6.1.: HEALTH RISKS OF THE TOBACCO PRODUCT

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6.1. HEALTH RISKS OF THE TOBACCO PRODUCT

Smokeless tobacco (ST) products are not risk-free. The U.S. Surgeon General and other public health authorities have determined that ST products are addictive and can cause serious diseases, some of which are addressed by the federally mandated warnings.

We present, however, evidence that shows ST is less harmful than cigarettes. We provide evidence demonstrating that use of ST products in the U.S. results in far lower serious consequences to health than smoking conventional cigarettes, primarily driven by the meaningful difference in lung cancer mortality risk. The evidence supports the proposed modified risk claim that switching completely to the candidate product from cigarettes reduces risk of lung cancer. In addition to existing published literature, our analysis of two current national longitudinal health studies linking tobacco use with mortality incidence illustrates the substantial differences between ST use and smoking cigarettes in overall mortality risk from all-causes, malignant neoplasms including lung cancer, and diseases of the heart.

As described in Section 2.3.3.1 the epidemiological evidence on health risks of ST applies to the candidate product. The existing epidemiology on U.S. ST products is applicable to the candidate product for the following reasons. First, the candidate product has been on the market for many decades. Second, USSTC moist smokeless tobacco (MST) products were the predominant form of ST used during the time period of the major epidemiology studies and the candidate product occupied a sizeable market share among the MST products used during this time period. Third, during the time period of these studies, the candidate product was manufactured using a consistent process that did not change substantially over time, other than process improvements that reduced TSNA levels over time which did not increase the health risks of the candidate product.

While the differential health risks between ST use and cigarette smoking are evident in published tobacco use epidemiology studies, sufficient evidence in literature also indicates that ST use is not entirely risk-free. We believe that the data presented in the following discussion on overall mortality risks associated with the candidate product substantiates our proposed modified risk claim and does not conflict with currently mandated health warnings describing ST health risk.

6.1.1. Data Sources and Hierarchy of Evidence

We provide evidence from several data sources, including epidemiological evidence (Linked Mortality Analyses and published literature), clinical studies (biomarkers of exposure and biomarkers of potential harm) and nonclinical studies (chemical analysis, in-vitro toxicological assessments and animal studies) to assess the health risks of ST products and cigarettes. We assign significant weight to the epidemiological studies in the hierarchy of evidence as they provide the health outcome from long term product use behavior under real-world conditions. Nonclinical and clinical studies are also important and provide additional information regarding the likelihood of health outcomes and the mechanistic basis for the epidemiological findings.

6.1.1.1. Linked Mortality Analysis

Our analyses of two large, nationally representative linked mortality datasets provide the primary information source used to describe the health risks of the candidate product (Section 7.4.1). These are the National Health Interview Survey (NHIS)[1] mortality linkage and the National Longitudinal Mortality Study (NLMS)[2], a linked mortality dataset based on the Current Population Survey Tobacco Use Supplement. These surveys provide assessments of exposures and other health-relevant covariates. Survey respondents are then linked to the National Death Index[3] vital status data.

Linking public health survey data with mortality data allows for a baseline exposure assessment with prospective, cause-specific mortality follow-up. Our NHIS analyses included survey years 1987, 1991-92, 1998, 2000, and 2005 and consisted of 154,391 total respondents, including 3,006 current ST users.[4] The NLMS analyses included surveys administered from 1993 through 2005, comprising 210,090 total respondents including 3,492 current ST users. The 2011 update to the National Death Index provided mortality follow-up for both datasets. Because of the longer follow-up period for the NHIS study, the number of deaths recorded for any specific disease is generally greater than that recorded in the NLMS data.

