7.5.6-2: UPDATE - HEALTH RISKS - LITERATURE SUMMARY

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LIST OF ABBREVIATIONS

AE	adverse event
aFOR	adjusted fecundability odds ratio
AHS	Agricultural Health Study
ATP	alternative tobacco and nicotine product
CHD	coronary heart disease
CI	confidence interval
C. sputigena	Capnocytophaga sputigena
DCF-DA	2´,7´-dichlorofluorescin diacetate
FDA	Food and Drug Administration
FOR	fecundability odds ratio
γ-H2AX	γ-histone 2AX
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor;
HIV	human immunodeficiency virus
HNC	head and neck cancer (i.e., oral, pharyngeal, or laryngeal cancer)
HR	hazard ratio
ICSS	intracranial self-stimulation
INHANCE	International Head and Neck Cancer Epidemiology
IP-10	interferon gamma-induced protein 10
LC/MS	liquid chromatography/mass spectrometry
MDC	monodansylcadaverin
MRTPA	Modified Risk Tobacco Product Application
MTT	3-(4,5-dimethyl thiazolyl-2)-2,5-diphenyltetrazolium bromide
NNAL	4-(methylnitrosamino)-1(3-pyridyl)-butanol
NRT	nicotine replacement therapy
NS	nasal spray
NSDUH	National Survey on Drug Use and Health
OR	odds ratio
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
RANTES	regulated on activation, normal T cell expressed and secreted
ROS	reactive oxygen species
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
ST	smokeless tobacco
STAE	smokeless tobacco aqueous extract
TTP	time-to-pregnancy
TSNA	tobacco-specific N-nitrosamine
TUS-CPS	Tobacco Use Supplement to the Current Population Survey
UDB	unhealthy dieting behavior
U.S.	United States

7.5.6-2. HEALTH RISKS LITERATURE SUMMARY

Section VI (A) (1) of the Food and Drug Administration's (FDA's) Modified Risk Tobacco Product Applications (MRTPAs) Draft Guidance (2012) recommends that applicants submit data and information on "human studies that show the product's use will result in a signification reduction in harm and the risk of tobacco-related disease to individual tobacco users."

In particular, the FDA's MRTPA Draft Guidance recommends that applicants address:

- the health risks associated with initiating use of the candidate product as compared with never using tobacco products;

- nonclinical and/or human studies that demonstrate that use of the candidate product is expected to result in a measurable and substantial reduction in morbidity or mortality to individual tobacco users based on the effects of the candidate product on an endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict an effect on reducing harm or disease;

- the health risks associated with use of the candidate product as compared with the use of other tobacco products on the market, including tobacco products within the same class of products;

- the changes in health risks to users who switch from using another tobacco product to using the candidate product, including tobacco products within the same class of products;

- the health risks associated with switching to the candidate product as compared with quitting the use of tobacco products;

- the health risks associated with using the candidate product in conjunction with other tobacco products; and

- the health risks associated with switching to the candidate product as compared with using an FDA-approved tobacco cessation medication.

The intent of this literature review is to summarize information relevant to these categories.

7.5.6-2.1. Literature Search and Review Process

A comprehensive literature review was conducted through December 2014 that reviewed, among other topics, the health effects of smokeless tobacco (ST) (Section 7.5.1), and literature summaries were drafted in areas that are important in the assessment of the candidate product. 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 as possibly relevant to topics covered in the literature review, 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 to

determine how many of those articles provide information about the human or preclinical health risks of ST. There were 13 and 5 articles for each of the topics, respectively. In addition, two meta-analysis articles and one article published after the cut-off date of February 06, 2017 are included in Section 7.5.6-1.

This section is intended to supplement the previous literature review (Section 7.5.6-1) to provide a current, updated literature review of the health risks of ST.

7.5.6-2.2. Literature Review on Health Effects – Human

7.5.6-2.2.1.   Health Effects of Smokeless Tobacco

The majority of the articles found in the literature search discussed health effects observed during investigations of short-term use (1 year or less) of ST. Adverse events (AEs) were reported as part of studies of other topics related to tobacco use. In general, the AEs reported were mild or moderate in intensity and were reported at the frequencies expected. For example, Carpenter et al. (2016) conducted an investigation of quit attempts by daily smokers randomized to snus or no intervention and found that AEs were more frequently reported by the snus group than the control participants. Carpenter reported there were "no snus-related, FDA-defined instances of serious adverse events." Of participants randomized to the snus group, 98 (16 percent) were using snus regularly at the end of the intervention period.

There was one new longitudinal study investigating the health associations of long-term exposure in the additional literature. Andreotti et al. (2016) analyzed the data from the Agricultural Health Study (AHS) to evaluate the use of cigarettes, other combustible tobacco, and ST and their potential cancer risks. It was noted that the AHS population had a higher use of ST and a lower risk of lung cancer than the United States' general population. The lower risk of lung cancer has been attributed partially to the lower prevalence of cigarette smoking in the AHS population compared to the general U.S. population. Compared with never use of tobacco, exclusive cigarette use was significantly associated with an increased risk of total cancers (HR [hazard ratio] = 1.51; 95% CI [confidence interval], 1.39-1.63) and smoking-related cancers (HR = 2.89; 95% CI, 2.60-3.25). Exclusive ever-use of ST was also significantly associated with smoking-related cancers (HR = 1.27; 95% CI, 1.00-1.62) compared with never use of tobacco. Compared to never use of tobacco, exclusive use of chewing tobacco was associated with smoking-related cancers, including lung and head and neck, while exclusive use of snuff was associated with gastrointestinal cancer.

A cross-sectional study by Fu et al. (2014) examined the differences between exclusive use of snuff (n = 716), exclusive use of chewing tobacco (n = 901), dual use of snuff and chewing tobacco (n = 931), and non-smokeless tobacco users (n = 23,442) in relation to psychiatric disorders via structured diagnostic interviews. After controlling for sociodemographic variables and cigarette smoking, exclusive chewing tobacco use, exclusive snuff use, and dual use of snuff and chewing tobacco were all associated with alcohol disorder (all p-values < 0.05). Panic disorder, specific phobia, and inhalant/solvent use disorder were associated with use of chewing tobacco (all p values < 0.05); cannabis use disorder was associated with exclusive snuff use (p < 0.05).

7.5.6-2.2.2. Updated Findings

Information on health effects of ST use in adults in the update literature review is consistent with that seen in the initial literature review. The conclusions from the initial literature review (Section 7.5.6-1) have not changed based on the updated literature review.

A tabular summary of the literature informing the human health risks of ST is presented in Table 7.5.6-2-1.

