

## Review Article

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# Regulation of toxic contents of smokeless tobacco products

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**Effective regulation of contents of tobacco products is one of the primary milestones to reduce negative health effects associated with the use of smokeless tobacco (SLT) products. As per the available sources, testing of some SLT products has been done on *ad hoc* basis, but there is a lack of comprehensive and periodic analysis of these products. In addition, the available results indicate huge variations among the levels of pH, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, N-nitrosornicotine, benzo[a]pyrene, heavy metals and nicotine within different products as well as within different brands of the same product. This review was aimed to throw light on the variations and gaps in testing of SLT products and emphasize the need for strong policy regulation for monitoring the chemical constituents of these products.**

**Key words** Carcinogen - regulation - smokeless tobacco - tobacco-specific nitrosamine - toxic

## Introduction

Smokeless tobacco (SLT), a non-combustible form of tobacco, is consumed by 350 million people in 133 countries across the globe<sup>1</sup>. As per a recent survey, SLT use accounts to approximately 0.65 million deaths annually<sup>1</sup>. Consumption of these products has been reported to be associated with many diseases such as cancers, neurological disorders and oral and heart diseases<sup>2,3</sup>. This can be attributed to the presence of harmful chemicals along with 28 known carcinogens<sup>4-10</sup>.

While there are regulations on the concentrations of chemicals in other commercially available products

such as pesticides, medicines and food additives, no such policies are available for SLT products. Considering tobacco products, a lot of efforts have been employed for regulation of chemical contents of cigarette and cigarette smoke. One such effort includes mandating validation methods for testing of chemical constituents of cigarette<sup>11</sup>. International Organization for Standardization has been actively involved in the development of standards related to testing of cigarette smoke. Their technical committee has developed 64 international standards related to testing of tobacco and tobacco products, especially smoke<sup>11</sup>. However, majority of efforts are

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concentrated towards the regulation of cigarettes and cigarette smoke. In spite of many evidences on the hazardous effect of SLT products on humans, not much emphasis has been given on their regulation. Thus, there is a strong need for comprehensive identification and characterization of the toxic contents through analytical testing and extensive research about potential health hazards of these products. This type of analytical testing will help to establish a correlation between products, chemical constituents and their short-term and long-term toxicological effects on the organs and tissues.

Articles 9 and 10 of World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) call for regulation of the contents and disclosures of tobacco products. According to Global Progress Report on SLT, 2016, from FCTC, the average implementation rate of Article 9 was around 50 per cent and that comprised mostly for smoking<sup>12,13</sup>. Hence, the first step for regulation of SLT products has been taken up by the WHO FCTC focusing on implementation of Article 9 for regulation of SLT products<sup>14</sup>.

This review focuses on information on testing of SLT constituents, their regulation and challenges. It showcases the discrepancies and gaps in the regulation of toxic contents of SLT products highlighting country-wise and brand-wise differences in the previously tested samples. It also emphasizes the need for stringent policy regulations and their strong implementation for monitoring the chemical constituents of these products.

### ***Carcinogens in smokeless tobacco products***

SLT products contain a diversity of chemical compounds belonging to a variety of different classes such as organic tobacco-specific nitrosamines (TSNAs), polyaromatic hydrocarbons, inorganic metals and salts. TSNAs contain known potent carcinogens such as N-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosoanabasine (NAB). Volatile N-nitrosamines contain N-nitrosodimethylamine, N-nitrosopyrrolidine, N-nitrosopiperidine, N-nitrosomorpholine and N-nitrosodiethanolamine. Table I includes a list of available chemical compounds identified from SLT products along with their classification as per International Agency for Research on Cancer (IARC) monographs<sup>15</sup>. TSNAs are formed from tobacco alkaloids in the presence of nitrates as explained below.

### ***Role of nicotine and its conversion to tobacco-specific nitrosamines (TSNAs)***

Tobacco plant contains four major alkaloids namely nicotine, nornicotine, anabasine and anatabine. Nicotine is the primary alkaloid and constitutes a major proportion (90-95%) of all alkaloid pools present in the commercially used tobacco plants<sup>16</sup>. It can undergo demethylation to form nornicotine, anabasine and anatabine. TSNAs (NNN, NNK, NAT and NAB) are formed by nitrosation of these alkaloids during curing and processing of tobacco products. NNN, NNK, NAT and NAB are known carcinogens and are found to be associated with oral, oesophageal and pancreatic cancers<sup>17,18</sup>.

### ***Variation in tobacco-specific nitrosamines (TSNAs) and benzo[a]pyrene (B[a]P)***

Compiling all the published articles in Table II, there is a wide variation in the levels of TSNAs across different countries and across different brands within a country. There is a 60-fold variation (0.66-42.5 µg/g) in NNN content of moist snuff in USA, while for dry snuff, the variation is 100 folds (0.8-81.3 µg/g). Wide variations in the amount of other TSNAs are also observed. NNK content of most of the products in USA varies from 0.05 µg/g in dissolvables to 20.3 µg/g in dry snuff. In SLT products manufactured in India, NNN varies from 0.09 µg/g in *gutka* to 40 µg/g in *khaini*, while NNK varies from 0.04 µg/g in *gutka* to 24.1 µg/g in *zarda*.

Globally, variations in NNN range from 0.01 µg/g (*rapé* from Brazil) to 3085 µg/g (*toombak* from Sudan)<sup>47</sup>, NNK varies from 0.004 µg/g (*rapé* from Brazil and *mawa* from Pakistan) to 7870 µg/g (*toombak* from Sudan)<sup>47</sup>, NAT from 0.006 µg/g to 170 µg/g (moist snuff in Canada) and NAB from 0.001 µg/g (*rapé* in Brazil) to 4.8 µg/g (moist snuff in Canada). Variation of another potent Group 1 carcinogen, B[a]P ranges from 0 ng/g (snus in USA) to 104 ng/g in Iq'mik in USA (Table III). Such wide variations in the concentration of toxicants are influenced by various factors such as tobacco plant, tobacco type, nitrate and alkaloid content, method of cultivation, pesticides used, harvesting and processing techniques and storage conditions. As per a report, extremely high levels of TSNAs in Sudanese *toombak* have been attributed to high levels of tobacco alkaloids in *Nicotiana rustica*<sup>7</sup>.