There are some boundaries to our analysis results included in this application. Due to privacy concerns, NCHS[5] required that we not present data where the death counts are fewer than five or where the statistical estimates allow one to deduce the death counts where the death counts are less than five. For our analysis of NLMS data, we generally computed hazard ratio (HR) estimates for endpoints where low mortality numbers were present (i.e., <5). However, we note that these HR point estimates carry statistical uncertainty as indicated by the wide confidence intervals. Reliability of the analysis is proportional to the number of deaths

[1] The NHIS is an annual, nationally representative survey of the civilian non-institutionalized U.S. population. NHIS surveys from 1986 through 2009 are linked to National Death Index data, with vital status follow-up through December 31, 2011. We analyzed both the publicly available data and the restricted data. These surveys include 1987, 1991-1992, 1998, 2000, and 2005. The linked data include between six and 24 years of mortality follow-up depending on the survey year. There are 154,391 people (29,443 deaths) eligible for our public-use analysis and 154,286 people (29,707 deaths) eligible for our restricted-access analysis.

[2] The National Longitudinal Mortality Study (NLMS) Public Use Microdata Sample (PUMS) Tobacco-Use (TU) file is comprised of samples of Current Population Survey Tobacco Use Supplements (CPS-TUS) administered from 1993 through 2005 linked to National Death Index vital status data. We analyzed version five of the PUMS TU file, which contains demographic, vital status and tobacco use data for 493,282 CPS-TUS respondents. The PUMS TU data have five years of mortality follow-up for all respondents, with each decedent's underlying cause of death assigned to one of 113 aggregate causes.

[3] The National Death Index (NDI) is a centralized database of death record information on file in state vital statistics offices. https://www.cdc.gov/nchs/ndi/index.htm

[4] These survey years include survey items identifying current and former ST users, as well as current or former cigar and pipe users. Other survey years do not include these survey items. We report data from males (including white males – the predominant users of ST) and females.

[5] NCHS, the National Center for Health Statistics, administers the NHIS.

recorded, and HR based on a small number of mortality cases should therefore be interpreted with caution.

To probe the NHIS and NLMS data, we prepared several alternative comparisons using different combination of sample populations including never, current, or former ST users or smokers. The combination of various tobacco use groups used for risk estimate calculations are shown in Table 6.1-1. However, for this application we generally rely on models P0 (analysis of ST users vs. never-tobacco users), P3 (analysis of formers users), and P4 (all use groups) that address FDA questions related to health risk. We do not present every health endpoint appearing in the NHIS and NLMS datasets, nor discuss other possible tobacco user combinations (e.g., P1 and P2) in this section; however, we include this information in Section 7.4.1. We encourage FDA reviewers to prepare their own analysis of the datasets as warranted. We note that NCHS periodically updates the mortality linkages. The dataset analyzed comprised mortalities through 2011. Thus, due to ongoing updates of the mortality linkages, hazard ratio estimates may be slightly different with subsequent analyses.

We estimated the mortality HR using the Cox Proportional Hazards Model, incorporating the following covariates into the model: (1) gender; (2) race; (3) age; (4) BMI – only for the NHIS data, not available in the NLMS dataset; (5) educational attainment; (6) family income; (7) health status; (8) tobacco use and (9) cigarettes per day. We selected these covariates based on previously published research which used similar models for estimating mortality hazards ratio for other purposes [(Ford, Greenlund, & Hong, 2012) (Rostron, 2012a) (Rostron, 2012b) (Accortt, Waterbor, Beall, & Howard, 2002) (Bopp, Braun, Gutzwiller, & Faeh, 2012) (Robinson-Cohen et al., 2014) (Xu, Kochanek, Murphy, & Arias, 2014) (Carter et al., 2015) (Inoue-Choi, Hartge, Liao, Caporaso, & Freedman, 2018) (Timberlake, Nikitin, Johnson, & Altekruse, 2017)].

Table 6.1-1: Model Designations and Tobacco Use Combinations Used for Analysis of Linked Mortality Data from NLMS and NHIS Datasets

Model Designation	ST Status	Smoking Status[1]		
		Never	Former	Current
P0	Never	P_{NN}		
	Current	P_{CN}		
	Former			
P1	Never	P_{NN}		P_{NC}
	Current	P_{CN}		P_{CC}
	Former			
P2	Never			P_{NC}
	Current			P_{CC}
	Former			
	Never		P_{NF}	

Model Designation	ST Status	Smoking Status[1]		
		Never	Former	Current
P3	Current		P_{CF}	
	Former		P_{FF}	
P4	Never	P_{NN}	P_{NF}	P_{NC}
	Current	P_{CN}	P_{CF}	P_{CC}
	Former	P_{FN}	P_{FF}	P_{FC}

[1] P_{XX} = sample groups used in model calculation. Shading indicates groups excluded from the model. All models exclude pipe and cigar users.

