WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

RELEVANCE TO HUMAN CANCER OF *N*-NITROSO COMPOUNDS, TOBACCO AND MYCOTOXINS

Editors

I.K. O'Neill, J. Chen and H. Bartsch

IARC Scientific Publications No. 105

International Agency for Research on Cancer
Lyon, 1991

Relevance to Human Cancer of *N*-Nitroso Compounds,
Tobacco Smoke and Mycotoxins.
Ed. I.K. O'Neill, J. Chen and H. Bartsch
Lyon, International Agency for Research on Cancer

OCCURRENCE OF AND EXPOSURE TO *N*-NITROSO COMPOUNDS IN TOBACCO

A.R. Tricker & R. Preussmann

Institute of Toxicology and Chemotherapy, German Cancer Research Center, Heidelberg, Federal Republic of Germany

The concentrations of 21 *N*-nitroso compounds in smokeless tobaccos are presented. Tobacco-specific nitrosamines accounted for 70–90% of the total identified *N*-nitroso compounds. Daily exposure of smokeless tobacco users to preformed *N*-nitroso compounds may exceed 200 μg/day in certain populations.

We have identified 21 volatile, nonvolatile and tobacco-specific *N*-nitrosamines (TSNA) in smokeless tobacco products available commercially in 1987–88 (Tricker & Preussmann, 1988, 1989). Selected representative data are presented in Table 1. Currently, *N*-nitrosodimethylamine, *N*-nitrosoethylmethylamine, *N*-nitrosopiperidine and *N*-nitrosopyrrolidine are the most commonly found volatile nitrosamines; traces of *N*-nitrosodipropylamine and *N*-nitrosodibutylamine are present in heavily cured and/or fermented tobacco products. Trace levels of *N*-nitrosomorpholine are still found in some UK and Swedish oral tobacco products packed in waxed containers. The most commonly found nonvolatile *N*-nitrosamino acids and their derivatives are *N*-nitrosoproline, *N*-nitrosopipecolic acid, *N*-nitrosohydroxyproline, *N*-nitrososarcosine, 3-(*N*-nitroso-*N*-methylamino)propionic acid and 4-(*N*-nitroso-*N*-methylamino)butyric acid. Some heavily cured/fermented tobaccos, in particular *zarda* and some American moist snuffs (data not presented), were found to contain *N*-nitrosoazetidine 4-carboxylic acid (<200 μg/kg) and *N*-nitrosothiazolidine 4-carboxylic acid (<280 μg/kg). The presence of other nonvolatile *N*-nitrosamines, amenable to gas chromatography–thermal energy analysis only after methylation or silylation, were also found. TSNA are by far the most abundant *N*-nitroso compounds present in tobacco and usually account for 70–90% of the total. 4-(*N*-Nitrosomethylamino)-4-(3-pyridyl)-1-butanol (<8100 μg/kg) has been detected in about 60% of all tobacco samples analysed (n = >120), including various forms of smoking tobacco, indicating far greater exposure to this compound than previously reported (Hecht & Hoffmann, 1988).

In order to make a rough estimate of potential exposure to carcinogenic *N*-nitroso compounds, and in particular to 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanol and *N'*-nitrosonornicotine during use of smokeless tobacco, mean daily exposure to the identified *N*-nitroso compounds was estimated by multiplying the concentrations of individual compounds by the average amount of tobacco consumed by the tobacco-using population (Table 2). This method of calculating exposure is based on the assumption that

Table 1. *N*-Nitroso compounds in smokeless tobaccos (μg/kg)

