International Research Journal of Interdisciplinary & Multidisciplinary Studies (IRJIMS)
A Peer-Reviewed Monthly Research Journal
ISSN: 2394-7969 (Online), ISSN: 2394-7950 (Print)
Volume-II, Issue-III, April 2016, Page No. 7-16
Published by: Scholar Publications, Karimganj, Assam, India, 788711
Website: http://www.irjims.com

Smokeless Tobacco: Chemical Composition and Carcinogenicity

Dr. Neeraj Sangar
Head, Dept. of Chemistry, G.G.D.S.D. College, Hariana, Hoshiarpur, Punjab, India

Abstract

Smokeless tobacco products are easily available and commonly used worldwide. The consumption of SLT is increasing day by day. The use of SLT is not without risk and is associated with many types of serious diseases; cancer being the most dangerous one. Several carcinogens have been identified in smokeless tobacco. This form of tobacco use has become one of the most startling causes of premature death and disease in the present times. The present paper focuses on the chemicalcomposition of SLT and how these chemicals become the cause of cancer to SLT users. The paper also spotlights the various other health hazards posed to an individual because of the use of SLT.

Key Words: Tobacco, Smokeless Tobacco, Chemical Composition, Health Hazards, Carcinogens.

1. Introduction: Tobacco has proved itself to be a potential health threat and a major cause of death and disease in the world in the modern times. Approximately 5 million people are believed to die every year of the tobacco related causes. It has been estimated that by 2030, tobacco will prove itself to be the single biggest cause of death worldwide, with an estimated 8 million people dying worldwide of tobacco related causes. If concrete measures are not immediately taken, tobacco alone could kill 1 billion or even more people in the 21st century [1].

There are various methods of tobacco consumption worldwide. But broadly tobacco use can be divided into two categories: Smoking and Smokeless. Smokeless tobacco refers to the use of tobacco in a number of ways where the products made from tobacco are used by means other than smoking. They can be used orally or nasally. Oral smokeless tobacco products are used through placing them in the mouth, cheek or lip and sucked (dipped) or chewed. There are some methods where tobacco pastes or powders are used in a similar manner and applied to the gums or teeth. Other methods include when fine tobacco mixtures are inhaled and absorbed in the nostrils. Table-1 below illustrates the different types of smokeless tobacco (SLT) products and their mode of use [2]:

Table-1: Classification of smokeless tobacco products by mode of use

Oral use			**Nasal use**
Sucking	**Chewing**	**Other oral uses**	**Sniffing**
Dry snuff	Betel quid	Creamy stuff	Dry snuff
Gutka	Gutka	Gudhaku	Liquid snuff
Khaini	Khaini	Gul	
Loose leaf	Iq'mik	Mishri	
Maras	Khiwam	Red tooth powder	

Mishri	Loose leaf	Tuibur	
Moist snuff	Mawa		
Naswar	Plug		
Plug	Tobacco chewing		
Shammah	Gum		
Snus	Twist or roll		
Tobacco tablets	Zarda		
Toombak			

Source: IARC Monographs, Vol.89

The prevalence of smokeless tobacco is increasing worldwide, especially, among the most vulnerable of citizens of every country i.e. children. Internationally, the use of SLT is not as dominant as cigarette smoking, although some countries experience relatively high SLT use rates. SLT use in Europe is practically non-existent, Sweden has one of the highest rates of use in the world. The use of SLT is quite high in India, the United States and Canada [3].

2. Methodology: The present paper intends to evaluate the chemical composition and various ill effects of smokeless tobacco. For this purpose secondary datas from various government and non-government organisation reports, books, journals, websites, encyclopaedias, newspapers and periodicals were taken to endorse the points.

3. Chemical Composition Of Smokeless Tobacco (SLT): Smokeless tobacco (SLT) is assumed to contain approximately 4200 chemicals [4]. The chemical composition is subject to the type of tobacco used in a particular product. The chemical composition of tobacco varies with the growth of the plant and also during curing, fermentation, processing and storage of processed products [5-7].