Because we are able to present epidemiological data relevant to the candidate product, clinical evaluations of biomarkers of exposure or biomarkers of effect are lower in the hierarchy of evidence in establishing the health effects of the candidate product. Prospective epidemiological data from these linked mortality data provide insight into the potential health risks associated with long-term use of the product. We present actual health outcome data based on years of use, thus obviating the need for clinical investigations specifically with the candidate product. Nevertheless, we present evidence from clinical studies for biomarkers of exposure and potential harm related to ST products in Section 6.1.1.3.

We recognize certain limitations with these linked mortality data. These include lack of prospective reassessment of exposure after baseline, raising the possibility of misclassification, and a lack of specificity about the type of ST used by respondents. These limitations, however, apply generally to most of the published epidemiological studies relevant to U.S. ST products. Additionally, we have pooled "snuff" and "chewing tobacco" users in our Linked Mortality Analysis. We believe this approach is reasonable because (1) the health effects of the two product types do not significantly differ (Henley, Thun, Connell, & Calle, 2005; Rodu & Cole, 2002) (Table 6.1-13 and Table 6.1-14); and (2) snuff and chewing tobacco users may misclassify themselves.

Both mortality linkages are nationally representative and include a large number of current ST users. These datasets are more recent than other published epidemiology of ST health risks specific to the U.S. In addition, our analyses provide unique comparisons, not typically reported in the published scientific literature. These include the health risks of (a) ST use and cigarette smoking; (b) dual users of ST and cigarettes with exclusive users of each product; and (c) former cigarette smokers who currently use ST (switchers), directly compared with former smokers who do not use any tobacco products. In addition, these datasets provide a large source of data for female ST users. For these reasons, the linked mortality data are our primary information source on the health risks of ST use.

6.1.1.2. Published Epidemiological Studies of U.S. Smokeless Tobacco Use

We conducted a comprehensive review of published epidemiological studies of ST users in the U.S. The body of published studies is extensive and covers a range of disease outcomes, but there are some potential limitations to this data. Products used by study participants may

represent older ST product designs, since many of these studies were conducted between approximately 1950 and 1990, and very few studies are based on observations after 1990. Also, the designs of many of the published epidemiological studies are based on case-control designs that are subject to recall bias. Finally, some published studies did not control for potential confounding factors. While the age, study design, and lack of consideration for confounding factors constrain the relevance of some published epidemiology of U.S. ST use, we find that the body of published scientific evidence related to the health risks of ST use largely supports the results of our more current analyses of NHIS and NLMS linked mortality datasets. The converging lines of evidence from two independent nationally representative surveys add robustness to our conclusions.

6.1.1.3. Nonclinical and Clinical Studies

Our comprehensive review of the published scientific literature, included in Section 6.1.2.1.4 and in Section 7.5.6-1 and 7.5.6-2 of this application contains a discussion of published nonclinical and clinical studies of U.S. smokeless tobacco products. Nonclinical models can provide information about biological or chemical mechanisms regarding mode-of-action–related questions, including biological plausibility for a disease/exposure association.

Various *in vivo* and *in vitro* research techniques have been applied to the study of tobacco-related diseases. Some reports describe laboratory animal or cellular models in which MST specifically, or an individual HPHC, induces or aggravates a condition or disease. Nonclinical research conducted to assess mechanistic associations between ST and disease, however, should be interpreted with caution when it comes to actual disease outcomes in humans. The relevance of the dose tested, or the experimental exposure conditions used, may not reflect actual MST or ST use and human behavior.