Table 7.5.6-2-1:   Literature Review for Human Health Effects of Smokeless Tobacco Products

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Carpenter et al., 2016)	Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers	Adult smokers (N = 1,236) throughout U.S. who denied intention to quit in the next 30 days were randomized to receive (n = 626; mean age: 48.7 years; 70% female; 89% Caucasian) or to not receive (n = 610; mean age: 48.7 years; 65% female; 87% Caucasian) free snus during a 6-week sampling period. Subjects were then advised to quit all tobacco use and were followed for 1 year. Objective: The primary objective was to examine abstinence outcomes in the snus and control groups.	Abstinence outcomes among smokers who did not want to quit and who were randomized to receive free samples of snus versus not were compared. All subjects were advised to quit all tobacco products. Abstinence outcomes included self-reported quit attempts, floating abstinence (any 7-day period of non-smoking), and 7-day point-prevalence abstinence at 6 months and 12 months.	AEs were more frequent in the snus group, specifically 38% of participants in the snus group (n = 240) reported a total of 412 AEs, compared with 300 AEs reported by 31% of control participants. Self-rated symptom severity was similar between groups, and "there were no snus-related, FDA-defined instances of serious adverse events." "The most common side effects reported were nausea (12%), burning in throat or mouth (10%), and heartburn (8%) in the snus group; and headache (16%), nausea (10%), and dry mouth (8%) in the control group." Within the snus group, 82% used snus at least once, and 16% were using snus regularly at the end of the sampling period. Compared with control participants, smokers in the snus group were less likely to make any quit attempt (RR = 0.83; 95% CI, 0.70-1.00), and any 24-hour quit attempt (RR = 0.77; 95% CI, 0.63-0.95). There were no group differences in rates of floating or point prevalence abstinence, either at the 6-month or 12-month follow-up.	Strengths: Data were from a large nationwide U.S. cohort. Limitations: (1) Only one product was used; (2) study sample consisted primarily of Caucasian women; (3) participants were smokers who did not want to quit, which may create the impression that it was methodologically biased against snus; and (4) there is a lack of biochemical verification of abstinence.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Allen et al., 2016)	Gender differences in snus versus nicotine gum for cigarette avoidance among a sample of US smokers	A randomized, study of daily smokers for the past year who were willing to switch from cigarettes to snus or nicotine gum; n = 391; aged = 18-70 years. Snus group: n = 196, 45% women. Nicotine gum group: n = 195, 49% women. Objective: To examine "gender differences in response to snus versus nicotine gum for cigarette avoidance, as a means of harm reduction."	Smoking avoidance and biomarkers were assessed, and a secondary analysis comparing men and women by randomization to study product was conducted.	"Within the snus group, more women than men reported vomiting (6.7% versus 0.9%; p = 0.05), nausea (40.4% versus 23.4%; p = 0.03), and stomach ache (18% versus 5.6%; p = 0.02)." "Regardless of randomization, women used less study product than men and were less sensitive to the oral administration of nicotine in terms of smoking avoidance. Although men in this study tended to use snus at least as much as the nicotine gum, gum led to lower levels of total NNAL than snus and greater end of treatment cigarette avoidance rates. These results suggest that regardless of gender, no greater beneficial effects are observed with snus over nicotine gum as a harm reduction method."	Strengths: The study compared the AE profiles associated with snus use between genders. Limitations: (1) Men were more likely than women to use snus if they were assigned to that group. (2) Women also smoked more cigarettes per week than men during the treatment period. Therefore, the differences in reported AEs may be influenced by the differences in snus and cigarette usage between males and females.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Andreotti et al., 2016)	Tobacco use and cancer risk in the Agricultural Health Study	A prospective cohort study that enrolled former smokers; current smokers; and users of pipes, cigars, cigarillos, chewing tobacco, or snuff on a regular basis for ≥6 months; n = 84,015; age at enrollment ranged from <30 to >70 years. Among men and women who used tobacco, cigarette use was most common (84.9% and 98.6%, respectively). Of tobacco users, 9.5% exclusively used smokeless tobacco (12% of men, 1.2% of women). Of tobacco users, 11.5% used both cigarettes and smokeless tobacco (14.6% of men, and 1.2% of women). Objective: To examine the incidence of cancer in relation to the use of cigarettes, other combustible tobacco products, and smokeless tobacco (chewing tobacco and snuff).	Cancer incidence in relation to exclusive use of six tobacco products in the Agricultural Health Study was assessed. The added cancer risks associated with use of cigarettes and other tobacco products were also examined.	There were 9,134 total cancer cases diagnosed during the follow-up period (median = 16 years), and of these, 3,401 cases occurred at smoking-related sites. Compared to never use of tobacco (n = 41,026), exclusive cigarette use was associated with an increased risk of total (HR = 1.51; 95% CI, 1.39-1.63) and smoking-related cancers (HR = 2.89; 95% CI, 2.60-3.25). Compared to never use of tobacco, exclusive ever-use of smokeless tobacco was significantly associated with smoking-related cancers (HR = 1.27; 95% CI, 1.00-1.62). Compared to never use of tobacco, exclusive use of chewing tobacco was associated with smoking-related cancers, including lung and head and neck, while exclusive use of snuff was associated with gastrointestinal cancer. Dual cigarette-smokeless tobacco users generally had cancer risks similar to exclusive cigarette use.	Strengths: (1) Data were generated from a large, prospective study with a long median follow-up time (16 years). (2) Prevalence of ST use in the study population was higher than in the general U.S. population. Limitations: (1) At the time of the study, the prevalence of smokers at enrollment was lower than in the general U.S. population, and the smokers used somewhat less than the average U.S. smoker in the 1990s. (2) Participant enrollment stopped in 1997, so changes in tobacco use trends, especially in younger individuals, may not be accounted for. (3) Analysis of non-cigarette products was limited to ever versus never for both exclusive and dual use, limiting data on duration or frequency of use.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Bandiera, Wilkinson, Perry, & Loukas, 2016)	Associations between tobacco and nicotine product use and depressive symptoms among college students in Texas	A cross-sectional statewide convenience sample study (n = 5,438; 63.8% of subjects were female; aged 18-29) was conducted. Cigarette use and use of four ATPs (ST/snus, large cigars/cigarillos/little cigars, hookahs, and e-cigarettes) were considered. Objective: To examine associations of ATP use with depressive symptoms using an online survey of 18-29 year olds attending one of 24 colleges in Texas. A multilevel logistic regression model was used to examine the associations between each of the ATPs and the dichotomous dependent variable of depressive symptoms.	Sex, age, type of college (2-year or 4-year), and race/ethnicity were included as covariates. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression 10 Scale.	"E-cigarettes were the only ATP that were uniquely associated with depressive symptoms. The association was significant even after controlling for current cigarette use, socio-demographic characteristics, and current use of the other three ATPs. None of the interactions between each of the tobacco products and race/ethnicity or gender were significant."	Strengths: The study used a large sample size and used well-accepted standard methods for analyzing clinical depression symptoms. Limitation: The study only sampled college students, which may limit its generalizability to other young adult populations.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Hatsukami et al., 2016)	Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching	A randomized study in daily smokers who do not regularly use other nicotine or tobacco products. Baseline characteristics were measured, then participants were assigned to either a snus or nicotine gum cohort and encouraged to use only the assigned product; n = 391; 52.9% male; 81.8% non-Hispanic whites; aged 18-70 years, mean = 43.9 years. Snus group: n = 196, 45.4% female. Gum group: n = 195, 48.7% female. Objectives: "[T]o 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. The secondary goals were to compare the effects of both products on withdrawal symptom relief, product evaluation and adverse events."	Urine samples were collected to analyze for carcinogenic tobacco-specific nitrosamine metabolites and nicotine metabolites levels. At follow-up, 26 weeks after start of treatment, smoking abstinence and use of any other tobacco or medicinal nicotine products were assessed using time line follow-back, and biochemical verification was obtained.	Withdrawal symptoms (excluding cravings) were not significantly altered by product (gum versus snus). AEs were similar between snus and nicotine gum groups, except that mouth sores and excessive salivation occurred significantly more frequently in the snus group (p = 0.020 and p < 0.0001, respectively), and headaches were less frequent in the snus group (p = 0.022). Of treatment-emergent AEs that were definitely or possibly related to snus or gum or that were of unknown cause, the majority were mild. "Snus performed similarly to nicotine gum in cigarette smokers who were interested in completely switching to these products, but was associated with less satisfaction and greater toxicant exposure than nicotine gum."	Strengths: Detailed breakdown of adherence to sole use of the study product versus continuing use of cigarettes as well as study product was provided. Limitations: "(1) potential lack of generalizability to a general population of smokers because we examined smokers interested in trying an alternative product in a clinic setting, (2) testing only one snus product, which has lower levels of nicotine and higher TSNA than some of the Swedish snus products, (3) encouragement to use a specified number of pieces of each of the products; (4) implementation of a tapering period, which might have constrained substitution behavior; and (5) not examining the data by gender…"

