

## **7.5.8-2: UPDATE – TOPOGRAPHY - LITERATURE SUMMARY**

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### **LIST OF ABBREVIATIONS**

BOE	biomarker of exposure
CES	Cigarette Evaluation Scale
ECG	electrocardiogram
ECO	expired carbon monoxide
EEG	electroencephalogram
FTND	Fägerstrom Test for Nicotine Dependence
IVRS	interactive voice response system
NMR	nicotine metabolite ratio
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
PBMC	peripheral blood mononuclear cell
pH	potential of hydrogen
QSU	Questionnaire on Smoking Urges
RT-PCR	reverse transcription polymerase chain reaction
SCQoL	Smoking Cessation Quality of Life Questionnaire
SGRQ	St. Georges Respiratory Questionnaire
ST	smokeless tobacco
U.S.	United States

## **7.5.8-2. TOPOGRAPHY LITERATURE SUMMARY**

### **7.5.8-2.1.Literature Summary on Topography**

This section addresses the 2012 United States (U.S.) Food and Drug Administration’s Modified Risk Tobacco Product Applications Draft Guidance recommendations for “human studies regarding actual use of the product.”

The intent of this literature review is to summarize information in respect of this category.

### **7.5.8-2.2.Literature Search and Review Process**

A comprehensive literature review was conducted through December 2014 that reviewed, among other topics, topography of smokeless tobacco (ST) (Section 7.5.1), and literature summaries were drafted in areas that are important in the assessment of a modified risk tobacco product candidate. A second literature review was conducted for the period of December 08, 2014, to February 06, 2017, to update the original search. During the new search, 1,029 citations were identified, and, after applying predetermined inclusion and exclusion criteria, 165 articles were deemed to be in-scope. In general, the in-scope articles were peer-reviewed and studied ST products commercially available in the U.S.

A keyword assignment exercise was performed, and 13 articles that provide information regarding ST topography were identified. However, as new references became available after December 2014, they were, initially, included in the original narratives if they added new information. Of the 13 articles that provide information on topography in the updated search, one had already been included in the original literature summary in Section 7.5.8-1, even though it was published after the cutoff date. A summary of the remaining 12 articles is provided in Table 7.5.8-2-1.

This section is intended to supplement the previous literature summary of ST topography (Section 7.5.8-1) to provide a current, updated literature summary of ST topography.

### **7.5.8-2.3.Cross-sectional Studies**

Three cross-sectional studies in the updated literature summary evaluated the topography of ST use (Jitnarin, 2016; Liu, 2015; Mushtaq, 2016). These studies provide data regarding the use of ST in natural environments, in which the subjects may use the product as they would without the limitations inherent in a controlled setting.

Liu et al. (2015) reported ST use statistics in their cross-sectional study of ST (chew and snuff) risk perceptions. Subjects were adolescents (n = 53, mean age = 17 years) and adults (n = 63, mean age = 33.6 years) who were residents of four Appalachian counties in Ohio. The highest proportion of adolescent ST users (47.8%) used 2 to 4 tins or pouches of ST per week, and 26.1% used greater than 5 tins or pouches a week. The highest proportion of adult ST users (50.0%) used 2 to 4 tins or pouches of ST per week, and 31.6% used greater than 5 tins or pouches a week. The frequency of ST use was slightly higher among adult ST users

than among adolescent ST users; 65.8% of adults reported using ST 6 or 7 days per week, as compared with 43.5% of adolescents.

One of the studies published during the review period examined the topography of ST use in a specific occupation. [Jitnarin et al. \(2016\)](#) performed a secondary analysis of baseline data from two large cohort cross-sectional studies to examine ST use by male U.S. firefighters. In total, 207 of the 1,474 participants (14 percent) had complete and useable data on ST use at baseline and were included in the secondary analysis. Of these firefighters, 15.9 percent initiated ST use after joining the fire service. Mean ST use was similar between firefighters who initiated ST use before joining the fire service (2.85 cans per week of ST) and those who initiated ST use after joining the fire service (2.9 cans per week of ST). Weekly ST consumption reported by [Jitnarin et al. \(2016\)](#) and by [Mushtaq et al. \(2016\)](#) falls within the range of baseline weekly ST consumption presented in Section 7.5.8-2.5.

#### **7.5.8-2.4. Longitudinal Observational Studies**

Two of the articles published during the review period reported the results of longitudinal studies.