The various chemicals in SLT include alkaloids such as nicotine, nornicotine, cotinine, anabasine, anatabine, aliphatic hydrocarbons, and hundreds of isoprenoids that produce typical aroma of tobacco leaves. A number of phytosterols such as cholesterol, campesterols and alcohols, phenolics, chlorogenic acid, rutin, carboxylic acids, turpenes, polyphenols, aromatic hydrocarbons, aldehydes, ketones, amines, nitrites, N- and O-heterocyclic hydrocarbons, pesticides, and alkali nitrates have also been detected. It has also been concluded that SLT contains many toxic metals which include mercury, lead, chromium, and other trace elements [8].

3.1 Carcinogenic Compounds in Smokeless Tobacco: Researches have revealed that 28 carcinogens have been recognised in smokeless tobacco [9]. The most prominent group of carcinogens are the non-volatile alkaloid-derived tobacco-specific *N*-nitrosamines (TSNAs) and *N*-nitrosoamino acids. Other carcinogens which have been reported in SLT include volatile *N*-nitrosamines, certain volatile aldehydes, traces of some polynuclear aromatic hydrocarbons such as benzo[*a*]pyrene, certain lactones, urethane, metals, polonium- 210 and uranium-235 and -238 [9].The various chemical agents identified in smokeless tobacco products are given in following table 2:

Table-2: Chemical agents identified in SLT products

Chemical agent	Type of tobacco where it has been detected	Concentration (ng/g)
Benzo[*a*]pyrene	NT, MS, DS, MI	> 0.1–90
α-Angelica lactone	NT	Present
β-Angelica lactone	NT	Present
Coumarin	NT	600
Ethyl carbamate (urethane)	CT	310–375
Volatile aldehydes		
Formaldehyde	NT,MS,DS	1600–7400
Acetaldehyde	NT,MS,DS	1400–27 400
Crotonaldehyde	MS,DS	200–2400
Volatile N-nitrosamines		
N-Nitrosodimethylamine (NDMA)	CT,MS	ND–270
N-Nitrosopyrrolidine (NPYR)	CT,MS	ND–860
N-Nitrosopiperidine (NPIP)	CT,MS	ND–110
N-Nitrosomorpholine (NMOR)	CT,MS	ND–690
N-Nitrosodiethanolamine (NDELA	CT,MS	40–6800
N-Nitrosamino acids		
N-Nitrososarcosine (NSAR)	MS	ND–6300
3-(N-methylnitrosamino) propionic acid (MNPA)	CT, MS	200–70 000
4-(N-methylnitrosamino) butyric acid (MNBA)	CT, MS	ND–17 500
Nitrosoazetidine-4-carboxylic acid (NAzCA)	CT, MS	4–140
Tobacco-specific N-nitrosamines (TSNAs)		
N′-Nitrosonornicotine (NNN)	CT,MS	400–3 085 000
4-(Methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK)	CT,MS	ND–7 870 000
4-(Methylnitrosamino)-1-(3-pyridyl)-1- butanol (NNAL)	MS	0.07–22 900
N′-Nitrosoanabasine (NAB)	ST,MS	Present–2 370 000
Inorganic compounds		
Arsenic	NT	500–900
Nickel compounds	ST,MS	180–2700
Radioelements		***(pCi/g)***
Polonium-210	NT, MS, DS	0.16–1.22

Uranium-235	MS	2.4
Uranium-238	MS	1.91

CT, chewing tobacco; DS, dry snuff; MI, *mishri*; MS, moist snuff; ND, not detected; NT, natural tobacco; ST, smoking tobacco.

Source: IARC Monograph, Vol. 89.

3.1.1 Tobacco-specific N-nitrosamines (TSNAs): Tobacco-specific nitrosamines (TSNAs) pose the most dangerous health hazard and prove to be the most harmful carcinogens which are present in smokeless tobacco. The quantity of TSNAs in some SLT products has been found at levels 100 times higher than what is allowed in foods, such as bacon and beer. These include the carcinogens N′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK).