### ***Variation of heavy metals in smokeless tobacco products***

A variety of toxic metals such as arsenic, cadmium, chromium, lead and nickel have also been identified. These are either absorbed by the tobacco plant from

**Table I.** List of available chemical compounds identified from smokeless tobacco products along with their classification as per the International Agency for Research on Cancer (IARC), France

Chemical compounds	IARC classification*	Chemical compounds	IARC classification*
NNN	1	Chlordane	2B
NNK	1	Heptachlor	2B
Benzo[a]pyrene	1	MNPN	2B
Formaldehyde	1	Cobalt	2B
Beryllium	1	Ochratoxin A	2B
Arsenic	1	Aflatoxin M1	2B
Cadmium	1	Lead	2B
NDMA	2A	NAT	3
NDEA	2A	NAB	3
Dibenz[a,h]anthracene	2A	NPRO	3
DDT	2A	NHPRO	3
Nitrate	2A	3-(N-nitrosomethylamino) propionaldehyde	3
Nitrite	2A	Benzo[e] pyrene	3
Hydrazine	2A	Triphenylene	3
Ethyl carbamate	2A	Pyrene	3
NDBA	2B	Fluoranthene	3
NSAR	2B	Acenaphthene	3
NEMA	2B	Fluorene	3
NPYR	2B	Phenanthrene	3
NPIP	2B	Anthracene	3
NMOR	2B	Benzo[g, h, i] perylene	3
NDELA	2B	Crotonaldehyde	3
Benz[a]anthracene	2B	Acrolein	3
Chrysene	2B	Endrin	3
Benzo[fluoranthenes (j)	2B	Maleic hydrazide	3
Indeno[1,2,3- cd]pyrene	2B	NGL	3
5MC	2B	N-Nitrosoguvacine	3
Naphthalene	2B	Eugenol	3
Benzo[b]fluoranthene	2B	Chromium	3
Benzo[k]fluoranthene	2B	Mercury	3
Dibenzo[a,i]pyrene	2B	Quercetin	3
Acetaldehyde	2B	Morpholine (precursor of NMOR)	3

\*Source: Ref. 15

Group 1: Compounds having sufficient evidence of carcinogenicity in humans or experimental animals. Group 2A: Compounds showing limited evidence of carcinogenicity in humans and sufficient in experimental animals. Group 2B: Compounds showing limited carcinogenicity in humans and less than sufficient in experimental animals. Group 3: Compounds in which evidence of carcinogenicity is inadequate in humans and animals. Group 4: Evidences suggest lack of carcinogenicity. NNN, N-nitrosornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NDMA, N-nitrosodimethylamine; NDEA, N-Nitrosodiethylamine; NDBA, N-nitrosodibutylamine; DDT, dichlorodiphenyltrichloroethane; NSAR, N-nitrososarcosine; NEMA, N-nitrosoethylmethylamine; NPYR, N-nitrosopyrrolidine; NPIP, N-nitrosopiperidine; NMOR, N-nitrosomorpholine; NDELA, N-Nitrosodiethanolamine; 5MC, 5-methylchrysene; NGL, N-nitrosoguvacoline; NAT, N-nitrosoanatabine; MNPN, 3-methylnitrosaminopropionitrile; NAB, N-nitrosoanabasine; NPRO, N-nitrosoproline; NHPRO, N-nitrosohydroxyproline

**Table II.** Concentration of tobacco-specific nitrosamines (TNSAs) ( $\mu\text{g/g}$ ) and benzo[a]pyrene (B[a]P) ( $\text{ng/g}$ ) in different smokeless tobacco products worldwide

Country	SLT products	NNN	NNK	NAT	NAB	B[a]P
USA <sup>4,19-32</sup>	Moist snuff	0.66-42.5	0.21-9.9			
	Dry snuff	0.8-81.3	0.12-20.3			
	Dissolvable	0.076-2.66	0.05-0.353	0.18-2.3	0.01-0.12	0.3-0.4
	Snus	0.36-2.4	0.08-0.73	0.50-2.24	0.03-0.17	0.0-15.6
	Iq'mik	1.9-4.0	0.19-0.96	3.1-4.9	0.16-0.34	13-104
	Loose leaf	0.662-2.83	0.140-0.898			1.2-8.0
India <sup>33-35</sup>	<i>Khaini</i>	13.2-76.9	0.11-28.4	2.8-13.8	2.19-12.9	
	<i>Gutka</i>	0.09-1.09	0.04-0.43	0.01-0.08	0.01-0.05	
	<i>Zarda</i>	4.79-19.9	0.22-24.1			
	<i>Mishri</i>	0.3-4.21	0.29-1.1	2.55	0.15	
	Chewing tobacco	0.47-0.85	0.13-0.60			
Bangladesh <sup>36</sup>	<i>Zarda</i>	4.3-28.6	0.45-3.8	3.1-11.8	1-6	
	<i>Gul powder</i>	5.2-8	1.3-1.4	4.2-4.7	1.9-2.3	
	Tobacco leaf	0.16	0.02	0.29	0.069	
Oman <sup>37</sup>	<i>Afzal</i>	1.18-1.22	1.01-1.02			
Pakistan <sup>36</sup>	<i>Gutka</i>	0.04-0.91	0.01-0.20	0.01-0.29	0.005-0.09	
	<i>Mawa</i>	0.065	0.004	0.016	0.005	
	<i>Mainpuri</i>	0.10	0.006	0.06	0.01	
	<i>Naswar</i>	0.36-0.54	0.03-30	0.05-0.34	0.01-0.08	
Sweden <sup>14,38,39</sup>	Snus	0.42-3.28	0.09-1.1			1.59-2.93
	Moist snuff	1.0-154	0.19-2.95	0.06-21.4	0.04-1.7	
Canada <sup>14,40</sup>	Moist snuff	0.8-79	0.38-5.8	0.57-170	0.26-4.8	11.8-83.2
	Chewing tobacco	2.09	0.24	1.58	0.1	
Kyrgyzstan <sup>5</sup>	<i>Nasvai</i>	1.12-1.26	0.17-0.21			
Uzbekistan <sup>5,36</sup>	<i>Nasvai</i>	0.59-0.69	0.07-0.07	0.071	0.29	
Turkey <sup>41</sup>	Maras powder	2.2-2.8	0.63-0.77			
Sudan <sup>36,42</sup>	<i>Toombak</i>	115-3085	147-7870	16.6-59.6	11.1-302	
Germany <sup>34,43</sup>	Dry snuff	2.4-18.1	0.58-6.4			
	Nasal snuff (ppm)	1.8-2	0.5-0.7	0.9-0.1	<0.02	
	Chewing tobacco	1.4-2.3	0.03-0.3			
Belgium <sup>14</sup>	Chewing tobacco	7.38	0.13			
Thailand <sup>14</sup>	Chewing tobacco	0.5	0.1	0.5		
Japan <sup>44</sup>	SLT	0.34-1.5	0.06-0.28	0.27-1.1	0.03-0.07	
Nigeria <sup>36,45</sup>	Snuff	0.71-1.4	0.28-0.36	0.41-0.44	0.05-0.06	0.50-15.23
South Africa <sup>32,36</sup>	Moist snuff	0.79-1.4	0.11-0.51	0.57-0.93	0.03-0.06	1.7-5.1
	Snus	0.92-2.9	0.17-1.3	0.52-1.3	0.04-0.11	
Brazil <sup>46</sup>	<i>Rapé</i>	0.01-14.5	0.004-3.3	0.006-7.29	0.001-0.74	3.5-24.3
Venezuela <sup>36</sup>	<i>Chimó</i>	0.31-4.6	0.31-2.6	0.22-0.96	0.01-0.17	