N-Nitrosamine[a]	UK oral tobacco (5 samples)		Swedish moist snuff (5 samples)		Indian *zarda* (11 samples)		European nasal snuff (10 samples)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
NDMA	37	6.0–82	1.5	1.0–2.5	11	2.0–31	20	2.0–82
NEMA	1.0	ND–2.	ND		1.0	ND–2.0	1.6	ND–8.5
NPIP	20	2.5–40	ND		0.3	ND–2.0	3.8	ND–17
NPYR	120	64–190	5.0	4.5–6.0	100	6.0–69	44	1.5–13
NMOR	0.5	ND–1.	1.0	ND–1.0	ND		ND	
NDELA	105	ND–220	19	8–31	9.5	ND–54	12	ND–42
NSAR	120	29–240	19	8–31	49	ND–350	21	ND–85
NPMA	3980	1360–8300	1340	1040–1820	2050	22–18 000	1620	490–4260
NBMA	640	62–1470	70	53–94	170	ND–2040	160	76–410
NAzCA	ND		ND		18	ND–140	ND	
NPRO	2260	330–4950	1100	630–1820	2850	280–18 000	3950	770–873
NPIC	540	83–1760	36	ND–130	260	ND–2040	80	ND–310
NTCA	6	ND–28	21	ND–69	48	ND–280	7.4	ND–46
NHPRO	330	92–610	140	ND–230	69	ND–190	98	46–27
iso–NNAl	65	ND–150	27	ND–80	1420	120–8100	360	ND–1590
NAB/NAT	3520	1980–4800	2640	1650–3250	16 030	780–99 100	3120	1030–7830
NNN	3960	1090–7630	3360	2100–4800	13 420	400–79 000	7840	2390–18 750
NNK	2800	400–8250	790	400–1040	4030	220–24 100	2430	580–6430
Total[b]	19 770	6130–36 450	9570	6220–12 500	40 530	1670–241 000	19 780	7190–42 530

[a] NDMA, *N*-nitrosodimethylamine; NEMA, *N*-nitrosoethylmethylamine; NPIP, *N*-nitrosopiperidine; NPYR, *N*-nitrosopyrrolidine; NMOR, *N*-nitrosomorpholine; NDELA, *N*-nitrosodiethanolamine; NSAR, *N*-nitrososarcosine; NPMA, *N*-nitrosopropylamine; NBMA, *N*-nitrosobutylmethylamine; NAzCA, *N*-nitrosoazetidine 4-carboxylic acid; NPRO, *N*-nitrosoproline; NPIC, *N*-nitrosopipecolic acid; NTCA, *N*-nitrosothiazolidine 4-carboxylic acid; NHPRO, *N*-nitrosohydroxyproline; *iso*-NNAl, 4-(*N*-nitrosomethylamino)-4-(3-pyridyl)-1-butanol; NAB/NAT, *N′*-nitrosoanabasine/*N′*-nitrosoanatabine; NNN, *N′*-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

[b] Total identified *N*-nitroso compounds

ND, not detected; limits of detection: volatile nitrosamines, 0.1 μg/kg; nonvolatile nitrosamines, 1.0 μg/kg; tobacco-specific nitrosamines, 1.0 μg/kg tobacco

100% of TSNA are extracted from saliva. Österdahl and Slorach (1988) have shown that this is not true in Swedish snuff dippers, whose saliva contains higher levels of TSNA than can be accounted for by levels of preformed nitrosamines in tobacco. Thus, endogenous formation of TSNA in saliva (Österdahl & Slorach, 1988) and under simulated gastric conditions (Tricker *et al.*, 1988) probably results in higher exposure to TSNA than indicated in Table 2.

Table 2. Exposure to *N*-nitroso compounds from use of oral tobacco

Tobacco-using population	Use (g/day)	Daily nitrosamine exposure (μg/day)	
		Total	NNN/NNK[a]
Dry snuff (Europe)	2.0	39.6	20.5
Oral tobacco (UK)	4.5	89.0	30.4
Moist snuff (Sweden)	15.9	152.1	66.0
Zarda (India)	5.0	203.0	87.5

[a]NNN, *N'*-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

We conclude that high levels of *N*-nitroso compounds present in smokeless tobaccos expose the consumer to a considerable exogenic burden of potentially carcinogenic compounds, and in particular TSNA.

References

Hecht, S.S. & Hoffmann, D. (1988) Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis*, **9**, 875-884

Österdahl, B.-G. & Slorach, S. (1988) Tobacco-specific *N*-nitrosamines in saliva of habitual male snuff dippers. *Food Addit. Contam.*, **5**, 581-586

Tricker, A.R. & Preussmann, R. (1988) The occurrence of *N*-nitroso compounds in zarda tobacco. *Cancer Lett.*, **42**, 113-118

Tricker, A.R. & Preussmann, R. (1989) Preformed nitrosamines in smokeless tobacco. In: Maskins, A.P., ed., *Tobacco and Cancer, Perspectives in Prevention Research*, Amsterdam, Elsevier, pp. 35-47

Tricker, A.R., Haubner, R., Spiegelhalder, B. & Preussmann, R. (1988) The occurrence of tobacco-specific nitrosamines in oral tobacco products and their potential formation under simulated gastric conditions. *Food Chem. Toxicol.*, **26**, 861-865