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Ozga, Felicione, Elswick, & Blank, 2016)	Acute effects of snus in never-tobacco users: a pilot study	Six men (4 Caucasian and 2 African American) and 5 Caucasian women who reported <100 lifetime uses of tobacco and no tobacco use in the last 3 months (aged ≥18 years, range 19-26 years) were included in the study. During a single session, participants used six pouches in ascending dose order (0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine per pouch).

Objectives: To examine "the acute effects of snus on physiological and subjective assessments in a sample of never-tobacco users." | Physiological (heart rate and blood pressure) and subjective measures were assessed. | Dose-dependent increases in average heart rate and systolic blood pressure were observed after pouch use over the baseline values, but were statistically significant ($p < 0.05$) for 8.0 mg nicotine only.

Diastolic blood pressure was increased after consumption of the 8.0-mg nicotine pouch compared with all other nicotine dose levels ($p < 0.05$).

Excessive salivation was significantly increased from prepouch to postpouch use ($p < 0.05$), independent of dose. | Strengths: Study measures both subjective, reported effects and physiological effects of acute snus use in non–tobacco users.

Limitations: Small sample size was used. Study does not examine the effects of acute snus use in middle-aged or elderly subjects. |

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Sapra, Sundaram, Buck, Barr, & Maisog, 2016)	Time-to-pregnancy associated with couples' use of tobacco products	Longitudinal, observational study in couples (n = 501 couples) discontinuing contraception to become pregnant; male ≥18 years, females aged 18-40 years; of males, 208 were characterized as never used tobacco, 48 used cigarettes, 46 used cigars, 28 used snuff/chew, 12 used cigarettes + snuff/chew, and 159 had other patterns of tobacco use; 65%-96% of males in each group were non-Hispanic white; women were characterized as current cigarette users or never users. Objectives: To examine how the use of tobacco products by males and females influence the TTP for couples.	Participants were interviewed on lifetime and current cigarette, cigar, and chew/snuff (smokeless) use and provided blood samples for quantification of heavy metals and cotinine. FORs and 95% CIs were estimated and adjusted for demographics/lifestyle. FORs less than 1 reflect longer TTP.	Among males, cigarette smokers and smokeless tobacco users had similar serum cotinine concentrations to each other, but both had significantly higher levels than nonusers. Cigarette use, but not smokeless tobacco use, was associated with longer TTP compared with never users among male partners (aFOR = 0.41; 95% CI, 0.24-0.68). Cigarette use was associated with longer TTP compared with never users among female partners when blood cadmium levels were not adjusted for. Compared with cigarette smokers, smokeless tobacco users had a shorter TTP (aFOR = 2.86; 95% CI, 1.47-5.57).	Strengths: (1) Study examined the effects of both male and female tobacco use on TTP. (2) Tobacco use was stratified by product type for males. (3) Couples were enrolled at the start of pregnancy attempts instead of retrospectively. (4) Study design allowed for assessment of possible biological mechanisms using blood sample results. Limitations: (1) Females were not stratified by the amount of cigarette use. (2) Low numbers of smokeless tobacco use among men and an absence of smokeless tobacco use among women underpowered the study to determine the effects of smokeless tobacco on TTP.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Stanton et al., 2016)	Trends in tobacco use among US adults with chronic health conditions: National Survey on Drug Use and Health 2005–2013	Longitudinal analysis of data from NSDUH surveys; n = 335,080 (211,991 current non–tobacco users, 123,089 [29.6%] used tobacco in the previous 30 days). Subjects include 105,392 cigarette users, 26,827 cigar smokers, 3,887 pipe smokers, and 16,093 smokeless tobacco users; 51.9% female; age ≥18 years; 68.3% non-Hispanic white. Objective: To identify the associations between chronic diseases and change in the rate of tobacco use over time.	Chronic conditions examined included anxiety, asthma, coronary heart disease, depression, diabetes, hepatitis, HIV, hypertension, lung cancer, stroke, and substance abuse. The study controlled for sociodemographics, trends in product use for most conditions and a composite of any condition among those with chronic conditions were compared with respondents with no condition in weighted logistic regression analyses.	"Cigarette smoking declined significantly over time among adults with no chronic condition. Adults with one or more chronic condition showed no comparable decrease, with cigarette smoking remaining especially high among those reporting anxiety, depression, and substance abuse. Cigar and pipe use remained stable and more prevalent among those with any chronic condition, with the exception of pipe use declining among those with heart disease. Smokeless tobacco use increased over time, with higher prevalence among those with asthma, mental health, and substance abuse conditions." Of current non–tobacco users, 28.0% had one chronic condition, while 11.8% had more than one condition; the most common conditions in current non–tobacco users were hypertension (20.9%), diabetes (8.0%), and depression (6.4%). Of current cigarette smokers, 31.1% had one chronic condition, while 14.8% had more than one condition; most common conditions in cigarette smokers were substance abuse (19.4%), hypertension (13.8%), and depression (10.5%). Of current smokeless tobacco users, 33.6% had one chronic condition, while 11.9% had more than one condition; most common conditions in smokeless tobacco users were substance abuse (21.4%), hypertension (16.3%), and asthma (5.4%).	Strengths: Data were from a large cohort. Study followed participants for a long period of time after enrollment. Limitations: Study was stratified on the basis of current tobacco use (within the last 30 days) and did not stratify non–current users on the basis of past use. Study was designed to detect associations between chronic conditions and changes in tobacco use, not the impact of tobacco use on the development or progression of the chronic conditions. Only 11 chronic conditions were considered.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Sutter, Nasim, Veldheer, & Cobb, 2016)	Associations between unhealthy dieting behaviors and tobacco use among adolescents	Cross-sectional survey of adolescents in Virginia; n = 6,903; 3,501 (50.7%) were female; 3,316 subjects were non-Hispanic white, 1,330 were non-Hispanic black, and 891 were classified as other; aged 12-18 years. Objective: To examine the associations between tobacco use and social perceptions on UDBs.	UDBs assessed included past 30-day fasting, diet pill use, and vomiting/laxative use. Tobacco-related items were ever and past 30-day cigarette smoking, past 30-day smokeless tobacco and cigar use, and the perception that smokers have more friends.	"Individuals who endorsed UDB use were proportionally more frequent relative to those who did not for all tobacco use items: ever cigarette smoking, past 30-day cigarette use, past 30-day smokeless tobacco use, past 30-day cigar use (all ps < 0.001)"; for females, ever cigarette use and past 30-day cigarette use were positively associated with reporting 2 or more UDBs relative to none; for males, ever cigarette smoking and past 30-day cigar use were positively associated with engaging in 1 UDB relative to none; for males, ever cigarette smoking was also positively associated with engaging in 2 or more UDBs relative to none.	Strengths: Study had a large cohort size and investigated tobacco use and unhealthy dieting in a vulnerable population (adolescents). Limitations: Because data were cross-sectional, the causality between smoking behaviors, perceived social factors, and UDB cannot be determined. Data were only obtained from adolescents in Virginia.