NNN, N-nitrosornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, N-nitrosoanabasine

**Table III.** Concentration of metals ( $\mu\text{g/g}$ ) in different smokeless tobacco products worldwide

Countries	SLT products	Arsenic	Lead	Chromium	Nickel	Cobalt	Zinc	Cadmium
	GOTHIATEK®	0.25	1	1.5	2.25	-	-	0.5
USA <sup>25,32</sup>	Dissolvable, moist snuff, dry snuff, loose leaf, plug	0.07-0.31	0.18-0.79	0.58-5.7	0.65-7.5	-	-	0.25-1.8
India <sup>8,54</sup>	<i>Khaini, Jarda, Gutka, Mishri</i>	0.11-3.5	0.03-68	4.2-10.1	1.3-13.5	-	27.5-82.7	0.01-3.2
Tunisia <sup>55</sup>	<i>Nefa</i>	-	-	2.7-3.9	0.75-1.9	0.22	-	-
Libya <sup>56</sup>	Chewing tobacco	-	-	9.3-9.6	-	34.7-41.7	20.5-28.7	-
Pakistan <sup>57-59</sup>	<i>Naswar</i> (sniffing/dipping), moist and dry snuff, chewing tobacco	0.25-14.04	0.08-111.1	0.69-78.8	2.2-64.8	0.06-2.7	9.1-66.9	0.25-9.2
Nigeria <sup>49,60</sup>	Snuff, tobacco leaves	-	0.02-22	2.8-11.4	0.2-0.7	0.01-0.03	67-87	0.01-0.19
Oman <sup>48</sup>	Afzal	-	1.56-1.6	15-16.4	1.4-1.77	-	-	1.75-1.85
UK <sup>61</sup>	<i>Gutka, Zarda</i> , toothpowder, tobacco leaves	0.04-0.46	0.15-1.39	0.26-3.54	1.22-5.88	-	-	-
Sweden <sup>32</sup>	Moist snuff	0.73-1.02	0.44-0.74	1.2-2.8	1.4-2.6	-	-	0.58-0.96
Saudi Arabia <sup>62</sup>	<i>Shamma</i>	0.2-7.2	26.2	7.4	0.6-267	0.4-26.2	-	0.3
Ethiopia <sup>63</sup>	Tobacco leaves	-	-	1.4-1.7	1.9-4.7	-	33.2-101	1.2-1.9
Ghana <sup>62</sup>		0.1-0.2	-	0.9-1.4	-	-	-	1.1
South Africa <sup>32</sup>	Moist snuff	1.1-1.5	0.89-1.76	3.1-6.0	2.1-3.6	-	-	0.52-0.77

-, not available

soil or enter during the curing and processing of tobacco plants. Among these, arsenic and cadmium are classified as Group 1 carcinogens. Also, nickel and lead have been classified as Groups 2B carcinogens and chromium as Group 3 carcinogen, respectively<sup>48</sup>. It has been previously studied that toxicity of heavy metals has a direct correlation with the burden of metals in our body. Therefore, change in their concentration by consumption of SLT leads to severe toxicity<sup>49</sup>. Some other diseases include diseases of bone and kidney (excess of cadmium), neurological disorders (excess of lead)<sup>50,51</sup> and metabolic disorders (excess of zinc and copper)<sup>52,53</sup>. Table III indicates the amounts of metals in different SLT products tested worldwide.

Only a few countries listed in Table III have tested their SLT products for estimation of metal contents. It is also important to note that all these reports are published one time by individual research groups following no standard operational procedures. Since there is no government agency involved, periodic testing and monitoring does not take place. For instance, Houas *et al*<sup>55</sup> compared the mineral concentrations of SLT, water pipe tobacco and cigarettes from the Tunisian Market, while Brima<sup>62</sup> estimated the concentration of metal level in Shamma, found in Saudi Arabia. Table IV indicates different standards for testing of SLT products.

According to Tables III and IV, concentration of arsenic, lead and chromium in some of the SLT products from Pakistan (*Naswar*) was found to be 50 times more than GOTHIATEK® limits<sup>57</sup>. Nickel concentration in Shamma, a SLT product found in Saudi Arabia, was 118 times greater than GOTHIATEK® limits<sup>62</sup>. In India, lead content in one of the brands of *gutka* was found to be 68 times greater than the defined limit<sup>54</sup>. In general, there was a large variation in concentration in most of the metals, which was much more than the acceptable limits.