FDA has provided a list of certain ST constituents of interest in its 2012 Draft Guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act." We include analysis of these constituents in the candidate products in Section 7.1. The relevance of these HPHC levels should be assessed in the context of epidemiology evidence. ALCS, on behalf of USSTC assesses the toxicological impact of ingredients and their use levels as part of the evaluation conducted according to the Product Integrity Review and Toxicological Evaluation Guideline and Framework (Appendix 3.1-1 and Appendix 3.1-2).

We also summarize human studies on ST products and cigarettes comparing biomarkers of exposure to select HPHCs in Section 6.1.2.1.4.2. Biomarkers of exposure undoubtedly provide more reliable estimates of HPHC exposure compared to product chemistry analysis, since these studies incorporate actual human use of tobacco products and account for factors that cannot be replicated in *in vitro* studies, including differences in routes of administration, absorption, distribution, metabolism, and excretion. We further describe biomarkers of potential harm related to chronic inflammation that provide insights to smoking-related disease mechanisms in Section 6.1.2.1.4.2. Overall, the nonclinical and clinical studies provide relevant mechanistic basis for the reduction in risks from ST use compared to cigarette smoking. Ultimately, well conducted, prospective, epidemiological data provide a

more informative understanding of the potential health risks associated with long-term use of ST and cigarettes.

6.1.1.4. Summary

Overall, the Linked Mortality Analysis, supported by published literature on epidemiology, nonclinical, and clinical studies, provides the evidence representing the current state of knowledge regarding the health risks of the candidate product. This data informs the review of our conclusion that switching completely to the candidate product from cigarettes reduces risk of lung cancer.

6.1.2. The Health Risks Associated with Product Use as Compared with Using Other Tobacco Products, Including Tobacco Products within the Same Product Class

Cigarette smoking remains the predominant form of tobacco use in the U.S., and is the most likely tobacco form currently used by the consumer who may adopt the candidate product. Chewing tobacco is another form of oral tobacco used in the U.S. Although a variety of tobacco product types are available in the U.S. market, we concentrate comparisons of the health risks of the candidate product to those we believe are most relevant: cigarette smoking and chewing tobacco.

"Swedish Snus-type products" are also currently in the U.S. market. Chemical analysis shows MST products generally have higher levels of TSNA, polycyclic hydrocarbons, and aldehydes compared to snus products in the U.S. market (Stepanov, Jensen, Hatsukami, & Hecht, 2008). Comparative long-term epidemiological evidence based on U.S. populations using snus or e-cigarettes are not available. Therefore, we do not make a head-to-head comparison between the epidemiological evidence presented here against Swedish Snus or other emerging classes of tobacco products. A similar situation holds for other emerging classes of tobacco products, such as e-vapor where extensive confirmatory epidemiology assessments have not yet been published. Based on the simple formulas often used for e-vapor products, it is expected that MST products would contain greater levels of tobacco constituents.

6.1.2.1. ST Compared to Cigarette Smoking

Cigarette smoking remains the most prevalent form of tobacco use and presents the greatest risk for the tobacco user Surgeon General Report (2014). Table 6.1-2 In contrast, many well conducted investigations have found that while ST use confers health risks, the risks for serious and fatal diseases are lower than cigarette smoking. Table 6.1-2 provides an overview of some of the various quantitative risk estimates and the U.S. Surgeon General's conclusions regarding the specific health risks of ST and cigarette smoking.

Table 6.1-2: Comparison of Selected Major Health Risks of Smokeless Tobacco Use and Cigarette Smoking