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Ogden, Marano, Jones, & Stiles, 2015)	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology	Randomized, multicenter longitudinal interventional study; n = 163; 50.9% female, 73% non-Hispanic white; 131 smokers, 32 never smokers; adult smokers were randomly switched to tobacco-heating cigarettes (n = 44), snus (n = 43), or ultra-low machine yield tobacco-burning cigarettes (n = 44), with a comparison group of never smokers at baseline only; aged 28-55 years. Objective: to examine the effects of switching from cigarettes to tobacco-heating cigarette or snus on "potential improvement in health status measures, as well as changes in biomarkers of tobacco exposure and biomarkers of biological effect."	Subjects' experience with the assigned study products was followed for 24 weeks. Basic safety monitoring, clinical laboratory evaluations, and spirometry were performed.	No subject in the never smoker group reported an AE. For AEs the principal investigator considered to be related to the study product, 17 (in 8 subjects), 31 (in 15 subjects), and 13 (in 7 subjects) were reported in the groups switched to tobacco-heating cigarettes, snus, or ultra-low machine yield tobacco-burning cigarettes, respectively. The mild AEs were evenly distributed across the three groups. The highest occurrence of moderate AEs was in the snus group (n = 35), but only 5 were thought to be potentially product related. All 3 serious AEs were reported in the tobacco-heating cigarette group, but none were related to study treatment. AEs were most frequently reported for respiratory, thoracic, and mediastinal disorders and gastrointestinal disorders, with no differences among the three interventions. For all three interventions, a subset of participants (n = 5-6) experienced a positive response to bronchodilation.	Strengths: The study had a well-designed methodology with well-defined treatment interventions and follow ups. Limitations: There was a relatively small sample size.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Ogden, Marano, Jones, Morgan, & Stiles, 2015a)	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure	Randomized, multicenter longitudinal interventional study; n = 163; 50.9% female, 73% non-Hispanic white; 131 smokers, 32 never smokers; adult smokers were randomly switched to tobacco-heating cigarettes (n = 44), snus (n = 43), or ultra-low machine yield tobacco-burning cigarettes (n = 44), with a comparison group of never smokers at baseline only; aged 28-55 years. Objective: to assess differences in biomarkers of tobacco exposure between smokers and never smokers at baseline and among groups relative to each other and over time.	Subjects' experience with the assigned study products was followed for 24 weeks. Basic safety monitoring, clinical laboratory evaluations, and spirometry were performed.	Results indicated that adult cigarette smokers who switched from their usual brand of cigarettes to alternate tobacco products, including tobacco-heating cigarettes, snus, and ultra-low machine yield tobacco-burning cigarettes, had significantly reduced exposure to many potentially harmful constituents found in cigarette smoke. In comparison with subjects who switched to ultra-low machine yield tobacco-burning cigarettes, subjects switching to tobacco-heating cigarettes or snus had greater reductions in these biomarkers of tobacco exposure, both in number of constituents and magnitude of reductions. These reductions were likely associated with the elimination and near elimination of tobacco combustion in the use of snus and tobacco-heating cigarettes, respectively, although reductions in biomarkers of exposure were also observed in the ultra-low machine yield tobacco-burning cigarette group.	Strengths: Strengths included the long duration of the study (24 weeks), the extensive number of biomarkers evaluated, and the inclusion of the ultra-low machine yield tobacco-burning cigarette group as a control and for comparison. Limitations: The predominantly white subject sample in general and the predominantly male sample in the per-protocol sample of smokers switching to snus, limits the ability to generalize the findings.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Ogden, Marano, Jones, Morgan, & Stiles, 2015b)	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect	Randomized, multicenter longitudinal interventional study; n = 163; 50.9% female, 73% non-Hispanic white; 131 smokers, 32 never smokers; adult smokers were randomly switched to tobacco-heating cigarettes (n = 44), snus (n = 43), or ultra-low machine yield tobacco-burning cigarettes (n = 44), with a comparison group of never smokers at baseline only; aged 28-55 years. Objective: to examine the effects of switching from cigarettes to tobacco-heating cigarette or snus on "potential improvement in health status measures, as well as changes in biomarkers of tobacco exposure and biomarkers of biological effect."	Subjects' experience with the assigned study products was followed for 24 weeks. Basic safety monitoring, clinical laboratory evaluations, and spirometry were performed.	Results demonstrated that there were decreases in markers of inflammation and oxidative stress among smokers who switched to tobacco-heating cigarettes, snus, and ultra-low machine yield tobacco-burning cigarettes; switching to tobacco-heating cigarettes had the greatest number of consistent reductions for markers of inflammation and oxidative stress.	Strengths: Strengths included the 24-week duration of the study and comparisons between the effects of three different types of alternative tobacco products on a large number of health-related biomarkers. Limitations: Compliance with study product differed among participations; significant changes in the biomarkers assessed may not be predicative of clinical significance.

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Health Effects of Smokeless Tobacco	Comments
(Fu et al., 2014)	Psychiatric Correlates of Snuff and Chewing Tobacco Use	Subjects (N = 43,093; age 18+ years), who were non-institutionalized civilians selected from U.S. population in 2001 and 2002, were interviewed in person. ST use was classified as exclusive snuff use (n = 716; 91.16% male), exclusive chewing tobacco use (n = 901; 94.39% male), and dual use of both snuff and chewing tobacco at some time in the ST user's life (n = 931; 95.89% male). Objective: To examine differences between lifetime smokeless tobacco users and non-users of smokeless tobacco in relation to psychiatric disorders and to delineate exclusive snuff use or exclusive chewing tobacco from dual use with respect to psychiatric disorders.	Lifetime psychiatric disorders were obtained via structured diagnostic interviews.	"The prevalence of lifetime exclusive snuff use, exclusive chewing tobacco, and dual use was 2.16%, 2.52%, and 2.79%, respectively. After controlling for sociodemographic variables and cigarette smoking, the odds of exclusive chewing tobacco in persons with panic disorder and specific phobia were 1.53 and 1.41 times the odds in persons without those disorders, respectively [p < 0.05]. The odds of exclusive snuff use, exclusive chewing tobacco use, and dual use for individuals with alcohol use disorder were 1.97, 2.01, and 2.99 times the odds for those without alcohol disorder, respectively [p < 0.05]. Respondents with cannabis use disorder were 1.44 times more likely to use snuff exclusively than those without cannabis use disorder (p<0.05). Respondents with inhalant/solvent use disorder were associated with 3.33 times the odds of exclusive chewing tobacco [p < 0.05]."	Limitations: (1) The study is a cross-sectional study, causal relations between ST and psychiatric disorders and lifetime ST use cannot be determined; (2) majority of participants were adult male and it may not apply equally well to the adolescent population; and (3) the study could not examine the subtypes of ST use in relation to heroin use disorder due to a small proportion of ST users who met the lifetime Diagnostic and Statistical Manual of Mental Disorders IV diagnostic criteria for heroin use disorder.

