9 µg/g wet weight. The amounts in the brand with the highest levels of NNN and NNK are reminiscent of tobacco-specific nitrosamine levels in smokeless tobacco products of the 1970s.

While NNN and NNK have not been detected in oral gum nicotine-replacement therapy products, two recent studies demonstrate that NNN can be formed endogenously in trace amounts in some users of these products (Stepanov *et al.*, 2009a, b).

2 Cancer in Humans

Two molecular epidemiology studies investigated the relationship of NNK to lung cancer in smokers using nested case–control designs. In one, urinary levels of NNAL plus its glucuronides (total NNAL), metabolites of NNK, were

significantly associated with risk for lung cancer in a dose-dependent manner (Yuan *et al.*, 2009). Relative to the lowest tertile, risks associated with the second and third tertiles of total NNAL were 1.4 (95%CI: 0.9–2.4) and 2.1 (95%CI: 1.2–3.5), respectively (P for trend = 0.005) after adjustment for smoking history and total cotinine. In a second study, after adjustment for sex, age at randomization, family history of lung cancer, cotinine, *r*-1,*t*-2,3,*c*-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), and years of cigarette smoking, total NNAL was significantly associated with risk for lung cancer (odds ratio (OR), 1.6 per unit SD increase; 95%CI: 1.1–2.3) (Church *et al.*, 2009). A similar statistically significant result was obtained for adenocarcinoma risk, but not for nonadenocarcinoma. Although these results demonstrate an association of NNK metabolites with lung cancer in smokers, it is impossible to exclude the potential confounding effect of other carcinogens present in tobacco smoke.

3. Cancer in Experimental Animals

NNK and NNN have been tested for carcinogenicity by various routes of administration in adult mice, rats, and Syrian hamsters, and in limited experiments in mink and ferrets. NNK has also been tested for carcinogenicity in neonatal and infant mice and transplacentally in hamsters. NNK and NNN in combination have been tested in rats and minks. Of all the numerous studies on tumour development in animal models, a selection is presented in this *Monograph*. Table 3.1 includes the studies considered the most representative of the carcinogenicity of NNK and NNN.

3.1 Administration of NNN and NNK

3.1.1 Oral administration

(a) Mouse

Mice given NNK or NNN orally developed both lung and forestomach tumours and a few liver tumours in one study (Padma *et al.*, 1989).

(b) Rat

Oral administration of NNK in drinking-water caused tumours of the lung, nasal cavity, and liver (Rivenson *et al.*, 1988; Prokopczyk *et al.*, 1991). In two studies, tumours of the exocrine pancreas were observed following administration of NNK in drinking-water (Rivenson *et al.*, 1988; Hoffmann *et al.*, 1993). Rats given NNN orally developed tumours of the oesophagus and of the nasal cavity (Hoffmann *et al.*, 1975; Hecht *et al.*, 1983).

3.1.2 Subcutaneous administration

(a) Rat

NNK given to rats subcutaneously caused tumours of the lung, nasal cavity, and liver (Hoffmann *et al.*, 1984; Hecht *et al.*, 1986a; Belinsky *et al.*, 1990). Rats given NNN subcutaneously developed tumours of the oesophagus and of the nasal cavity (Castonguay *et al.*, 1984; Hoffmann *et al.*, 1984).

(b) Hamster

NNK given subcutaneously to Syrian hamsters caused lung tumours (Hoffmann *et al.*, 1981; Schüller *et al.*, 1990). NNN given subcutaneously to hamsters caused tumours of the trachea (Hilfrich *et al.*, 1977).

(c) Mink

In one study, NNK caused malignant tumours of the nasal cavity after subcutaneous injection (Koppang *et al.*, 1997). Subcutaneously injected NNN caused malignant tumours of the nasal cavity in mink (Koppang *et al.*, 1992, 1997).