Disease	Quantitative Estimates		Surgeon General's Findings	
	Smokeless Tobacco Meta-analysis[1] RR/OR (95 % CI)	**Cigarette Smoking CPS-II[2] RR**	**Smokeless Tobacco[3]**	**Cigarette Smoking[4]**
Bladder Cancer	Overall data: 1.11 (0.85-1.45) Smoking-adjusted data: 1.24 (0.83-1.85)	Males: 3.27 Females: 2.22	"…risk of bladder cancer is not altered to any large extent in users of smokeless tobacco products…"	Sufficient to infer a causal relationship
Esophageal Cancer	Overall data: 1.56 (1.11-2.19) Smoking-adjusted data: 1.89 (0.84-4.25)	Males: 6.76 Females: 7.75	"Inconclusive" (upper aerodigestive tract)	Sufficient to infer a causal relationship
Kidney cancer	Overall data: 1.52 (0.94-2.46) Smoking-adjusted data: 1.41 (0.64-3.10)	Males: 2.72 Females: 1.29	"…results from studies of kidney cancer are inconsistent."	Sufficient to infer a causal relationship
Laryngeal cancer	Overall data: 1.56 (1.21-2.00) Smoking-adjusted data: 2.01 (1.15-3.51)	Males: 14.60 Females: 13.02	"Inconclusive" (upper aerodigestive tract)	Sufficient to infer a causal relationship
Lung cancer	Overall data: 1.22 (0.82-1.83) Smoking-adjusted data: 1.38 (0.72-2.64)	Males: 23.26 Females: 12.69	No conclusion presented	Sufficient to infer a causal relationship
Oral cavity and pharyngeal Cancer	Overall data: 2.16 (1.55-3.02) Smoking/alcohol adjusted data: 1.04 (0.80-1.35)	Males: 10.89 Females: 5.08	"Evidence is strong" (oral cavity) "Inconclusive" (upper aerodigestive tract)	Sufficient to infer a causal relationship
Pancreatic cancer	Overall data: 0.86 (0.47-1.57) Smoking-adjusted data: 0.99 (0.51-1.91)	Males: 2.31 Females: 2.25	No conclusion presented	Sufficient to infer a causal relationship
Prostate cancer	Overall data: 1.20 (1.03-1.40)[5] Smoking-adjusted data: 1.29 (1.07-1.55)	Not reported	No conclusion presented	Suggestive of no causal relationship[6]

Disease	Quantitative Estimates		Surgeon General's Findings	
	Smokeless Tobacco Meta-analysis[1] RR/OR (95 % CI)	**Cigarette Smoking CPS-II[2] RR**	**Smokeless Tobacco[3]**	**Cigarette Smoking[4]**
Stomach cancer	Overall data: 1.41 (0.95-2.10) Smoking-adjusted data: 1.41 (0.93-2.12)	Males: 1.96 Females: 1.36	"Inconclusive"	Sufficient to infer a causal relationship
Cerebrovascular disease	Fixed effects: 1.44 (1.30-1.60) Random effects: 1.41 (1.17-1.71)	Males (35-64 y): 3.27 Females (35-64 y): 4.00	No conclusion presented	Sufficient to infer a causal relationship
Ischemic heart disease	Fixed effects: 1.14 (1.06-1.22) Random effects: 1.14 (0.96-1.34)	Males (35-64 y): 2.80 Females (35-64 y): 3.08	No conclusion presented	Sufficient to infer a causal relationship
COPD	1.28 (0.71-2.32)[7]	Males: 10.58 Females: 13.08	No conclusion presented	Sufficient to infer a causal relationship
Dental caries	Not established	Not established	"Combination of smokeless tobacco use in individuals with existing gingivitis may increase the prevalence of dental caries"	Sufficient to infer a causal relationship

CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disease; CPS-II = Cancer Prevention Study II; RR/OR = Random effect relative risk/odds ratio

[1] Data obtained from Lee & Hamling (2009a), cardiovascular disease data from Lee (2007). Meta-analysis results shown in the table represent United States data.

[2] Data obtained from Rostron (2013). 95% CI data were not available.

[3] From The Health Consequences of Using Smokeless Tobacco, A Report of the Advisory Committee to the Surgeon General, (U.S. Dept. Health Human Services, 1986)

[4] From "The Health Consequences of Smoking – 50 Years of Progress, A Report of the Surgeon General" (2014)

[5] Includes one study from Norway and six U.S. studies

[6] The Surgeon General concluded that the evidence was suggestive of no causal relationship between smoking and prostate cancer incidence. However, the Surgeon General did find that the evidence was suggestive of a higher death risk from prostate cancer in smokers and a higher risk of advanced-stage disease, less well-differentiated cancer and a higher risk of disease progression.