7.5.6-2.3. Literature Review on Health Effects – Preclinical

7.5.6-2.3.1. Studies of the Health Effects of Smokeless Tobacco on Human Ex Vivo and Human Cell Models

Arimilli et al. (2017) conducted a single-blind, cross-sectional study to compare gene expression in peripheral blood mononuclear cells (PBMCs) from male, healthy volunteers aged 35 to 60 years who were moist snuff consumers (≥3 years, n = 40), cigarette smokers (≥3 years, n = 40), or non–tobacco consumers (≥5 years, n = 40). Total PBMCs and the percentage of CD2+ cells (T lymphocytes) in isolated PBMCs were significantly (α = 0.05, Tukey-Krammer) higher in cigarette smokers than in moist snuff consumers and non–tobacco consumers. The number of PBMCs or CD2+ cells did not differ significantly between moist snuff consumers and non-tobacco consumers. In contrast, the average number of CD56+ cells (natural killer cells) was significantly different across all three groups, with non-tobacco consumers showing the highest number of CD56+ cells, followed by moist snuff consumers and then cigarette smokers. Analysis of the expression level of over 47,000 genes showed no significant difference between non–tobacco consumers and moist snuff consumers. In contrast, gene expression was significantly altered by more than ±1.25-fold for 100 genes between smokers and non–tobacco consumers, and 46 genes between moist snuff consumers and smokers. Functional analysis showed that glial cell line–derived neurotrophic factor, inflammatory, and chemotaxis signaling pathways were significantly enriched in smokers compared with non–tobacco consumers. No disease categories and very few pathways and process networks were found to be significantly enriched in the pairwise comparison of differentially expressed genes in smokers and moist snuff consumers. Through Random Forest classification approach, the authors identified a group of genes, whose expression levels in PBMCs could accurately distinguish smokers from either moist snuff consumers or non–tobacco consumers.

Ganguli et al. (2016) investigated the toxicity of smokeless tobacco aqueous extract (STAE) on the human squamous carcinoma epithelial cell line, SCC-25. Incubation of SCC-25 cells with STAE for 24 to 48 hours resulted in reduced cell viability and increased apoptosis and reactive oxygen species (ROS) generation in a concentration-dependent manner. In addition, STAE treatment resulted in the induction of autophagy in SCC-25 cells, a result that was shown to occur via an ROS-dependent mechanism.

7.5.6-2.3.2. Studies of the Health Effects of Smokeless Tobacco on Commensal Bacteria Models

Liu et al. (2016) investigated the toxicity of ST products, including seven STAEs and three tobacco-specific N-nitrosamines (TSNAs) (N'-nitrosonornicotine [NNN], 4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanone [NNK], and 4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanol [NNAL]), on 38 species of oral bacteria. The seven ST products included two major brands of snus (Camel Snus Large Robust and Marlboro Snus Mint) and five major brands of moist snuff (Copenhagen® Snuff Original Fine Cut, Copenhagen® Long Cut Wintergreen, Grizzly® Long Cut Premium Wintergreen, Skoal® Long Cut Classic Wintergreen, and Skoal® Banditis Wintergreen). All seven STAEs showed concentration-

dependent effects on the growth and viability of tested oral bacteria under anaerobic culture conditions. All seven STAEs could promote the growth of four bacterial strains, including *Eubacterium nodatum*, *Peptostreptococcus micros*, *Streptococcus anginosus*, and *Streptococcus constellatus*. Exposure to STAEs modulated the viability of some bacterial strains, with decrease for four strains at 1 mg/mL, decrease for 10 strains at 10 mg/mL, decrease for 27 strains at 50 mg/mL, and no significant effect for 11 strains at up to 50 mg/mL. STAEs from moist snuff products inhibited more bacterial strains than those from snus, indicating that moist snuff may be more toxic to the oral bacteria than snus. In general, cell growth and viability of 34 tested strains were not significantly affected by TSNAs at the tested concentrations.

Sun et al. (2016) evaluated the physiological and toxicological effects of ST on one species of oral bacteria, *Capnocytophaga sputigena* (*C. sputigena*), using an ultra–high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry–based metabolomics approach. Pathway analysis of the metabolome profiles indicated that STAE caused oxidative stress in the bacterium. No significant changes in levels of nicotine and its major metabolites were found when *C. sputigena* was exposed to STAE, although hydroxynicotine and cotinine N-oxide were detected in the bacterial metabolites, suggesting that nicotine metabolism might be present as a minor degradation pathway in the bacterium.

7.5.6-2.3.3.   Studies of the Health Effects of Smokeless Tobacco in Animal Models

Theophilus et al. (2015) evaluated the carcinogenicity and toxicity of ST extracts in a 2-year study performed in male and female Wistar Han rats. This rat species was the most sensitive species in earlier toxicology studies that were used to determine appropriate doses for a potential chronic toxicology/carcinogenicity study, and the authors considered Wistar Han rats as the most predictive animal model for humans. ST was administered as a tobacco blend or an STAE at three doses of nicotine (0.2, 2, or 5 mg/kg/d) via dosed feed. The study included a 1-year interim subgroup to assess toxicity at that intermediate time point. Plasma nicotine and cotinine values increased with a corresponding increase in tobacco blend or STAE administered dose, indicating a generally proportional increase in exposure relative to increases in dietary doses of test articles for male and female rats. The feed consumptions for all treated groups were generally similar over 2 years compared to their respective control groups, except for the 5 mg/kg/d tobacco blend and STAE female groups. There were no treatment-related effects on survival or clinical signs of toxicity during the 2-year study. All histopathology findings occurred at incidences typical for the rats of the strain and age and were typical of spontaneous age, developmental, or degenerative changes. No treatment-related increases in tumor incidence were observed. The authors concluded that "chronic exposure of male and female Wistar Han rats to either a tobacco blend used in snus, or a tobacco extract of that blend does not lead to increased toxicity or carcinogenicity, based on the specified outcomes measured."

7.5.6-2.3.4.   Updated Findings

Information from nonclinical studies on the health effects of ST use in the update literature review is consistent with that seen in the initial literature review. The conclusions from the

initial literature review (Section 7.5.6-1) have not changed based on the updated literature review.

A tabular summary of the literature informing the preclinical health risks of ST is presented in Table 7.5.6-2-2.