#### **Variation in pH and its effect on nicotine absorption**

Nicotine content of a SLT product is the primary determinant of cause of addiction among users. The unprotonated form of nicotine or 'free nicotine' is easily absorbed by the oral mucosa<sup>66</sup>. Absorption of nicotine at the buccal surface is governed by the pH of SLT product<sup>67</sup>. Higher pH facilitates more absorption and vice versa. At low pH, nicotine gets ionized and is thus unable to cross biological membranes<sup>67</sup>.

Table V depicts wide variations in the pH levels of various SLT products. As an example, the level of pH ranges from as low as is from 5.1 mg/g in Brazilian *rapè* to 10.2 mg/g in Swedish snus and Brazilian *rapè*. Variation in free nicotine content is from 0.01 mg/g in the USA moist snuff to 65 mg/g in Indian *zarda*.



**Table IV.** Different standards for the chemicals of smokeless tobacco

Chemicals	WHO TobReg <sup>64</sup>	GOTHIATEK® <sup>65</sup>
NNN + NNK	≤2 µg/g (dry wt)	0.95 µg/g
B[a]P	5 ng/g (dry wt)	1.25 ng/g
Lead	-	1 µg/g
Arsenic	-	0.25 µg/g
Nickel	-	2.25 µg/g
Chromium	-	1.5 µg/g
Cadmium	-	0.5 µg/g
NNN, N-nitrosornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone		

**Table V.** Concentration of free or unprotonated nicotine (mg/g) and pH from different brands of smokeless tobacco products available worldwide

Country	SLT products	Nicotine	pH
USA <sup>4,19,20</sup>	Moist snuff	0.01-7.8	5.5-8.6
	Snus	0.57-5.09	6.7-7.8
	Dissolvable	0.30-2.12	6.8-8.1
India <sup>68,69</sup>	<i>Khaini</i>	0.53-21.3	9.47
	<i>Zarda</i>	13.8-65	
	<i>Gutka</i>	1.23-11.4	5.24
Canada <sup>40</sup>	Moist snuff	2.44-31.2	5.34-5.63
Brazil <sup>46</sup>	<i>Rapé</i>	0.03-18.5	5.1-10.2
Sweden <sup>38</sup>	Snus	0.35-6.1	7.45-10.2
South Africa <sup>32,36</sup>	Moist snuff	1.1-19	6.4-9.8
Venezuela <sup>36</sup>	Snus	0.47-1.2	6.5-7.0
	<i>Chimó</i>	1.32-27.4	6.98-9.2
Sudan <sup>36</sup>	<i>Toombak</i>	5.1-10.6	7.3-10.1

## Regulation of tobacco products

Given the huge variation in the toxic contents of currently available SLT products, it becomes extremely imperative to consider the acceptable levels of harm. According to Gray and Borland<sup>70</sup>, there are three major regulatory possibilities for tobacco: (i) regulation of carcinogens and toxins such as TSNAs, B[a]P and metals; (ii) regulation of nicotine for addictiveness, and (iii) regulation of additives. Considering the wide variations in chemical content and lack of monitoring agencies, there is an immediate need to develop validated methods for estimating the toxicity/carcinogenicity of SLT products<sup>70</sup>.

Two of the widely used standards are TobReg<sup>64</sup> and GOTHIATEK®<sup>65</sup>. Tobacco Product Regulation

(TobReg) group of WHO has set the maximum acceptable limit of NNN+NNK to ≤2 µg/g dry weight of tobacco and B[a]P to 5 ng/g dry weight of tobacco (Table IV). Swedish Match has published standards for maximum allowable levels of TSNAs, metals and trace elements, which are collectively known as GOTHIATEK® standard<sup>65</sup> (Table IV). Rickert *et al*<sup>40</sup> have stated in their report that some but not all experts on this topic have suggested that this standard is safe enough to be recommended by health authorities. GOTHIATEK® standard has been adopted by two big tobacco companies: British-American Tobacco and European Smokeless Tobacco Council (ESTOC)<sup>71</sup>.

## Role of WHO FCTC

### TobReg

The WHO established a tobacco-free initiative (TFI) in July 1998 to provide international attention to global tobacco epidemic. Its mandate is to reduce the global burden of disease and death caused by tobacco and thus working on a mission to protect the present and future generations from the consequences of tobacco consumption and exposure to tobacco smoke. TFI encompasses a Scientific Advisory Committee on Tobacco Product Regulation (SACTob)<sup>72</sup> whose aim is to provide scientific information and recommendation on tobacco product regulation related to Articles 9, 10 and 11 of the WHO FCTC. Most of the efforts regarding tobacco regulation have been done for cigarettes. TobReg has defined three models for cigarettes, each mentioning mandatory limits for emissions of nine different smoke toxicants<sup>73</sup>.

### Tobacco Laboratory Network (TobLabNet)

As a step towards regulation, the WHO has established Tobacco Laboratory Network (TobLabNet) with the aim to regulate and provide testing and research of contents and emissions of tobacco products. Its major goal is to establish testing and research capacity of tobacco products for regulatory compliance. The report by WHO FCTC at the Conference of Parties 7 at New Delhi in November 2016 states that the already available WHO TobLabNet methods for analysis of TSNAs, B[a]P and nicotine can be adapted or applied to other SLT<sup>74</sup>. Furthermore, owing to the wide range of SLT products, there is a need to perform product-specific analysis in South Asia which is not presently performed by the TobLabNet due to lack of relevant laboratory expertise and/or capacity. The analytic procedures for metals, humectants, aldehydes and many other toxicants present in SLT need to be

standardized. It was also recommended that the Parties should consider asking SLT manufacturers to provide levels of pH and toxicants (TSNAs, B[a]P and nicotine) using WHO-recommended methods/ Standard Operating Procedures (SOPs), as recommended for cigarettes, from approved laboratories.

### **WHO Collaborating Centre on Tobacco Control**

The WHO Collaborating Centre is a part of TFI whose aim is to form part of an international collaborative network carrying out activities on tobacco control and strengthen institutional capacity in countries and Regions. There are 16 WHO collaborating centres for tobacco control which work closely with TFI. Among these, six collaborating centres are working on tobacco testing and research (Table VI). However, the laboratories of these centres focus on technical training on testing compounds and emissions of smoking products, especially cigarettes.