[Flanagan et al. \(2016\)](#) assessed cigarette and ST use in pregnant Alaskan women at baseline and delivery and assessed nicotine and tobacco biomarkers in the women and their infants at delivery. The study enrolled 30 ST users: 10 users of commercial ST and 20 users of iqmik (“a homemade chewing tobacco made with tobacco leaves and ash”). ST use was quantified as commercial ST-size cans, or iqmik cans of equivalent size (1.2 oz. per can), per week. At study baseline, ST users overall reported using a mean of 0.8 cans per week (commercial ST: 1.2 cans per week; iqmik: 0.6 cans per week); after delivery, ST users overall reported using a mean of 0.9 cans of ST per week.

[Mushtaq et al. \(2015\)](#) examined ST use, among other factors related to tobacco abstinence, in 959 exclusive ST users who registered for services with the Oklahoma Tobacco Helpline, of whom 374 completed a 7-month follow-up survey. Of those who completed the follow-up survey, 61% of participants had used ST products for at least 20 years, and 68% had used three or more cans or pouches of ST per week. Of subjects who had abstained from tobacco for at least 30 days at follow-up, 43.0% had used ST products for at least 20 years; 54.5% had used less than one can or pouch of ST per week, and 43.6% had used three or more cans or pouches of ST per week at registration. Mean duration and ST use at registration were higher in subjects who had not abstained from tobacco for at least 30 days at follow-up; 57.0% had used ST products for at least 20 years; 45.5 % used less than one can or pouch of ST per week, and 56.4% used three or more cans or pouches of ST per week.

#### **7.5.8-2.5. Interventional Studies**

A number of interventional studies published during the updated review period only provided baseline data on ST topography ([Arimilli, 2017](#); [Buzzell, 2016](#); [Ebbert, 2016](#); [Pickworth, 2014](#)). The mean rate of baseline ST use ranged from to 1.7 ([Buzzell, 2016](#)) to 7.7 ([Pickworth, 2014](#)) tins per week. The mean duration of ST use in these studies ranged from 21.72 months ([Buzzell, 2016](#)) to 20.6 years ([Arimilli, 2017](#)).

Three studies provided topography data during the interventional phase ([Hatsukami, 2016](#); [Krautter, 2015](#); [Ogden, 2015](#)). [Hatsukami et al. \(2016\)](#) investigated tobacco-product switching in male and female adult daily smokers who did not regularly use other nicotine or tobacco products and were randomized to switch from cigarettes to either snus (n = 196) or nicotine gum (n = 195) for 12 weeks. Subjects were encouraged to use only the assigned product and at least six to eight pieces a day for about 30 minutes each or optimally every 1 to 2 hours, and more if necessary. Per instructions described for nicotine gum, all participants (regardless of randomization group) were advised to reduce consumption by half during weeks 7 to 9 and three-quarters between weeks 10 to 12 to minimize the risk of persistent use or withdrawal from the products when they were no longer provided. At Week 6, prior to tapering, the mean ( $\pm$ SD) number of snus pouches used per week was 39.1 ( $\pm$ 24.0) among the subjects in the snus group, which reduced to less than 20 snus pouches per week by Week 12. [Ogden et al. \(2015\)](#) investigated the change in health status of current adult cigarette smokers who switched to tobacco-heating cigarettes, snus, or an ultra-low yield, tobacco-burning cigarettes for 24 weeks. Over the duration of the study, average daily assigned product usage (either tobacco-heating cigarettes, snus pouches, or ultra-low yield, tobacco-burning cigarettes) was 20.8 (range: 18.2–23.5) for the tobacco-heating cigarette group, 10.6 (range: 9.5–11.5) for the snus group, and 24.6 (range: 21.5–26.6) for the ultra-low yield, tobacco-burning cigarette group.

[Krautter et al. \(2015\)](#) conducted a study of consumption patterns and biomarkers of exposure in cigarette smokers (n = 167, mean age = 40.6 years) switched to snus, dissolvable tobacco products, dual use of snus and cigarettes, or tobacco abstinence. Daily use rates of all the smokeless test products were uniform throughout the 5-day intervention period, with no statistical differences between the days. At baseline, subjects randomized to the snus or dual use group smoked 16.33 or 19.24 cigarettes per day, respectively. During the intervention period, subjects in the snus group used approximately 6 pouches per day and did not smoke any cigarettes. Subjects in the dual use group used approximately 3 pouches of snus per day and their cigarette consumption decreased to approximately 7.6 cigarettes per day.