Table 7.5.6-2-2:   Literature Review for Preclinical Health Effects of Smokeless Tobacco Products

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Preclinical Health Effects	Comments
(Arimilli et al., 2017)	Gene expression profiles associated with cigarette smoking and moist snuff consumption	Microarray analysis of gene expression in PBMCs isolated by flow cytometry from moist snuff consumers (≥2 cans/wk for ≥3 y), cigarette smokers (≥ 10 cigarettes/d for ≥3 y), and non–tobacco users (non-use of any tobacco or nicotine-containing product for ≥5 y) (n = 40 per cohort) in a single-blind, cross-sectional study. Subjects were males aged 35-60 years; majority were Caucasian. Objective: To examine the gene expression profiles of PBMCs from moist snuff consumers compared with cigarette smokers and non–tobacco consumers.	Number of PBMCs and proportion of $CD2^+$ cells, $CD56^+$ cells, monocytes, and B lymphocytes assessed by flow cytometry. Gene expression analysis of >47,000 transcripts assessed by microarray analysis. Gene expression of differentially expressed genes assessed by quantitative RT-PCR.	Total PBMCs were significantly increased in smokers compared with moist snuff consumers and non–tobacco consumers. PMBC gene expression was similar between non–tobacco consumers and moist snuff consumers. One hundred genes had significantly altered expression levels (±1.25-fold) in the smoker cohort compared with the non–tobacco user cohort; 46 genes had significantly altered expression levels (±1.25-fold) in the smoker cohort compared with the moist snuff consumers. Many of the alternations associated with smokers were involved in immune-related pathways.	Strengths: Moderate sample sizes composed of individuals with long-term product use. Limitations: Data are not longitudinal and cannot be used to predict how length of product use or changes in product use will affect gene expression of PBMCs. Since, gene expression was only determined using PBMCs, the effects of cigarette smoke and moist snuff use on gene expression were not determined in other relevant tissue, such as the lungs and mouth.

Table 7.5.6-2. Literature Review for Preclinical Health Effects of Smokeless Tobacco Products (continued)

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Preclinical Health Effects	Comments
(Ganguli et al., 2016)	Potential role of autophagy in smokeless tobacco extract-induced cytotoxicity and in morin-induced protection in oral epithelial cells	Human oral carcinoma cell line (SCC-25) incubated with STAEs for 24 or 48 h. Assessment of cell toxicity by cellular assays. Objective: To evaluate toxicity of STAEs in human oral cells.	Cell viability assessed by MTT assay. Apoptosis assessed using Annexin V and propidium iodide staining and Western blotting for apoptotic proteins. Autophagy as assessed by the presence of autophagic vacuoles using an (MDC) stain. ROS generation determined by DCF-DA staining.	In SCC-25 cells, STAE treatment reduced cell viability, increased ROS levels, and increased autophagic vacuole formation in a concentration-dependent manner. Induction of autophagy was a ROS-dependent response and occurred at earlier time points (3-6 h). During later time points (6-24 h), apoptosis levels were increased in a dose-dependent manner. All morin treatments increased cell viability, inhibited ROS-induced microtubule disruption, and prevented autophagy in response to STAE treatment, but treatments given before STAE exposure were most effective.	Strength: The authors use well-validated and standard *in vitro* analytical techniques. Limitation: (1) The ST used to prepare the STAE was likely acquired from India, but the authors do not specify. (2) The authors used only one cancer cell line, and cancer cell lines may respond differently to external stimuli than normal oral tissues.

Table 7.5.6-2. Literature Review for Preclinical Health Effects of Smokeless Tobacco Products (continued)

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Preclinical Health Effects	Comments
(Liu et al., 2016)	Effect of smokeless tobacco products on human oral bacteria growth and viability	Thirty-eight oral bacterial species or subspecies incubated with STAEs (1, 10, or 50 mg/mL) or TSNAs (1 µg/mL or 100 µg/mL). Assessment of cell proliferation and toxicity by cellular assays. Objective: To analyze the toxicity of seven STAEs and three TSNAs on 38 strains of human oral bacteria.	Bacterial cell number and viability assessed by flow cytometry.	In a concentration-dependent manner, STAEs promoted the growth of some bacterial species associated with oral diseases and inhibited the growth of other species. Some of the growth and viability effects on certain strains were STAE specific. Cell growth of the oral bacteria was not significantly affected by TSNAs at the tested concentrations. Cell viability was not significantly affected by TSNAs in 32 of 38 strains.	Limitations: This study examines the growth of the strains in isolation of one another and may not be generalizable to the growth competition that would occur in a human mouth. Furthermore, this study was limited to 38 strains out of over 200 species of oral bacteria.
(Sun et al., 2016)	Metabolomics evaluation of the impact of smokeless tobacco exposure on the oral bacterium *Capnocytophaga sputigena*	Incubation of the human oral commensal bacteria, *C. sputigena*, with STAEs. Assessment of cell metabolism by LC/MS-based metabolomics. Objective: To evaluate the toxicological and physiological effects of STAE on metabolism and function of one species of oral bacteria and to evaluate nicotine metabolism by oral bacteria.	Metabolic analyte levels in bacteria before STAE exposure, and at 2 min and at 48 h after STAE exposure, were assessed by LC/MS-based metabolomics.	There were no major changes in nicotine metabolite abundance in the two time points after STAE exposure. The authors observed decreases in glutamate- and sulfur-containing metabolites as well as increases in pyroglutamate, indicating that STAE treatments caused oxidative stress in *C. sputigena*.	Limitations: This study only tested one bacterial strain and one brand of STAE.

Table 7.5.6-2. Literature Review for Preclinical Health Effects of Smokeless Tobacco Products (continued)

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Related to Preclinical Health Effects	Comments
(Theophilus et al., 2015)	Toxicological evaluation of smokeless tobacco: 2-year chronic toxicity and carcinogenicity feeding study in Wistar Han rats	*In vivo* 2-y toxicity and carcinogenicity study in Wistar Han rats treated with ST extracts at three nicotine doses (0.2, 2, or 5 mg/kg/d) by dosed feed. Examined nicotine plasma concentrations and toxicity after 1 y of chronic exposure to three concentrations of STAEs and tobacco blends mixed into food. Measured tumor incidences after 2 y of chronic exposure. Objective: To evaluate toxicity and carcinogenicity of ST extracts in Wistar Han rats.	Lesions evaluated via whole body necropsy, followed by histopathology. Toxicity evaluated using weekly (for 13 wk), followed by monthly (every 4 wk) body weight measurements and comprehensive serum chemistry, hematology, and urinalysis.	"No treatment-related clinical signs of toxicity were apparent over the course of the study." "There were, however, statistically significant differences (p ≤ 0.05) in mean body weight gain for some treated groups compared to controls…" There were no significant differences in tumor incidences in nearly all cases when comparing exposed groups with the corresponding control.	Strengths: This was a GLP study, in which the authors performed comprehensive necropsy and autopsy of all organs and tissues. Limitations: Although plasma levels of nicotine were equivalent or greater than human physiological levels, the ST extracts were administered via feeding. This method is perhaps not comparable to normal modes of human ST consumption, and could have led to differences in exposure to other potential toxicants that were not measured.

7.5.6-2.4. Health Risks of Smokeless Tobacco Products Compared with Food and Drug Administration–Approved Tobacco Cessation Medication

This section addresses the U.S. FDA's MRTPA Draft Guidance recommendations for data and information on the health risks associated with switching to the candidate product as compared with using FDA-approved tobacco cessation medications.