TSNAs are present in fresh green tobacco leaves in *Nicotiana tabacum* species, at levels of up to 0.39 μg/g NNN and 0.42 μg/g NNK in the top leaves of tobacco (flue-cured type) grown in the USA [10], up to 0.035 μg/g NNN and 0.0115 μg/g NNK in *Nicotiana tabacum* grown in India and up to 46.1 μg/g NNN and 2.34 μg/g NNK in *Nicotiana rustica* species grown in India [11].

An international comparison of the concentrations of NNN and NNK in smokeless tobacco products compiled by IARC has been shown in the following Table-3[2]. The ranges differ widely and are productand country specific. Some moist snuff brands in the USA, contain the highest concentrations of NNN and NNK which measured 147and 17.8 μg/g tobacco, respectively. The home-made *toombak* from Sudan reportedly measure values as high as 3085 and 7870 μg/g dry weight tobacco, respectively [12,13].

Table-3:- International comparison of the concentration ranges of NNN and NNK in smokeless tobacco products (μg/g tobacco)

Country	**Product**	**Concentration (μg/g tobacco)**		
		Reported as	**NNN**	**NNK**
Belgium	CT	Dry	7.38	0.13
Canada	MS	Dry	50.4-79.1	3.2-5.8
	CT	Dry	2.09	0.24
Denmark	CT	Wet	0.08-1.6	0.02-1.9
Germany	CT	Dry	1.4-2.3	0.03-0.30
	DS	Dry	2.4-18.8	0.58-6.4
India	MS	Wet	0.56	0.24
	CT	Dry	0.47-0.85	0.13-0.60
		Wet	15.3-24.4	2.7-6.5
	DS	Wet	137-1356	110-245
	Khaini	Dry	25.8-40.0	0.11-5.3
		Wet	39.4-76.9	2.3-28.4
	Gutka	Wet	0.09-1.1	0.04-0.43
	Mishri	Dry	0.3-7.0	0.29-1.1
	Creamy snuff	Wet	2.5-48.7	1.3-12.5
	Zarda	Dry	0.4-79.0	0.22-24.1
Norway	MS	Wet	21.0	3.3
Sudan	Toombak	Dry	141-3085	188-7870
Sweden	MS	Dry	1.12-154	0.19-2.95

		Wet	0.49-4.4	0.19-1.3
	CT	Wet	0.7-1.7	0.01-0.46
UK	MS	Dry	1.1-52.0	0.4-13.0
	CT	Dry	0.9	0.3
	DS	Wet	1.8	0.26
USA	MS	Dry	ND-147	ND-17.8
	CT	Dry	0.67-6.5	ND-1.05
	DS	Dry	9.4-116.1	0.88-84.4

CT, Chewing tobacco; MS, Moist snuff; DS, Dry snuff; ND, Not detected

3.1.2 N-Nitrosamino Acids: Since 1985, numerous studies have reported the presence of *N*-nitrosamino acids in smokeless tobacco products [2]. To date, 11 *N*-nitrosamino acids have been identified in smokeless tobacco: N-nitrososarcosine (NSAR), N-nitrosoazetidine-4-carboxylic acid (NAzCA), 3-(methylnitrosamino)propionic acid (MNPA), 4-(methylnitrosamino) butyric acid (MNBA), N-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), N-nitrosopipecolic acid (NPIC), N-nitrosothiazolidine-4-carboxylic acid (NTCA), N-nitroso-2- ethylthiazolidine-4-carboxylic acid (MNTCA), 4-(methylnitrosamino)-4-(3-pyridyl)butyric acid (*iso*-NNAC) and 2-(methylnitrosamino)- 3-phenylpropionic acid (MNPhPA) [14-16]. Of these, NSAR, MNPA, MNBA and NAzCA have been established as carcinogens in experimental animals.

The levels of *N*-nitrosoamino acids in smokeless tobacco products worldwide are presented in Table-4 [2].