#### **7.5.8-2.6.Updated Findings**

Information on ST topography in the updated literature summary, while largely limited to years of use and daily or weekly rates of use, is consistent with that seen in the initial literature summary. The conclusions from the initial literature summary (Section [7.5.8-1](#)) have not changed based on the updated literature review.

A tabular summary of the topography literature summary is presented in [Table 7.5.8-2-1](#).

**Table 7.5.8-2-1: Literature Review for Topography**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Arimilli, 2017)	Gene expression profiles associated with cigarette smoking and moist snuff consumption	<p>This was a single-blind, cross-sectional study. Microarray analysis of gene expression in PBMCs isolated by flow cytometry from moist snuff consumers (consumption of <math>\geq 2</math> cans per week of moist snuff per week for <math>\geq 3</math> years and ECO level 0-5 ppm), cigarette smokers (consumption of <math>\geq 10</math> cigarettes per day for <math>\geq 3</math> years and ECO level 10-100 ppm), and nonusers of tobacco (<math>\geq 5</math> years and ECO level of 0-5 ppm) (n = 40/cohort). Subjects were males aged 35-60 years, inclusive. The majority of subjects were Caucasian.</p> <p>Objective: To characterize gene expression profiles in PBMCs from moist snuff consumers as compared with PBMCs from consumers of cigarettes and nonconsumers of tobacco.</p>	<p>Number of PBMCs and proportion of CD2<sup>+</sup> cells, CD56<sup>+</sup> cells, monocytes, and B lymphocytes assessed by flow cytometry.</p> <p>Gene expression analysis of &gt;47,000 transcripts assessed by microarray analysis.</p> <p>Gene expression of differentially expressed genes assessed by quantitative RT-PCR.</p>	Moist snuff users had used the product for an average of 20.6 years, and had used a mean of 6.3 cans per week in the month before enrollment.	Limitation: Females were excluded.

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Buzzell, 2016)	Using electrophysiological measures to assess the consumer acceptability of smokeless tobacco products	<p>This was a randomized crossover study. EEG was used in combination with traditional subjective measures to assess acceptability (liking) of four ST products (Verve® discs, Ariva® dissolvables, Skoal® snuff, Camel® snus) or Nicorette® lozenges over five study visits. Subjects (n = 30, 28 Caucasian, one African American, and one Asian American) were male ST users, aged 19 to 61 years, inclusive (mean age = 22.2 years).</p> <p>Objective: To characterize cognitive changes associated with tobacco-product use by assessing EEG measures of attention/arousal in combination with traditional subjective measures.</p>	<p>At each study visit, subjects completed questionnaires (modified FTND [first lab visit only], modified CES, modified QSU-brief) that subjectively assessed smoking urges (before and after product use) and evaluated the product (after product use). Subjects also practiced and completed an oddball cognitive task while EEG was recorded. A resting state EEG recording was taken before and after product usage to index cortical arousal. Subjects were exposed to the product for 30 minutes at each visit, with 90-second resting state and EEG recordings taken every 6 minutes.</p>	At enrollment, subjects used ST at a mean rate of 1.7 tins or 8.9 pouches/lozenges per week for a mean of 21.72 months (SD = 15.01).	Limitations: (1) The study did not include any females; and (2) five of the ST users were dual users, potentially confounding findings.