Table 3.1 (continued)

Species, strain (sex) Reference	No/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
NNK				
Rat, F344 (M) Hoffmann et al. (1984)	27, 27, 15, 15 SC, 3 × /wk, 20 wk: total average doses 0, 0.312, 0.936, 2.81 mmole (1.0, 3.0, 9.0 mmole/kg) Lifespan (70–120 wk)	<i>Nasal cavity</i> benign: 0, 19, 6, 4 malignant: 0, 1, 7, 10 total: 0, 20 ^a , 13 ^a , 14 ^a <i>Lung</i> benign: 0, 7, 1, 7 malignant: 0, 16, 12, 7 total: 0, 23 ^a , 13 ^a , 14 ^a <i>Liver</i> benign: 3, 2, 1, 2 malignant: 0, 1, 3, 4 total: 3, 3, 4, 6 ^b <i>Oesophagus</i> benign: 0, 1, 1, 0	^a <i>P</i> < 0.01 ^a <i>P</i> < 0.01 ^b <i>P</i> < 0.05	NNK analysed for purity by HPLC Benign nasal cavity tumours included papillomas and polyps. Malignant nasal cavity tumours included anaplastic and squamous cell carcinomas, esthesioneuroepitheliomas and a sarcoma. Lung carcinomas included adenocarcinomas and squamous cell carcinomas
Rat, F344 (F) Hoffmann et al. (1984)				
	27, 27, 15, 15 SC, 3 × /wk, 20 wk: total average doses 0, 0.18, 0.54, 1.62 mmole (1.0, 3.0, 9.0 mmole/kg) Lifespan (60–120 wk)	<i>Nasal cavity</i> benign: 0, 10, 9, 3 malignant: 0, 0, 3, 11 total: 0, 10 ^a , 12 ^a , 14 ^a <i>Lung</i> benign: 1, 5, 4, 8 malignant: 0, 3, 3, 1 total: 1, 8 ^b , 7 ^b , 9 ^a <i>Liver</i> benign: 1, 3, 2, 2 malignant: 0, 1, 2, 3 total: 1, 4, 4, 5 ^b <i>Oesophagus</i> benign: 0, 0, 0, 0	^a <i>P</i> < 0.01 ^a <i>P</i> < 0.01 ^b <i>P</i> < 0.05 ^b <i>P</i> < 0.05	

Table 3.1 (continued)

Species, strain (sex) Reference	No/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rat, F344 (F) Hoffmann et al. (1984)	27, 27, 15, 15 SC, 3 × /wk, 20 wk: total average doses 0, 0.18, 0.54, 1.62 mmole (1.0, 3.0, 9.0 mmole/kg) Lifespan (50–120 wk)	<i>Nasal cavity</i> benign: 0, 12, 4, 0 malignant: 0, 0, 5, 15 total: 0, 12 ^a , 9 ^a , 15 ^a <i>Lung</i> benign: 1, 2, 1, 1 malignant: 0, 1, 0, 0 total: 1, 3, 1, 1 <i>Liver</i> benign: 1, 2, 0, 0 malignant: 0, 0, 0, 0 total: 1, 2, 0, 0 <i>Oesophagus</i> benign: 0, 1, 2, 3 ^b	^a P < 0.01	
NNN + NNK				
Rat, F344 (M) Hecht et al. (1986b)	21, 30 0, 68µg NNN + 14µg NNK in 0.5 mL aqueous solution by oral swabbing, twice/d 131 wk	<i>Lung</i> adenomas: 1/21 (5%), 1/30 (3%) carcinomas: 0/21, 4/30 (13%) <i>Oral cavity</i> papillomas: 0/21, 8/30 (27%) (9 tumours in 8 animals)	NS	Purity NR
			P < 0.05	

d, day or days; F, female; M, male; mo, month or months; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosornicotine; NR, not reported; NS, not significant; SC, subcutaneous; wk, week or weeks

3.1.3 Intraperitoneal administration

(a) Mouse

NNK or NNN given to mice intraperitoneally increased the incidence of lung adenomas and carcinomas after less than one year ([Hecht et al., 1978, 1988, 1989](#); [Rivenson et al., 1989](#); [Belinsky et al., 1992](#); [Amin et al., 1996](#)). Intraperitoneal NNK increased both lung and liver tumours in one study ([Castonguay et al., 1983](#)).

(b) Hamster

NNN given intraperitoneally to hamsters caused tumours of the trachea and nasal cavity ([McCoy et al., 1981](#)).

3.1.4 Skin application

When applied topically to SENCAR mice, NNK was weakly active as a skin tumour initiator, but lung tumours were observed, while NNN was inactive ([LaVoie et al., 1987](#)). A few skin tumours developed in mice given NNN by skin application for 104 weeks ([Deutsch-Wenzel et al., 1985](#)).