### **Effort at country level**

#### **India**

India is the largest consumer of SLT products by number. Prevalence of SLT use among men and women is 29.6 and 12.8 per cent<sup>75</sup>, respectively. Although the burden is highest in India, not much effort except

a few studies<sup>76</sup> towards testing of harmful contents of SLTs has been made. The Government of India in 2003 has established a law regarding tobacco known as Cigarettes and Other Tobacco Products Act which includes prohibition of advertisement and regulation of trade and commerce, production, supply and distribution. This also includes testing of nicotine and tar for all tobacco products<sup>77</sup>. To implement this law, the governments piloted National Tobacco Control Programme in 2007-2008; one of its components was to establish tobacco product testing laboratories for building regulatory capacity<sup>77</sup>. The Ministry of Health and Family Welfare, Government of India, has established National Tobacco Testing Laboratory at National Institute of Cancer Prevention and Research, Noida, Central Drug Testing Laboratory, Mumbai, and Regional Drug Testing Laboratory, Guwahati, with the sole purpose of providing scientific and analytical information to the Government of India and other regional countries and organizations such as the WHO [File No. T-20018/25/2016-NCD/FTS: 3059618/16, Ministry of Health and Family Welfare, National Tobacco Control Programme (Tobacco Control/NTTLs) dated 29<sup>th</sup> August 2017].while in some Asian countries like Thailand and South Korea, the responsibility of testing tobacco products has been given to the industry<sup>78</sup>.

#### **USA**

Most of the testing procedures of SLT products around the world have been done in various laboratories of the USA (although the USA is not the signatories to the WHO FCTC). The Food and Drug Administration has proposed a rule that mean level of NNN in any batch of finished SLT products should not exceed 1.0 µg/g of tobacco on a dry weight basis<sup>79</sup>.

#### **Europe**

GOTHIA TEK® standards have been accepted by ESTOC (a pan European SLT lobby) members and have become a voluntary standard for most of the SLT products manufactured in Europe<sup>80,81</sup>. The United Kingdom has enforced regulation regarding tobacco products, especially cigarettes, which states that a person cannot produce, supply or manufacture for export of any cigarettes with emission level greater than 10 mg of tar/cigarette, 1 mg nicotine/cigarette and 10 mg of carbon monoxide/cigarette<sup>82</sup>.

#### **Gaps**

The available data indicate that very few laboratories, which are not funded by industry, are

**Table VI.** List of WHO Collaborating Centres on Tobacco Control working on tobacco testing research and regulation

Institute name
WHO Collaborating Center on Tobacco Product Testing and Research, Direction de la Toxicologie, du Contrôle de l'Environnement et de l'Hygiène Publique, Laboratoire National de Santé Publique, Rue Tansoba Kiéma, Kadiogo, Ouagadougou, Burkina Faso
WHO Collaborating Centre for Tobacco Product Testing and Research, USA Centre for the Study of Tobacco Products, Virginia Commonwealth University, USA
WHO Collaborating Centre on Tobacco Control, Germany German Cancer Research Centre, Germany
WHO Collaborating Centre for Tobacco Product Regulation and Control, The Netherlands National Institute for Public Health and the Environment, The Netherlands
WHO Collaborating Centre for Tobacco Testing and Research, Japan National Institute of Public Health, Wako, Japan
WHO Collaborating Centre for Tobacco Testing and Research, Singapore Health Sciences Authority, Singapore

working on the chemical composition of tobacco. Most of these efforts are primarily on cigarettes with only meagre focus on SLT. There is no centralized facility in almost all countries to perform these tests and produce results with certain regulatory standards. No global standards are provided for testing and measuring most of the compounds of SLT products. There is no regulation for additives and other flavouring agents in SLT products. Moreover, only partial guidelines have been proposed by the WHO FCTC for Articles 9 and 10.

### Conclusion

Although the toxicological and clinical risks associated with many of the SLT products are known, little effort has been taken to regulate their constituents. Considering the hazardous impact of SLT products on human health and wide prevalence among different parts of the world, there is an urgent need to pay more attention towards research on SLT products, their ingredients and emissions. More emphasis should be given on the establishment of tobacco testing laboratories in every region, which will be precisely the driving force behind the successful implementation of Articles 9 and 10 of WHO FCTC. In addition, major initiatives are required that promote collaborations between academia, researchers, scientists and governments to ensure that reports from the laboratory are quickly interpreted and efficiently translated for implementation. It will provide better avenues for researchers to find out newer ways of reducing hazardous compounds from tobacco products. This will in turn help governments to fund better research and help eradicate the problems associated with SLT. Another important step is to develop SOPs for testing of each toxic chemical compound of SLT products. These steps will help in the establishment of permissible upper limits of all chemical ingredients of SLT. And finally, the regulation will also reduce the burden on medical system which is catering to the affected individuals and will also help in strengthening economy worldwide.