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Ebbert, 2016)	Nicotine metabolite ratio is associated with lozenge use but not quitting in smokeless tobacco users	This was a randomized trial. Subjects (n = 152, mean age = 36.5) were 97% male and 96% white/non-Hispanic. Objective: To evaluate whether NMR (higher NMR corresponds to faster nicotine clearance) correlates with nicotine lozenge use and tobacco abstinence.	Secondary analysis of ST users enrolled in one arm of a large randomized trial. Subjects received quitting support materials and lozenges plus three coaching phone calls. Measurements include Severson ST Dependency Scale, self-reported lozenge use, and NMR. Self-reported tobacco and lozenge use was assessed at 3 months.	At baseline, subjects had been using ST for a mean of 15.0 years, at a mean rate of 5.6 tins, pouches or cans per week.	Limitations: (1) Small sample size, and (2) self-reported abstinence and lozenge use.
(Flanagan, 2016)	Fetal exposure to carcinogens with tobacco use in pregnancy: Phase 1 MAW Study findings	This was a longitudinal study. Subjects (n = 148, age ≥18) were Alaskan Natives. Among subjects, 64 were nonusers of tobacco, 54 were smokers, and 30 were ST users (n = 10 commercial ST users; n = 20 iqmik users). Objective: To examine BOEs to nicotine and NNK among maternal-infant pairs at delivery as a potential biomarker feedback intervention to motivate tobacco cessation during pregnancy.	Demographic and tobacco use data were collected from a convenience sample of pregnant Alaskan smokers, ST users, and nonusers during pregnancy. Maternal and neonatal urine samples collected at delivery were analyzed for maternal urine cotinine and neonatal urine NNAL levels.	At baseline, ST users overall reported using a mean of 0.8 ST cans per week. However, the mean number of equivalent size cans chewed per week by iqmik users was half (0.6, SD = 0.3) the number of cans per week reported by commercial ST users (1.2, SD = 1.1). After delivery, ST users reported using a mean of 0.9 (SD = 1.06) ST cans per week.	Limitations: (1) Small sample size; (2) Multiproduct users were assigned to a tobacco group based on the tobacco type most frequently used; and (3) Subjects were Alaskan pregnant women, and therefore not representative of the general population.



**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Hatsukami, 2016)	Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching	<p>This was a randomized, parallel-group study. Male and female (47.1%) daily smokers aged 18 to 70 years (mean age = 43.9) who did not regularly use other nicotine or tobacco products were randomized to switch from cigarettes to either snus (n = 196) or nicotine gum (n = 195) for 12 weeks. Subjects were 81.8% non-Hispanic white. Subjects were encouraged to use only the assigned product and at least 6-8 pieces a day for about 30 min each or optimally every 1-2 h, and more if necessary. Per instructions described for nicotine gum, all participants (regardless of randomization group) were advised to reduce consumption by half during Weeks 7-9 and three-quarters between Weeks 10-12 to minimize the risk of persistent use or withdrawal from the products when they were no longer provided.</p> <p>Objectives: (1) To compare snus versus nicotine gum on the extent to which smokers can completely switch to these products, the pattern of product use, and effects on biomarkers of exposure; and (2) to compare the effects of snus and nicotine gum on withdrawal symptom relief, product evaluation, and adverse events in smokers.</p>	<p>Urine samples were collected to analyze for carcinogenic tobacco-specific nitrosamine metabolites NNAL and N'-nitrosonornicotine and their glucuronides) and nicotine metabolites (total cotinine and nicotine equivalents) levels. Urine biomarkers were assessed at baseline and Week 4. Daily self-reported product use and cigarette use were assessed. Responses to products (satisfaction, psychological reward, sensation in mouth, and aversion) were assessed by questionnaire. Smoking abstinence and the use of other tobacco products were assessed at follow-up.</p>	<p>At Week 6, prior to tapering, the mean (<math>\pm</math>SD) number of snus pouches used per week was 39.1 (<math>\pm</math>24.0) among the subjects in the snus group, which reduced to less than 20 snus pouches per week by Week 12.</p>	<p>Limitations: (1) Investigational study; assigned product use is not reflective of ad libitum use in general population. (2) Study participation was restricted to smokers interested in quitting; therefore, results may not be broadly applicable to the general population.</p>



**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Jitnarin, 2016)	Prevalence and correlates of late initiation of smokeless tobacco in US firefighters	<p>This study was a secondary analysis of the baseline assessments from two firefighter surveillance cross-sectional studies, which included male firefighters from the International Association of Fire Chief's Missouri Valley Region and 20 career departments across 14 U.S. states and territories. The combined data set included 1,474 male firefighters, of whom 207 had complete and useable data on ST use at baseline and were included in this secondary analysis. Mean ages of subjects were 36.4 and 36.8 years for those who used ST before and after joining the service, respectively. About 89% of the subjects who used ST before joining the service were white, and about 80% of the subjects who used ST after joining the service were white.</p> <p>Objective: To examine characteristics associated with late ST initiation in a sample comprising male career firefighters from two large cohort studies.</p>	<p>Age-standardized prevalence of ST use before and after joining the fire service was assessed by questionnaire. Demographics, occupational history, and physical and behavioral health were assessed by questionnaire.</p>	<p>Fourteen percent (207/1,474) of firefighters in the combined sample reported using ST. Of these firefighters, 15.9% initiated ST use after joining the fire service. The mean amount of snuff used was 2.85 (SD = 3.06) cans/week by ST users before joining the fire service and 2.90 (SD = 3.13) cans/week for ST users after joining the fire service.</p>	<p>Strength: The study used a large sample size as well as standardized and validated health measures.</p> <p>Limitation: (1) The study did not include female firefighters; and (2) the study was cross-sectional, which limited the authors' ability to explore longitudinal relationships.</p>