Table-4: Comparison of the major carcinogenic *N*-nitrosamino acids in smokeless tobacco (μg/g dry wt) across countries

Country	Type of tobacco	NSAR	MNPA	MNBA
Belgium	Chewing tobacco	NE	1.63	0.09
Germany	Nasal snuff	ND-0.085	0.49-4.26	0.08-0.41
India	Zarda	ND-0.35	0.02-18.0	ND-2.04
	Khiwam	0.01-0.04	0.26-1.38	0.01-0.19
Sweden	Moist snuff	0.01-0.68	0.38-4.40	0.03-0.26
UK	Moist snuff	0.03-1.1	1.36-19.0	0.06-8.0
	Nasal snuff	ND-0.04	1.0-2.8	0.1-0.28
USA	Moist snuff	ND-6.3	0.15-70.0	ND-17.5
	Chewing tobacco	NE	0.6	0.03
	Dry snuff	NE	1.2-4.5	0.14-0.46

MNBA, 4-(*N*-methylnitrosamino)butyric acids; MNPA, 3-(*N*-methylnitrosamino)propionic acids; ND, not detected; NE, not evaluated; NSAR, *N*-nitrososarcosine

3.1.3 Volatile N-Nitrosamines: These include N-nitrosodimehtylamine (NDMA), N-nitrosopyrrolidine (NPYR) and N-nitrosopiperidine (NPIP).Volatile N-nitrosamines are formed from volatile amines and nitrosating agents. The levels of volatile N-nitrosamines in smokeless tobacco products worldwide are presented in Table 5. The highest amounts were found in moist snuff (NDMA up to 265 ng/g dry wt. and NPYR up to 860 ng/g dry wt.) [2].

Table-5: Comparison of the major carcinogenic volatile *N*-nitrosamines in smokeless tobacco (ng/g dry wt.) across countries

Country	Type of product	NDMA	NPYR
Canada	Moist snuff	23-72.8	321-337
Denmark	Chewing tobacco	5.5	16
Germany	Nasal snuff	2.0-82	1.5-75
	Chewing tobacco	ND	ND
India	Zarda	2.0-31	6.0-69
	Khiwam	1.5-28	11-250
	Chewing tobacco	ND-0.56	1.55-4.48
	Mishri	12-80	21-99
Norway	Moist snuff	130	8.9
Sweden	Moist snuff	ND-63	ND-155
	Chewing tobacco	0.2	0.8
UK	Moist snuff	6.0-212	64-860
	Nasal snuff	4.5-82	1.5-130
USA	Moist snuff	ND-265	ND-575
	Chewing tobacco	4.12-64	ND-0.8
	Dry snuff	ND-19	72-148

ND, not detected; NDMA, N-nitrosodimethylamine; NPYR, N-nitrosopyrrolidine

3.1.4 Other Carcinogenic Compounds: Apart from the above listed compounds, the other carcinogenic compounds and constituents reported in smokeless tobacco products include volatile aldehydes, uranium and polonium-210. Levels of the volatile aldehydes formaldehyde, acetaldehyde, acrolein and crotonaldehyde in smokeless tobacco products ranged from 0.207– 10.6, 0.97–72.3, 0.27–7.85, and 0.55–19.4 μg/g dry weight tobacco, respectively [17].

Uranium was reported in Indian snuff at a concentration of about 3 pCi/g tobacco [18]. Levels of polonium-210 in commercial moist and dry snuff in the USA were reported to be 0.16–1.22 and 0.23–0.39 pCi/g, respectively [3].

Traces of polycyclic aromatic hydrocarbons were also detected in various smokeless tobacco products. These include benzo[a]pyrene, benz[a]anthracene, chrysene, benzofluoranthenes, and dibenz[a,h]anthracene [17].

4. Health Effects of Smokeless Tobacco: Though SLT is lesser harmful than smoked tobacco, yet it poses significant health risks to the individuals who use it. Some SLT products, such as the low-nitrosamine Swedish style of snuff known as snus, have been found to be at least 90% less hazardous than conventional cigarettes [19]. It is precisely for these reasons that many scientists and health professionals have suggested that use of SLT so that tobacco related harms could be reduced. But it has to be kept in mind that SLT products have a potential to serve as starter from which young people may get addicted to tobacco and later on shift to cigarettes and other higher risk products. So

irrespective of what the tobacco companies may claim, it is by no means a safe alternative to smoking or method of quitting.

