

Tobacco-Specific Nitrosamines: How Nicotine Becomes A Carcinogen

Tobacco-specific nitrosamines (TSNA) are found only in tobacco products, and are highly carcinogenic. They are found in chewing tobacco, in smoking tobacco, and in snuff, and they are known to induce tumors of the lung, oral cavity, esophagus, pancreas, and liver.^{1,2}

High levels of TSNA have been found in the cervical mucus of female smokers, indicating that exposure to TSNA may also be linked to cancer of the cervix;³ TSNA may also cause reproductive damage. There is no safe level of exposure to the most potent of the TSNA carcinogens (Table 1).

In 1989, the U.S. Surgeon General released a list of carcinogens found in tobacco, and included among these nine nitrosamines.² Because TSNA are not known to occur in any other product, their study helps to characterize the cancerous nature of tobacco.⁴ TSNA binds to haemoglobin and DNA;⁵ the TSNA adduct in blood (quantified by gas chromatography) is used as a biochemical marker to determine exposure to tobacco smoke.²

Nitrosamines contain the organic functional group N-N=O, and are formed by the nitrosation (addition of an N=O group) of secondary and tertiary amines. In tobacco, these amines are nicotine, nor nicotine, anabasine, and anatabine, and their nitrosation is summarized in Figure 1. Another chemical term for these tobacco amines is an "alkaloid", an organic base that contains nitrogen and is located in a seed plant.⁴

TSNA are created during fermentation, curing and burning of the tobacco leaf. Research has been conducted to ascertain whether TSNA may be created, after exposure to tobacco alkaloids, within the human body.⁶ If this proves to be the case, then tobacco products labeled "nitrosamine-free" could continue to expose the user to harmful doses of TSNA.

Table 1 on the following page shows the carcinogenic ratings for each of the tobacco-specific nitrosamines (incomplete). Figure 1 illustrates the chemical formation of TSNA from tobacco alkaloids including nicotine.

¹ D. Hoffmann, A. Rivenson, and S. S. Hecht, "The biological significance of tobacco-specific N-nitrosamines: smoking and adenocarcinoma of the lung", *Critical Reviews in Toxicology*, 26(2): 199-211 (1996).

² U.S. Department of Health and Human Services, "Reducing the Health Consequences of Smoking: 25 Years of Progress. A report of the Surgeon General 1989".

³ B. Prokopczyk, J.E. Cox, D. Hoffmann, S. E Waggoner, "Identification of Tobacco-specific carcinogen in the cervical mucus of smokers and non-smokers". *Journal of the National Cancer Institute*, Vol. 89, No. 12, June 18, 1997

⁴ S. S. Hecht and D. Hoffmann, "Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke". *Commentary, American Health Foundation*, pages 875-884.

⁵ B. Prokopczyk, D. Hoffmann, J. E. Cox, M. V. Djordjevic, K. D. Brunnemann, "Supercritical Fluid Extraction in the Determination of Tobacco-Specific N-Nitrosamines in Smokeless Tobacco". *Chemical Research in Toxicology* 1992, 5, page 336.

⁶ N. L. Benowitz, [Nicotine Safety and Toxicity](#), Oxford University Press, New York, 1998, pages 67 – 73.

Table 1: Tobacco specific nitrosamines and their carcinogenic rating.

Name	Acronym	Carcinogenicity
N-nitrosornnicotine	NNN	Group 2B IARC
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	Group 2B IARC
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	NNAL	Group 2B IARC
N'-nitrosoanatabine	NAT	Group 3 IARC
N'-nitrosoanabasine	NAB	Group 3 IARC
4-(methylnitrosamino)-4-(3-pyridyl)butanal	NNA	Group 3 IARC
4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol	iso-NNAL	
4-(methylnitrosamino)-4-(3-pyridyl)butyric acid	iso-NNAC	

Figure 1: Nitrosation of tobacco alkaloids to form tobacco specific nitrosamines (TSNA)