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Mushtaq, 2016)	Assessment of the tobacco dependence screener among smokeless tobacco users	This was a cross-sectional study. Subjects (n = 95, aged 18 to 64 years) were exclusive ST users living in Oklahoma who were recruited through e-mail distribution lists between May 2010 and Dec 2010.  Objective: To evaluate a self-administered 10-item scale termed as a measure of tobacco dependence among ST users.	Demographics, tobacco use characteristics, and ST dependence were assessed by the modified Tobacco Dependence Screener and Fagerstrom Test for Nicotine Dependence questionnaires. Salivary cotinine levels were assessed in saliva samples.	All 95 exclusive ST users were male, and the majority were everyday users (92%). The mean age of regular ST use was 18.8 years, and average consumption of ST was 3.6 cans or pouches per week.	Limitations: (1) All subjects enrolled were male. (2) Subjects were from a single state in the U.S.
(Krautter, 2015)	Consumption patterns and biomarkers of exposure in cigarette smokers switched to snus, various dissolvable tobacco products, dual use, or tobacco abstinence	A randomized, controlled, open-label, parallel group study. Subjects (94.6% non-Hispanic, 78.4% white, 53.9% male, mean age = 40.6 years) included 167 healthy U.S. male and female smokers.  Objective: To evaluate changes in tobacco product use and levels of selected BOEs for smokers who switched to exclusive use of one of six conditions: Camel snus, sticks, strips or orbs, controlled dual use of cigarettes and Camel snus, or tobacco abstinence.	Subjects were randomized to six groups (n = 25-30/group) and allowed to smoke cigarettes ad libitum for 1 day, followed by exposure to the designated product for 5 days. The levels of BOEs in plasma, whole blood, urine, and feces were assessed before and after switching. Nicotine dependence and withdrawal were assessed by questionnaire.	Daily use rates of all the smokeless test products were uniform throughout the intervention period, with no statistical differences. Of note was the use of approximately 6 pouches per day in the exclusive Snus group as compared with approximately 3 pouches per day in the dual use group.	Limitations: (1) Small sample size. (2) Interventional study.

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Liu, 2015)	Risk perceptions of smokeless tobacco among adolescent and adult users and nonusers	<p>This was a cross-sectional study. Subjects were adolescents (n = 53, mean age = 17, 66% male, 84.9% white, and 86.8% non-Hispanic) and adults (n = 63, mean age = 33.6, 79.4% male, 98.4% white, and 95.2% non-Hispanic) who were residents of four Appalachian counties in Ohio. ST in this study includes chew and snuff.</p> <p>Objective: To examine risk perceptions of ST products among adolescent and adult users and nonusers in the Appalachian region of Ohio.</p>	ST use, perceptions of ST-related health risks, ST safety, and the relative safety of ST as compared with cigarettes were assessed by questionnaire.	In the study, 43.4% of adolescents and 60.3% of adults reported daily use of chew or snuff or use on most days. Of the adolescent ST users, 17.4% used snuff only, 34.8% used chew only, and 47.8% used both chew and snuff. The majority of adolescent ST users (47.8%) used 2 to 4 tins or pouches of ST per week, and 26.1% used greater than 5 tins or pouches a week. The use of snuff was greater in the adult population; 60.5% used snuff only, 15.8% used chew only, and 23.7% used both chew and snuff. The majority of adult ST users (50.0%) used 2 to 4 tins or pouches of ST per week, and 31.6% used greater than 5 tins or pouches a week. The frequency of ST use was slightly higher among adult ST users than among adolescent ST users; 65.8% of adults reported using ST 6 or 7 days per week, as compared with 43.5% of adolescents.	Limitations: (1) Subjects were from Appalachian region of Ohio and not representative of the general U.S. population, and (2) the study excluded females.