[7] Meta-analysis has not estimated COPD risk from ST use. The data shown are from CPS-II analysis conducted by Henley et al. (2005).

In the following sub-sections, we discuss the existing scientific evidence illustrating the comparative risk of ST use with cigarette smoking. We base much of our discussion on our Linked Mortality Analysis of the NHIS and NLMS datasets using models that incorporate various combinations of tobacco use behaviors including never, former, and current ST users

and cigarette smokers (Table 6.1-1), and provide relevant findings appearing in the literature, where appropriate. We focus most of our discussion on the major mortality risks seen in the published literature for tobacco, including all-cause mortality, diseases of the heart, and malignant neoplasms. Malignant neoplasms, particularly lung cancer, are a leading cause of mortality among smokers. Section 7.5.6-1 and 7.5.6-2 contains additional published information related to other disease endpoints.

On the basis of our review of the existing scientific information, the use of ST in the U.S. has substantially lower risk of serious fatal diseases, such as lung cancer, than continued cigarette smoking.

6.1.2.1.1. Mortality from All-Causes

All-cause mortality provides a measure of the excess mortality attributable to tobacco product use that integrates, across all identified and unidentified associations of tobacco product use, diseases that could eventually result in mortality. The category of all-cause mortality incorporates the widest collection of possible fatal diseases and provides the most fundamental platform for absolute overall risk evaluation of ST use and cigarette smoking compared to never-tobacco use. Data from the NHIS and NLMS surveys do not indicate excess mortality risk from all-causes among current ST users compared to never-tobacco users. In contrast, current adult smokers (AS) (all respondents) in both the NLMS and NHIS datasets had significantly elevated risk for mortality from all-causes compared to never-tobacco use (Table 6.1-3).

Table 6.1-3: Mortality from All-causes: Adjusted Hazard Ratio Estimates for Smokeless Tobacco Users (Exclusive) and Adult Cigarette Smokers (Exclusive) Compared to Never-Tobacco Users

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
All Respondents	NLMS	1,863	48	0.815 (0.593-1.120)	38,076	1,505	1.878 (1.744-2.023)
	NHIS[2]	1,562	347	1.110 (0.959-1.285)	36,112	7525	2.130 (2.048-2.215)
Males	NLMS	1,646	25	0.656 (0.410-1.049)	16,597	726	1.661 (1.485-1.857)
	NHIS	1,219	142	1.167 (0.921-1.479)	13,536	2,887	2.187 (2.035-2.351)
White Males	NLMS	1,545	22	0.736 (0.445-1.216)	13,893	594	1.823 (1.612-2.062)
	NHIS	1,119	110	1.196 (0.915-1.564)	10,600	2,200	2.306 (2.135-2.490)
Females	NLMS	217	23	1.002 (0.646-1.553)	21,479	779	2.050 (1.858-2.262)

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
	NHIS	343	205	1.054 (0.890-1.249)	22,576	4,638	2.107 (2.011-2.208)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs NTU)
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1]Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). Note: The analysis was conducted on all respondents (P4 analysis) with the reference group comprising individuals who never used tobacco (according to survey defined parameters). The estimates may vary slightly from those shown in Table 6.1-1, since this statistical model includes smokers in addition to ST.
[2] NHIS data obtained from analyses of the restricted access data file.

When analyzed by gender, no excess all-cause mortality risk was indicated for ST use among males or females compared to respective never-tobacco groups in either dataset (Table 6.1-4). NHIS and NLMS studies contain gender assignments, which in some cases (e.g. all-cause mortality) provide a large enough sample allowing for reliable calculation of gender-specific risk estimates. Such estimates can be useful in determining if there is a disproportionate risk between genders or across special use groups. In contrast, all-cause mortality risk for males or females who smoked cigarettes was significantly elevated over the respective never-tobacco use reference groups.

Since white males are currently the predominant consumers of ST products, and both datasets confirmed this tobacco product use pattern (about 70-80% of either study), we conducted further analysis specific to only white males. No excess all-cause mortality was evident in white male ST users compared to never-tobacco users. Nonetheless, the data for females and for white females (data not shown) were consistent with that seen in males.