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### References

1. Sinha DN, Suliankatchi RA, Gupta PC, Thamarangsi T, Agarwal N, Parascandola M, *et al.* Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: Systematic review and meta-analysis. *Tob Control* 2018; 27 : 35-42.
2. Sinha DN, Abdulkader RS, Gupta PC. Smokeless tobacco-associated cancers: A systematic review and meta-analysis of Indian studies. *Int J Cancer* 2016; 138 : 1368-79.
3. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. *PLoS One* 2014; 9 : e113385.
4. Hatsukami DK, Stepanov I, Severson H, Jensen JA, Lindgren BR, Horn K, *et al.* Evidence supporting product standards for carcinogens in smokeless tobacco products. *Cancer Prev Res (Phila)* 2015; 8 : 20-6.
5. Stepanov I, Abrams J, Jain V, Walter K, Kittner DL. Variations of toxic and carcinogenic constituents in Nasvai: Call for systematic research and regulation. *Tob Control* 2017; 26 : 355-6.
6. Stepanov I, Gupta P, Parascandola M, Yershova K, Jain V, Dhupal G, *et al.* Constituent variations in smokeless tobacco purchased in Mumbai, India. *Tob Regul Sci* 2017; 3 : 305-14.
7. Stepanov I, Hatsukami D. Call to establish constituent standards for smokeless tobacco products. *Tob Regul Sci* 2016; 2 : 9-30.
8. Verma S, Yadav S, Singh I. Trace metal concentration in different Indian tobacco products and related health implications. *Food Chem Toxicol* 2010; 48 : 2291-7.
9. Klus H, Kunze M, Koenig S, Poeschl E. Smokeless tobacco - An overview. *Beiträge Zur Tab Int Tob Res* 2009; 23 : 248-76.
10. Vidhubala E, Pisinger C, Basumallik B, Prabhakar DS. The ban on smokeless tobacco products is systematically violated in Chennai, India. *Indian J Cancer* 2016; 53 : 325-30.
11. Wright C. Standardized methods for the regulation of cigarette-smoke constituents. *Trends Anal Chem* 2015; 66 : 118-27.
12. WHO Framework Convention on Tobacco Control. *Global Progress Report on Implementation of the WHO Framework Convention on Tobacco Control*. Geneva: World Health Organization; 2014. Available from: <http://www.who.int/fctc/reporting/2014globalprogressreport.pdf?ua=1>, accessed on June 20, 2017.
13. WHO Framework Convention on Tobacco Control. *Global Progress Report on Implementation of the WHO Framework Convention on Tobacco Control*. Geneva: World Health Organization; 2016. Available from: [http://www.who.int/fctc/reporting/2016\\_global\\_progress\\_report.pdf?ua=1](http://www.who.int/fctc/reporting/2016_global_progress_report.pdf?ua=1), accessed on June 20, 2017.
14. WHO Study Group on Tobacco Product Regulation. *Report on the scientific basis of tobacco product regulation: Third report of a WHO study group 2009*. Geneva: World Health Organization; 2009. Available from: [http://apps.who.int/iris/bitstream/handle/10665/44213/9789241209557\\_eng.pdf;jsessionid=89F04EDF81FEDB289DDC735B12F376B1?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/44213/9789241209557_eng.pdf;jsessionid=89F04EDF81FEDB289DDC735B12F376B1?sequence=1), accessed on September 16, 2017.



15. WHO International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Available from: [https://monographs.iarc.fr/wp-content/uploads/2018/07/List\\_of\\_Classifications.pdf](https://monographs.iarc.fr/wp-content/uploads/2018/07/List_of_Classifications.pdf), accessed on June 03, 2018.
16. Siminszky B, Gavilano L, Bowen SW, Dewey RE. Conversion of nicotine to nornicotine in *Nicotiana tabacum* is mediated by CYP82E4, a cytochrome P450 monooxygenase. *Proc Natl Acad Sci U S A* 2005; *102* : 14919-24.
17. Xue J, Yang S, Seng S. Mechanisms of cancer induction by tobacco-specific NNK and NNN. *Cancers (Basel)* 2014; *6* : 1138-56.
18. WHO International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Smokeless tobacco and some tobacco-specific n-nitrosamines*, Vol. 89. Lyon, France: IARC; 2007.
19. Stepanov I, Biener L, Knezevich A, Nyman AL, Bliss R, Jensen J, *et al.* Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: Findings from round 1 of the new product watch. *Nicotine Tob Res* 2012; *14* : 274-81.
20. Richter P, Hodge K, Stanfill S, Zhang L, Watson C. Surveillance of moist snuff: Total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. *Nicotine Tob Res* 2008; *10* : 1645-52.
21. Hoffmann D, Brunnemann KD, Prokopczyk B, Djordjevic MV. Tobacco-specific N-nitrosamines and areca-derived N-nitrosamines: Chemistry, biochemistry, carcinogenicity, and relevance to humans. *J Toxicol Environ Health* 1994; *41* : 1-52.
22. Hearn BA, Renner CC, Ding YS, Vaughan-Watson C, Stanfill SB, Zhang L, *et al.* Chemical analysis of Alaskan Iq'mik smokeless tobacco. *Nicotine Tob Res* 2013; *15* : 1283-8.
23. Richter P, Spierto FW. Surveillance of smokeless tobacco nicotine, pH, moisture, and unprotonated nicotine content. *Nicotine Tob Res* 2003; *5* : 885-9.
24. Djordjevic MV, Brunnemann KD, Hoffmann D. Identification and analysis of a nicotine-derived N-nitrosamino acid and other nitrosamino acids in tobacco. *Carcinogenesis* 1989; *10* : 1725-31.
25. Borgerding MF, Bodnar JA, Curtin GM, Swauger JE. The chemical composition of smokeless tobacco: A survey of products sold in the United States in 2006 and 2007. *Regul Toxicol Pharmacol* 2012; *64* : 367-87.
26. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res* 2006; *8* : 309-13.
27. Stepanov I, Yershova K, Carmella S, Upadhyaya P, Hecht SS. Levels of (S)-N'-nitrososonornicotine in U.S. tobacco products. *Nicotine Tob Res* 2013; *15* : 1305-10.
28. Stepanov I, Biener L, Yershova K, Nyman AL, Bliss R, Parascandola M, *et al.* Monitoring tobacco-specific N-nitrosamines and nicotine in novel smokeless tobacco products: Findings from round II of the new product watch. *Nicotine Tob Res* 2014; *16* : 1070-8.
29. Ammann JR, Lovejoy KS, Walters MJ, Holman MR. A survey of N'-nitrososonornicotine (NNN) and total water content in select smokeless tobacco products purchased in the United States in 2015. *J Agric Food Chem* 2016; *64* : 4400-6.
30. Lawler TS, Stanfill SB, Zhang L, Ashley DL, Watson CH. Chemical characterization of domestic oral tobacco products: Total nicotine, pH, unprotonated nicotine and tobacco-specific N-nitrosamines. *Food Chem Toxicol* 2013; *57* : 380-6.
31. Stepanov I, Villalta PW, Knezevich A, Jensen J, Hatsukami D, Hecht SS, *et al.* Analysis of 23 polycyclic aromatic hydrocarbons in smokeless tobacco by gas chromatography-mass spectrometry. *Chem Res Toxicol* 2010; *23* : 66-73.
32. Song MA, Marian C, Brasky TM, Reisinger S, Djordjevic M, Shields PG, *et al.* Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products. *Toxicol Lett* 2016; *245* : 68-77.
33. Stepanov I, Hecht SS, Ramakrishnan S, Gupta PC. Tobacco-specific nitrosamines in smokeless tobacco products marketed in India. *Int J Cancer* 2005; *116* : 16-9.
34. Sangar N. Smokeless tobacco: Chemical composition and carcinogenicity. *Int Res J Interdiscip Multidiscip Stud* 2016; *7969* : 7-16.
35. Stepanov I, Gupta PC, Dhumal G, Yershova K, Toscano W, Hatsukami D, *et al.* High levels of tobacco-specific N-nitrosamines and nicotine in *Chaini Khaini*, a product marketed as snus. *Tob Control* 2015; *24* : e271-4.
36. Stanfill SB, Connolly GN, Zhang L, Jia LT, Henningfield JE, Richter P, *et al.* Global surveillance of oral tobacco products: Total nicotine, unionised nicotine and tobacco-specific N-nitrosamines. *Tob Control* 2011; *20* : e2.
37. Al-Mukhaini N, Ba-Omar T, Eltayeb EA, Al-Shehi AA. Analysis of tobacco-specific nitrosamines in the common smokeless tobacco Afzal in Oman. *Sultan Qaboos Univ Med J* 2016; *16* : e20-6.
38. Review of the Scientific Literature on Snus (Swedish Moist Snuff). Project Number:24-18132C. Virginia: ENVIRON International Corporation Arlington, Virginia; 2013. Available from: <https://www.accessdata.fda.gov/Static/widgets/tobacco/MRTP/18%20appendix-6a-environ-snus-monograph-2013.pdf>, accessed on July 1, 2017.
39. McAdam KG, Faizi A, Kimpton H, Porter A, Rodu B. Polycyclic aromatic hydrocarbons in US and Swedish smokeless tobacco products. *Chem Cent J* 2013; *7* : 151.
40. Rickert WS, Joza PJ, Trivedi AH, Momin RA, Wagstaff WG, Lauterbach JH, *et al.* Chemical and toxicological characterization of commercial smokeless tobacco products available on the Canadian market. *Regul Toxicol Pharmacol* 2009; *53* : 121-33.
41. Kilinc M, Celik A, Buzkan N, Bakaris S, Saricicek E, Duyuran R, *et al.* Tobacco specific nitrosamine levels of Maras powder (Turkish Smokeless Tobacco). *Indian J Med Res Pharm Sci* 2015; *2* : 11-6.

42. Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, *et al.* The Swedish Snus and the Sudanese Toombak: Are they different? *Oral Oncol* 1998; 34 : 558-66.
43. Klus H, Kunze M, Koenig S, Poeschl E. Smokeless Tobacco - An Overview. *Beiträge Zur Tab Contrib Tob Res* 2014; 23 : 248-76.
44. Inaba Y, Utsugi R, Ohkubo T, Uchiyama S, Ohta T, Kunugita N, *et al.* Measurement of nicotine, tobacco-specific nitrosamines, and additives in the filler and gas from Japanese brand snuff. *Nihon Eiseigaku Zasshi* 2016; 71 : 76-83.
45. Orisakwe OE, Igweze ZN, Okolo KO, Udowelle NA. Human health hazards of poly aromatic hydrocarbons in Nigerian smokeless tobacco. *Toxicol Rep* 2015; 2 : 1019-23.
46. Stanfill SB, Oliveira da Silva AL, Lisko JG, Lawler TS, Kuklennyik P, Tyx RE, *et al.* Comprehensive chemical characterization of Rapé tobacco products: Nicotine, un-ionized nicotine, tobacco-specific N'-nitrosamines, polycyclic aromatic hydrocarbons, and flavor constituents. *Food Chem Toxicol* 2015; 82 : 50-8.
47. Idris AM, Nair J, Ohshima H, Friesen M, Brouet I, Faustman EM, *et al.* Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (Toombak). *Carcinogenesis* 1991; 12 : 1115-8.
48. Al-Mukhaini N, Ba-Omar T, Eltayeb E, Al-Shehi A. Determination of heavy metals in the common smokeless tobacco Afzal in Oman. *Sultan Qaboos Univ Med J* 2014; 14 : e349-55.
49. Orisakwe OE, Igweze ZN, Okolo KO, Ajaezi GC. Heavy metal hazards of Nigerian smokeless tobacco. *Tob Control* 2014; 23 : 513-7.
50. Pallavi S, Dubey RS. Lead toxicity in plants. *Braz J Plant Physiol* 2005; 17 : 35-52.
51. Nnorom IC, Osibanjo O. Cadmium determination in cigarettes available in Nigeria. *Afr J Biotechnol* 2005; 4 : 1128-32.
52. Zhang C, Miura J, Nagaosa Y. Determination of cadmium, zinc, nickel and cobalt in tobacco by reversed-phase high-performance liquid chromatography with 2-(8-quinolylazo)-4,5-diphenylimidazole as a chelating reagent. *Anal Sci* 2005; 21 : 1105-10.
53. Stojanović D, Nikić D, Lazarević K. The level of nickel in smoker's blood and urine. *Cent Eur J Public Health* 2004; 12 : 187-9.
54. Dhaware D, Deshpande A, Khandekar RN, Chowgule R. Determination of toxic metals in Indian smokeless tobacco products. *Scientific World Journal* 2009; 9 : 1140-7.
55. Houas I, Teyeb H, Rochina-Marco A, Douki W, Najjar MF, Gaha L, *et al.* Comparison of mineral contents in three different tobacco formulations. *Biomed Environ Sci* 2017; 30 : 52-8.
56. El-Amri FA, Saleh AI, El-Gnidy BA. Determination of trace element concentrations of Libyan chewing and cigarette tobacco by instrumental neutron activation analysis. *J Radioanal Nucl Chem Lett* 1989; 135 : 273-9.
57. Zakiullah, Saeed M, Muhammad N, Khan SA, Gul F, Khuda F, *et al.* Assessment of potential toxicity of a smokeless tobacco product (*naswar*) available on the Pakistani market. *Tob Control* 2012; 21 : 396-401.
58. Kazi TG, Arain SS, Afridi HI, Naemullah, Brahman KD, Kolachi NF, *et al.* Analysis of cadmium, nickel, and lead in commercial moist and dry snuff used in Pakistan. *Environ Monit Assess* 2013; 185 : 5199-208.
59. Musharraf SG, Shoaib M, Siddiqui AJ, Najam-Ul-Haq M, Ahmed A. Quantitative analysis of some important metals and metalloids in tobacco products by inductively coupled plasma-mass spectrometry (ICP-MS). *Chem Cent J* 2012; 6 : 56.
60. Nnoram IC. Copper, Iron and Zinc concentrations of tobacco leaves and ready-to-use snuff products on sale in Imo state Southeastern Nigeria. *J Appl Sci Environ Manag* 2015; 19 : 459-67.
61. McNeill A, Bedi R, Islam S, Alkhatib MN, West R. Levels of toxins in oral tobacco products in the UK. *Tob Control* 2006; 15 : 64-7.
62. Brima EI. Determination of metal levels in Shamma (Smokeless tobacco) with inductively coupled plasma mass spectrometry (ICP-MS) in Najran, Saudi Arabia. *Asian Pac J Cancer Prev* 2016; 17 : 4761-7.
63. Regassa G, Chandravanshi BS. Levels of heavy metals in the raw and processed Ethiopian tobacco leaves. *Springerplus* 2016; 5 : 232.
64. World Health Organization. WHO Tobacco Free Initiative. The scientific basis of tobacco product regulation: Report of a WHO study group. *World Health Organ Tech Rep Ser No.* 945, 2007 : 1-112.
65. Swedish Match Quality Standard. Available from: <https://www.swedishmatch.com/Snus-and-health/GOTHIATEK/>, accessed on June 24, 2017.
66. Al-Mukhaini NM, Ba-Omar TA, Eltayeb EA, Al-Shehi AH. Characterisation of nicotine and cancer-enhancing anions in the common smokeless tobacco Afzal in oman. *Sultan Qaboos Univ Med J* 2015; 15 : e469-76.
67. Pickworth WB, Rosenberry ZR, Gold W, Koszowski B. Nicotine absorption from smokeless tobacco modified to adjust pH. *J Addict Res Ther* 2014; 5 : 1000184.
68. Gupta PC, Arora M, Sinha D, Asma S, Parascondola M. (editors). *Smokeless tobacco and public health in India*. Ministry of Health and Family Welfare, Government of India; 2016. Available from: [http://www.searo.who.int/india/tobacco/smokeless\\_tobacco\\_and\\_public\\_health\\_in\\_india.pdf?ua=1](http://www.searo.who.int/india/tobacco/smokeless_tobacco_and_public_health_in_india.pdf?ua=1), accessed on June 25, 2017.
69. Hegde V, Nanukuttan A. Comparison of nicotine concentration and pH of commercially available smokeless tobacco products. *J Oral Res Rev* 2017; 9 : 21.
70. Gray N, Borland R. Research required for the effective implementation of the framework convention on tobacco control, articles 9 and 10. *Nicotine Tob Res* 2013; 15 : 777-88.