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Mushtaq, 2015)	Predictors of smokeless tobacco consumption cessation among telephone quitline participants	Subjects (n = 374) were exclusive ST users who registered with the Oklahoma Tobacco Helpline between Mar 2004 and Jun 2012 and completed an evaluation survey 7 months after registration. Subjects (mean age = 41.3 years) were 83% white. Objective: To examine factors related to tobacco abstinence among exclusive ST users registering for services with the Oklahoma Tobacco Helpline Longitudinal study.	Sociodemographic information, tobacco use behavioral factors, view on quitting, and medical history were assessed at baseline by questionnaire. Tobacco use in the previous 30 days was assessed at 7-month follow-up by questionnaire.	In total, 61% of participants had used ST products for at least 20 years, and 68% had used three or more cans or pouches of ST per week. At the 7-month follow-up, 43.0% of subjects had abstained from tobacco for at least 30 days. Of these subjects, 54.5% used 1 or less than 1 can or pouch of ST per week, and 43.6% used more than three cans or pouches of ST per week at enrollment. Of subjects who had not abstained from tobacco for at least 30 days at follow-up, 57.0% had used ST products for at least 20 years; 45.5% used one or less than one can or pouch of ST per week; and 56.4% used more than three cans or pouches of ST per week at enrollment.	Limitations: (1) Females excluded. (2) Participants were from a single state in the U.S.

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Ogden, 2015)	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology	<p>This was a randomized, multi-center study. Intent-to-treat samples (n = 163, mean age = 42) were 49.1% male, 73% not Hispanic/Latino, and 81.6% white. Per protocol samples (n = 120, mean age = 42) were 47.5% male, 75.8% not Hispanic/Latino, and 84.2% white. ST product used in the study includes snus (Camel SNUS: Frost, Spice, and Original varieties).</p> <p>Objective: To investigate whether current adult cigarette smokers, switched to tobacco-heating cigarettes, snus, or an ultra-low machine yield, tobacco-burning cigarettes, had improvement in health status measures, and biomarkers of tobacco exposure and biological effect.</p>	<p>Subjects were randomized to use tobacco-heating cigarettes, snus, or an ultra-low machine yield tobacco-burning cigarette for 24 weeks. Self-reported tobacco use was recorded daily by IVRS. Self-reported health status was assessed by the SGRQ and the SCQoL at baseline and every 4 weeks. Expired carbon monoxide concentrations were assessed at every 2-week visit. An ECG was performed at screening and Week 24. Spirometry was performed before and after administration of a bronchodilator at baseline and Weeks 12 and 24. Clinical laboratory evaluations were conducted at Weeks 0, 12, and 24.</p>	<p>Over the duration of the study (i.e., Weeks 1–24), average daily counts of assigned product usage were 20.8 (range: 18.2–23.5) for the tobacco-heating cigarette group, 10.6 (range: 9.5–11.5) for the snus group and 24.6 (range: 21.5–26.6) for the ultra-low machine yield tobacco-burning cigarette group.</p>	<p>Limitations: (1) This was an interventional study. (2) Occasional usage of other nicotine products was reported during nine of the 13 2-week intervals (i.e., non-compliance).</p>

**Table 7.5.8-2-1. Literature Review for Topography (continued)**

Author	Title	Study Methods	Primary Study Measurements	Author's Findings Related to Topography	Comments <sup>1</sup>
(Pickworth, 2014)	Nicotine absorption from smokeless tobacco modified to adjust pH	<p>This was a crossover study. Subjects (n = 7, all men, 4 whites, and 3 African Americans) were regular ST users. Subjects' average age was 45 years (range: 28-62).</p> <p>Objective: To measure nicotine absorption after experimentally manipulating pH and flavorings of a single referent product.</p>	<p>A single unflavored referent ST product (pH 7.7) was amended to either a high pH (8.3) or a low pH (5.4) with sodium carbonate or citric acid, respectively. At each of three study visits, subjects were exposed to one of three products (pH 7.7, 8.3 or 5.4) for 30 minutes. Plasma nicotine levels were assessed from blood samples collected 10 minutes before, and at 5, 10, 15, 20, 30, 35, 45, and 60 minutes after initiation of product use. Smoking history was assessed by questionnaire at baseline. Nicotine dependency, subjective strength of the product, and product experience were assessed by questionnaire at each study visit during and after product use.</p>	At baseline, subjects had been using ST for a mean of 15 years, at a mean rate of 1.1 (range: 0.3-2) tins or pouches per day.	Limitation: (1) Small sample size. (2) Interventional study.

<sup>1</sup> Comments are largely author-defined, methodological strengths and limitations. In addition, recall bias may have affected studies that only inform ST topography with baseline data.

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