3.1.5 Perinatal administration

NNK increased both lung and liver tumours when given intraperitoneally to neonatal and infant mice ([Anderson et al., 1991](#)) but was not a transplacental carcinogen when given intraperitoneally to pregnant females ([Beebe et al., 1993](#)). NNK injected subcutaneously to pregnant Syrian hamsters caused tumours of the nasal cavity, larynx, and trachea in offspring in one experiment ([Correa et al., 1990](#)).

3.1.6 Administration with known carcinogens

In one study, NNK and NNN in combination caused oral cavity papillomas and lung carcinomas when administered to rats by swabbing the lips and oral cavity with an aqueous solution of the nitrosamines ([Hecht et al., 1986b](#)); oral cavity tumours were rarely observed in rats

given NNK alone. In one study, NNK and NNN in combination caused nasal cavity tumours in mink of both sexes ([Koppang et al., 1997](#)). Offspring of Syrian hamsters given ethanol in drinking-water during pregnancy and NNK by intratracheal instillation on day 15 of pregnancy developed tumours of the nasal cavity, exocrine pancreas, and adrenal medulla ([Schüller et al., 1994, 2002](#)). In a single study of limited duration, NNK given by injection concurrently with cigarette smoke by inhalation caused lung tumours in 6 of 12 ferrets within six months ([Kim et al., 2006](#)).

3.2 NNK and NNN metabolites

NNN-1-*N*-oxide given in drinking-water caused tumours of the oesophagus and nasal cavity in rats but not in hamsters ([Hecht et al., 1983](#)). In a short-term study, NNK-1-*N*-oxide and 4-(methylnitrosamino)-1-(3-pyridyl) butan-1-ol (NNAL) given intraperitoneally caused lung tumours in mice and was as effective as NNK. Similarly, in a lifetime study in rats, NNAL was equally as effective as NNK in inducing lung tumours ([Rivenson et al., 1988](#)). 4'-Hydroxy-NNN given intraperitoneally slightly increased the incidence and multiplicity of lung tumours, while 3'-hydroxy-NNN and NNK-1-*N*-oxide had no significant carcinogenic effect ([Castonguay et al., 1983](#)).

3.3 Synthesis

NNK by various routes of administration consistently caused tumours of the lung in mice, hamsters and rats, and tumours of the nasal cavity in rats and mink. NNN given by various routes and particularly in drinking-water consistently caused tumours of the oesophagus in rats, and in many studies caused tumours of the nasal cavity in multiple species. NNN and NNK administered in combination caused tumours of the oral cavity in rats and nasal cavity in mink. [Table 3.2](#)

Table 3.2 Summary of reports of tumours induced in experimental animals by NNK and NNN

Compound/ species	Lung	Nasal cavity	Oral cavity	Trachea	Oesophagus	Fore- stomach	Pancreas (exocrine)	Liver	Adrenal gland	Skin
NNK										
Mouse	x					x		x		x ^a
infants	x							x		
Rat	x	x					x	x		
Hamster progeny	x						x ^c		x	
Mink		x								
Ferret	x ^b									
NNN										
Mouse	x									
Rat		x			x					x
Hamster		x		x						
Mink		x								
NNK + NNN										
Rat	x									
Mink										x

^a Initiator only (SENCAR mouse skin)

^b Co-exposure to NNK and cigarette smoke

^c Transplacental co-exposure to NNK and ethanol

NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosornicotine

From [IARC \(2007\)](#)

summarizes the reports of tumours induced in experimental animals after exposure to NNK and/or NNN.

4. Other Relevant Data

See Section 4 of the *Monograph on Tobacco Smoking* in this volume.

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *N'*-nitrosornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of *N'*-nitrosornicotine.

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N'*-nitrosornicotine are *carcinogenic to humans (Group 1)*.

In making the overall evaluation of NNK and NNN, the Working Group took into consideration the following mechanistic evidence; detailed in Section 4 of the *Monograph on Tobacco Smoking* in this volume.

NNK and NNN are the most abundant strong carcinogens in smokeless tobacco; their uptake and metabolic activation has been clearly documented in smokeless tobacco users. Combined application of NNN and NNK to the oral mucosa of rats induced oral tumours, consistent with their induction by smokeless tobacco. One of the mechanisms of carcinogenicity is cytochrome-P450-mediated α -hydroxylation, which leads to the formation of DNA and haemoglobin adducts that have been detected in users of tobacco.

References

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