71. Williamson J, Proctor C, British American Tobacco. Should the health community promote smokeless tobacco (snus): Comments from British American tobacco. *PLoS Med* 2007; 4 : 1703-4.
72. WHO Scientific Advisory Committee on Tobacco Product Regulation WTFI. *SACTob recommendation on tobacco product ingredients and emissions/scientific advisory committee on tobacco product regulation (SACTob)*. Geneva: World Health Organization; 2003. Available from: <http://www.who.int/iris/handle/10665/42654>, accessed on September 15, 2017.
73. Eldridge AC, McAdam KG, Betson TR, Gama MV, Proctor CJ. Impact assessment of WHO TobReg proposals for mandated lowering of selected mainstream cigarette smoke toxicants. *Regul Toxicol Pharmacol* 2017; 86 : 332-48.
74. World Health Organization. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Further Development of the Partial Guidelines for Implementation of Articles 9 and 10 of the WHO FCTC. FCTC/COP/7/9; 2016. Available from: [http://www.who.int/fctc/cop/cop7/FCTC\\_COP\\_7\\_9\\_EN.pdf?ua=1](http://www.who.int/fctc/cop/cop7/FCTC_COP_7_9_EN.pdf?ua=1), accessed on June 20, 2017.
75. Global Adult Tobacco Survey-2, Factsheet. New Delhi: Ministry of Health and Family Welfare, Government of India; 2010. Available from: [http://www.searo.who.int/india/mediacentre/events/2017/gats2\\_india.pdf?ua=1](http://www.searo.who.int/india/mediacentre/events/2017/gats2_india.pdf?ua=1), accessed on August 9, 2017.
76. Mishra GA, Pimple SA, Shastri SS. An overview of the tobacco problem in India. *Indian J Med Paediatr Oncol* 2012; 33 : 139-45.
77. Kaur J, Jain DC. Tobacco control policies in India: Implementation and challenges. *Indian J Public Health* 2011; 55 : 220-7.
78. Kaur J, Thamarangsi T, Rinkoo AV. Regulating smokeless tobacco and processed areca nut in South-East Asia region: The journey so far and the road ahead. *Indian J Public Health* 2017; 61 : S3-6.
79. Food and Drug Administration. Tobacco product standard for n- nitrosonornicotine level in finished smokeless tobacco products. *Fed Regist* 2017; 82 : 8004-53.
80. Rutqvist LE, Curvall M, Hassler T, Ringberger T, Wahlberg I. Swedish snus and the GothiaTek® standard. *Harm Reduct J* 2011; 8 : 11.
81. Peeters S, Gilmore AB. Transnational tobacco company interests in smokeless tobacco in Europe: Analysis of internal industry documents and contemporary industry materials. *PLoS Med* 2013; 10 : e1001506.
82. Tobacco and Related Products Regulations 2016; 2016. p. 2016. No. 507. Available from: [http://www.legislation.gov.uk/uksi/2016/507/pdfs/ukxi\\_20160507\\_en.pdf](http://www.legislation.gov.uk/uksi/2016/507/pdfs/ukxi_20160507_en.pdf), accessed on September 23, 2017.

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