To provide a foundation for addressing these concerns, a brief review of the health risks associated with the use of ST products and smoking cessation medications is presented in this section (health risks associated with ST products are also presented in Section 6.1 and Section 7.5.6-2.2). The smoking cessation medications addressed in this discussion will include nicotine replacement therapies (NRTs), bupropion (ZYBAN®), and varenicline (CHANTIX®).

A previous review on the health risks of using ST compared with using FDA-approved tobacco cessation medication was completed with a cutoff date of December 07, 2014, and has been included in this MRTPA in Section 7.5.6-1. This supplement provides an update on the warning labels and health risks associated with ST and FDA-approved tobacco cessation medication that covers the period of December 08, 2014, to February 06, 2017, and is intended to be used in conjunction with the previous review to provide a current, updated overview of the topic.

A rigorous literature review was not completed to characterize the health effects of FDA-approved tobacco cessation medications because their health effects are well known and are not subject to debate. Instead, updates on the warnings and precautions on product labels, along with review articles and government reports, form the basis for this section.

7.5.6-2.4.1.   Health Effects of Smokeless Tobacco

The health effects of ST were studied via a comprehensive literature review, and the relevant articles are summarized in this section and Section 7.5.6-1. Furthermore, articles that describe biomarkers of exposure and biological effect associated with ST use are summarized in Section 7.5.5-1 and Section 7.5.5-2.

Two meta-analysis articles and one article published after the cut-off date of February 06, 2017, are included in this summary because they inform the health risks associated with ST. Wyss et al. (2016) conducted an analysis of United States data in the International Head and Neck Cancer Consortium to ascertain the relationship between ST use and the risk of head and neck cancer. They found that head and neck cancer was weakly, but not statistically significantly, associated with ST use among never–cigarette smokers; however, there was a stronger and statistically significant association in never-smokers between use of chewing tobacco and oral cavity cancer (OR = 1.81; 95% CI: 1.04, 3.17). There were few or no associations between ST use and any head and neck cancers among ever–cigarette smokers. Cook et al. (2015) examined the associations between alcohol and tobacco exposure and male breast cancer from subjects in the Male Breast Cancer Pooling Project Consortium and found no association between ST use and male breast cancer. Finally, Timberlake et al. (2017) analyzed data from a subset of cohorts in the National Longitudinal Mortality Study

and, when adjusting for covariates, found no association between ST use and cancer-related mortality. Timberlake et al. did, however, find statistically significant associations between current use of ST and the risk of mortality due to coronary heart disease significant (adjusted HR = 1.24; 95% CI: 1.05, 1.46; p < 0.01); and between current snuff and chewing tobacco dual use and the risk of all-cause mortality (adjusted HR = 1.49; 95% CI: 1.05, 2.13; p < 0.05).

The three articles are summarized in Table 7.5.6-2-3.

Table 7.5.6-2-3:   Summary of Articles not Included in the Literature Review that Inform Health Risks of Smokeless Tobacco Products

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings	Comments
(Timberlake et al., 2017)	A longitudinal study of smokeless tobacco use and mortality in the United States	Data are from a subset of subjects from 18 of the 39 cohorts in the National Longitudinal Mortality Study that were administered a TUS-CPS from 1985 to 2011. Subjects who had ever smoked at least 100 cigarettes or had ever used cigars or pipes were excluded. The final sample included 349,282 subjects (38.6% age <35 y, 26.6% age 35-49 y, 34.8% age ≥50 y; 39.8% male; 71.7% non-Hispanic white), comprising never users of ST (n = 340,622), former users of ST (n = 3,741), and current users of ST (n = 4,919). Subjects had median and maximum follow up times of 8.8 and 26.3 y, respectively. Objective: To examine longitudinally the mortality risks associated with the use of ST.	Eight outcomes of interest were considered: five common (mortality from all causes, all cancers, coronary heart disease, cerebrovascular disease and digestive system cancers) and three uncommon (pancreatic cancer, esophageal cancer and cancer of the oral cavity or pharynx). For the uncommon outcomes, data from current and former ST users were pooled. Unadjusted and adjusted (for age, gender, race/ethnicity, education, and family income) regression analyses were performed.	"Regression analyses indicated that compared to the never tobacco users, the current [ST] users did not have elevated mortality risks from all cancers combined, the digestive system cancers and cerebrovascular disease." Current users of ST had a greater risk of all-cause mortality (unadjusted HR = 1.21; 95% CI: 1.12, 1.31; $p < 0.001$) and CHD mortality (unadjusted HR = 1.57; 95% CI: 1.34, 1.84; $p < 0.001$) than never users of ST. When the HRs were adjusted for covariates, only the association between current ST use and CHD mortality remained statistically significant (adjusted HR = 1.24; 95% CI: 1.05, 1.46; $p < 0.01$); however, current dual use of snuff and chewing tobacco did remain significantly associated with an increased risk of all-cause mortality compared to never users (adjusted HR = 1.49; 95% CI: 1.05, 2.13; $p < 0.05$). The authors speculate that, in current ST users, "[t]he associations with CHD mortality could be attributed to long-term nicotine exposure, other [ST] constituents (e.g., metals) or the confounding effects of CHD risk factors not accounted for in our study."	Strengths: (1) Data are from a nationally representative, longitudinal study, and (2) confounding effects of cigarette or other tobacco use were eliminated. Limitations: (1) Only a single, baseline measure of ST use was used in the analyses; (2) diet, alcohol use, and other behavioral factors were not collected in the TUS-CPS and could not be controlled for in the analyses; (3) the mortality status of individuals that moved abroad was not tracked; and (4) information was not available about diagnoses, which limited the analyses to fatal outcomes.

Table 7.5.6-2-3:   Summary of Articles not Included in the Literature Review that Inform Health Risks of Smokeless Tobacco Products   (Continued)

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings	Comments
(Wyss et al., 2016)	Smokeless tobacco use and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium	Data from 11 U.S. case-control studies from 1981 to 2006 of HNCs from the INHANCE Consortium were pooled for analysis. A total of 6,772 cases and 8,375 controls were included in the analyses for associations between ST and HNC (age: 17-94 years). Never–cigarette smokers comprised 18.56% (n = 1,257) of the cases and 39.80% (n = 3,333) of the controls. Roughly half of the cases (50.0%) and the controls (47.8%) were aged 50-65 years, and the majority of participants were non-Hispanic white (82.0% of the cases and 83.6% of the controls) and male (72.2% of the cases and 67.7% of the controls). Objective: to estimate associations between ST products and HNC, including associations for exclusive use of ST products and associations with specific tumor sites.	Cancers of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx overlapping or not otherwise specified, and larynx were included. Among oral cavity cancers, cancers of the gum, cheek mucosa, and vestibule of the mouth were analyzed as a subset. Cancers of the salivary glands, lip, nasopharynx, and esophagus were excluded. ORs and 95% CIs for ever use of each smokeless tobacco product, with never-users of that same product serving as the referent group.	Ever-use of snuff or chewing tobacco among never–cigarette smokers was weakly associated with HNC (OR = 1.30, 95% CI: 0.93, 1.81) but not among ever–cigarette smokers (OR = 0.93, 95% CI: 0.78, 1.11). Ever-use vs. never-use of snuff among never–cigarette smokers was strongly associated with HNC (OR = 1.71; 95% CI: 1.08, 2.70), particularly for oral cavity cancers (OR = 3.01; 95% CI: 1.63, 5.55). Ever-use vs. never-use of chewing tobacco among never–cigarette smokers was weakly associated with HNC (OR = 1.20; 95% CI: 0.81, 1.77), but analyses restricted to oral cavity cancers showed a stronger association (OR = 1.81; 95% CI: 1.04, 3.17). "Few or no associations between each type of [ST] and HNC were observed among ever–cigarette smokers, possibly reflecting residual confounding by smoking."	Strengths: The large number of cases and controls. Limitations: (1) Many subjects were selected from hospital settings and therefore may not be representative of population-based studies. (2) ST use was retrospectively recalled, which may have led to misclassification of ST type or some exposure miscalculation. (3) The authors were unable to consider current versus former use of ST products, including ages at starting and stopping, as well as type (e.g., brand of chewing tobacco and dry snuff vs. wet snuff) and amount (e.g., grams) of ST used, because many studies included in the analysis did not collect this information.