The SLT tobacco has many immediate health effects like bad breath, stained teeth, dizziness, high blood pressure, mouth sore etc. The use of SLT products over a long term can cause serious health problems like oral cancer, leukoplakia and extra- oral cancers. Given below are some of the major ill-effects that SLT can have on the user's health:

4.1 Nicotine Addiction: All forms of SLT products contain nicotine, which is addictive [20]. The users of SLT products have different levels of nicotine in the blood depending upon the type and quality of the product and the amount consumed. Nicotine is absorbed through the mouth tissues directly into the blood, and then through blood supply it goes to the brain. SLT releases more nicotine into the bloodstream than what cigarettes do. This is precisely the reason why people having the habit of chewing or dipping tobacco regularly may find quitting SLT even harder than quitting cigarette smoking. SLT quitting causes similar symptoms such as intense cravings, increased appetite, anxiety, irritability and depressed mood as quitting cigarettes do.

4.2 Pre-cancerous Mouth Lesions (Leukoplakia): Many studies made in different parts of the world have revealed that there is a high rate of leukoplakia at a place in the mouth where SLT users place their chew or dip. Nearly 3 out of 4 daily users of moist snuff and chewing tobacco had non-cancerous or pre-cancerous lesions in the mouth. The longer a person uses SLT, the more likelihood they have of having leukoplakia [21-24]. Oral leukoplakia is a premalignant lesion, having the risk of malignant transformation to oral cancer that varies in relation to the product used. With most products, the risk appears quite low, whereas toombak dipping (a regional term for snuff) has been associated with a high incidence of oral cancer in the Sudan [25].

4.3 Smokeless Tobacco and Oral Cancer: Researches have shown that certain SLT products increase the risk of oral cancer, specifically betel quid with tobacco, tobacco with lime, and other tobacco mixtures in South Asia, and smokeless tobacco in the United States [26]. The few available studies on certain other smokeless tobacco products, such as toombak in Sudan and other African countries [27], shammah in Saudi Arabia [28,29], nass and nasswar in Central Asia republics indicate their use increases oral cancer risk [30].

Oral cancer has become a major health concern in India also. The use of gutkha, jarda and other forms of SLT and betel nut is the single most important risk factor for oral cancer in India. It is the most common cancer among men and the third most common cancer among women [31].

The studies reviewed from other countries where SLT use is prevalent, were not found to be statistically significant but the researchers found that a positive association between tobacco and oral cancer could not be ruled out [32].

4.4 Smokeless Tobacco and Extra-oral Cancers: Researches have revealed that SLT does not cause oral cancer only but it causes some extra oral cancers also. In a study of men and women diagnosed with esophageal cancer in Assam, India, betel-quid chewing was found to be associated with increased risk for esophageal cancer [33]. The large US cancer prevention studies revealed that current use of snuff and chewing tobacco was connected with increased risk for all cancers combined, lung cancer and liver cirrhosis [34]. The two US case control studies suggested an association for men but not women between chewing tobacco use and pancreatic cancer as well as renal cell cancer [35-36]. Interestingly, a study of Norwegian men found an increased risk of pancreatic cancer for both current and former SLT users [37]. In contrast, Swedish population based

case control studies found no association between SLT use and any type of gastric cancer and esophageal cancer [38].

5. Conclusion: Hence it can be concluded that the use of SLT poses potent health hazards and one can say that it is a leading avoidable cause of mortality and morbidity all over the world.Several carcinogens have been identified in SLT, and tobacco-specific N-nitrosamines (TSNAs) being the most important. SLT not only harms nearly every organ of the body but also significantly reduces both quality of life and life expectancy. It causes a number of major diseases like addiction, pre-cancerous mouth lesions, oral cancer and extra oral cancers. Keeping in view these health hazards, it is necessary to take serious actions to control tobacco use.

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