Table 7.5.6-2-3:   Summary of Articles not Included in the Literature Review that Inform Health Risks of Smokeless Tobacco Products   (Continued)

Author	Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings	Comments
(Cook et al., 2015)	Tobacco and alcohol in relation to male breast cancer: an analysis of the Male Breast Cancer Pooling Project Consortium	Data from 10 case-control and 10 cohort studies from the Male Breast Cancer Pooling Project were pooled for analysis. A total of 2,378 cases and 51,959 controls were included in the analyses. The mean ages of the cases and controls were 65.6 and 66.8 years, respectively, and the majority (85.7%) of the subjects were white. Objective: To determine the association between tobacco and alcohol exposure to male breast cancer.	Unconditional logistic regression was used to estimate study design–specific (case–control/cohort) ORs and 95% CIs, which were then combined using fixed-effects meta-analysis.	Neither chewing tobacco use nor snuff use (ever-use vs. never-use) was significantly associated with male breast cancer. Chewing tobacco use (3 case-control studies; n = 401 cases and 1,344 controls): OR = 1.10; 95% CI: 0.72-1.68. Snuff use (2 case-control studies; n = 397 cases and n = 796 controls): OR = 0.97; 95% CI: 0.55-1.71. "Tobacco and alcohol do not appear to be carcinogenic for male breast cancer."	Strengths: The large number of male breast cancer patients available for analysis; use of individual participant data; no evidence for heterogeneity after false discovery rate adjustment. Limitations: potential recall bias and interviewer biases in use questionnaires.

7.5.6-2.4.2.   Health Effects of Nicotine Replacement Therapies

NRTs are designed to wean a person off cigarettes by supplying controlled amounts of nicotine via oral, intranasal, or transdermal administration. Warning labels and known health risks associated with over-the-counter NRTs have not changed in the updated reporting period.

7.5.6-2.4.3.   Health Effects of Bupropion (ZYBAN)

ZYBAN, which is indicated to aid in smoking cessation treatment, contains the same active ingredient (i.e., bupropion hydrochloride) as WELLBUTRIN®, which is indicated for the treatment of major depressive disorder. On December 16, 2016, the FDA announced that the boxed warning, FDA's most prominent warning, for serious mental health side effects would be removed from the WELLBUTRIN drug label based on new clinical evidence; however, the boxed warning for suicidal thoughts and behaviors remains in the label for ZYBAN and WELLBUTRIN:

> **WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**
> *See full prescribing information for complete boxed warning.*
> • **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants**
> • **Monitor for worsening and emergence of suicidal thoughts and behaviors.**

The current label for ZYBAN ("Package insert: ZYBAN® (bupropion hydrochloride) sustained-release tablets, for oral use,") identifies common adverse reactions, defined as an incidence of at least 5 percent and at least 1 percent more than the rate in placebo-treated patients, as insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia. In addition, the following warnings and precautions are stated in the label highlights section:

- **Neuropsychiatric adverse events**: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with ZYBAN for the occurrence of such symptoms and instruct them to discontinue ZYBAN and contact a healthcare provider if they experience such adverse events.

- **Seizure risk**: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 300 mg. Discontinue if seizure occurs.

- **Hypertension**: ZYBAN can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment, especially if used with nicotine replacement.

- **Activation of mania/hypomania**: Screen patients for bipolar disorder and monitor for these symptoms.

- **Psychosis and other neuropsychiatric reactions**: Instruct patients to contact a healthcare professional if reactions occur.

- **Angle-closure glaucoma**: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.

7.5.6-2.4.4.   Health Effects of Varenicline (CHANTIX)

On December 16, 2016, the FDA announced that the boxed warning, the FDA's most prominent warning, for serious mental health side effects would be removed from the CHANTIX drug label based on new clinical evidence. The current label ("Package insert: CHANTIX® (varenicline) tablets, for oral use,") identifies common adverse reactions, defined as an incidence of at least 5 percent and twice the rate seen in placebo-treated patients, as nausea, abnormal dreams, constipation, flatulence, and vomiting. In addition, the following warnings and precautions are stated in the label highlights section:

- **Neuropsychiatric Adverse Events**: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with CHANTIX for the occurrence of such symptoms and instruct them to discontinue CHANTIX and contact a healthcare provider if they experience such adverse events.

- **Seizures**: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold.

- **Interaction with Alcohol**: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them.

- **Accidental Injury**: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them.

- **Cardiovascular Events**: A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular (CV) disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

- **Somnambulism**: Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism.

- **Angioedema and Hypersensitivity Reactions**: Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur.

- **Serious Skin Reactions**: Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions.

- **Nausea**: Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful.

Additional information in the literature during the reporting period for this review includes a study by Schwartz et al. (2016), in which they conducted a systematic review and meta-analysis on the effectiveness and safety of varenicline in ST cessation. For effectiveness, they examined 7-day point prevalence of ST abstinence at the end of 12 and 26 weeks. Three randomized clinical trials were identified for the meta-analysis, and the trials randomized a total of 744 ST consumers to either varenicline (n = 370) or placebo (n = 374). The incidences of nausea and sleep disturbance were higher in the varenicline group (22.4% and 20.0%, respectively) than in the placebo group (5.1% and 11.2%, respectively), but the incidence of mood disorders was lower in the varenicline group (1.6%) than in the placebo group (2.4%). There were, however, no statistically significant differences in the incidences of adverse events between the two arms, but the authors caution that high heterogeneity for the analyses of nausea and sleep disturbance limits interpretation. One of the three studies reported no increase in nausea in the treatment arm compared to the placebo arm, which is quite different from most other reported studies with varenicline, and, if that study is removed from the meta-analysis, the increases in both nausea and sleep disturbances in the treatment arm compared to the placebo arm become statistically significant. The authors concluded that "[t]his pooled analysis suggests that varenicline is effective in achieving a 7-day point prevalence of [ST] abstinence at 12 weeks but showed that this effect was not sustained at 26 weeks."

7.5.6-2.4.5.   Updated Findings

Information on the health risks of ST compared to FDA approved smoking cessation medication in the update literature review is consistent with that seen in the initial literature review. The conclusions from the initial literature review (Section 7.5.6-1) have not changed based on the updated literature review.

7.5.6-2.5.Literature Cited

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