The all-cause mortality risks derived from our analysis of respondents in the NHIS and NLMS are consistent with those found in the published scientific literature for both ST use and for cigarette smoking. Table 6.1-4 presents data from the 2014 Surgeon General's report showing a pooled analysis of all-cause mortality estimates from five cohort studies followed from 2000 to 2010 [Surgeon General Report (2014)]. AS have approximately a two-fold to three-fold excess risk of mortality from all-causes when compared with that for never tobacco users, depending largely on age and the intensity and duration of smoking.

Table 6.1-4: All-Causes Mortality Risk among Current Adult Cigarette Smokers Stratified by Gender and Age

Gender	Age	RR (95% CI)[1]
Males	55-64	2.92 (2.69-3.18)
Males	65-74	3.00 (2.89-3.13)
Males	75+	2.36 (2.24-2.48)

Gender	Age	RR (95% CI)[1]
Females	55-64	2.64 (2.43-2.86)
Females	65-74	2.87 (2.76-2.99)
Females	75+	2.47 (2.37-2.58)

Source: Data extracted from (US Dept HHS, 2014). Table 11.13 and Table 11.14
CI = Confidence Interval; RR = Relative Risk
[1] Adjusted for age, cohort, race, and education

The cigarette smoking data presented in Table 6.1-4 are also consistent with a meta-analysis of 11 published studies from 1998 to 2006 (Shavelle, Paculdo, Strauss, & Kush, 2008). Results were stratified by light, medium, and heavy smoking intensity, although the authors noted variation between studies in the definitions of these groups (Light: less than 10 cigarettes per day in five studies and less than 21 in one study; Medium: most often defined as 10-25 cigarettes per day; Heavy: generally 21-25+ cigarettes per day). Among males, the weighted, average, all-cause mortality adjusted HR were 1.47 for light smokers, 2.02 for medium smokers, and 2.38 for heavy smokers (CIs were not provided). For females, the weighted, average, all-cause mortality hazards were similar: light smokers, 1.50; medium smokers, 2.02; and heavy smokers, 2.66.

The significantly increased all-cause mortality risk among cigarette smokers contrasts with the modest or insignificant all-cause mortality adjusted HR calculated for ST users (Table 6.1-5) (Accortt et al., 2002; Henley et al., 2005).

Table 6.1-5: Summary of Published All-Cause Mortality Risk Estimates for Smokeless Tobacco Users

Study	Group	Smokeless Tobacco Exposure	HR (95% CI)
Henley et al., 2005	Males: CPS-I	Current	1.17 (1.11-1.23)
Henley et al., 2005	Males: CPS-II	Current	1.18 (1.08-1.29)
Accortt et al., 2002	Males	Ever	1.0 (0.8-1.3)
Accortt et al., 2002	Females	Ever	1.3 (0.9-1.7)

CI = Confidence Interval; HR = Hazard Ratio; CPS-I = Cancer Prevention Study I; CPS-II = Cancer Prevention Study II; ST = Smokeless

Timberlake et al. (2017) recently published an analysis of NLMS and arrived at a similar conclusion to ours regarding the lack of an association between ST use and excess all-cause mortality risk. While Timberlake found that unadjusted all-cause mortality HR estimates for current ST users were significantly greater than never users, adjustment for covariates (age, sex, race/ethnicity, education, and family income) resulted in an all-cause mortality estimate

for ST users that was not significantly different from never-tobacco users (HR = 1.01 (95 percent CI: 0.93-1.10)).

Together, the totality of evidence presented in Table 6.1-2, Table 6.1-3, and Table 6.1-4 demonstrate that the all-cause mortality risks from smoking are higher compared to ST use, even if we consider some of the literature reports of significantly elevated mortality risks from ST use.

6.1.2.1.2. Mortality from Malignant Neoplasms (All-Cancer)

Cigarette smoking is an established, preventable risk factor for many cancers, with the most prevalent being lung cancer.[6]

Among all respondents (or gender-specific sub-groups) in the NLMS and NHIS datasets, AS had a significantly elevated risk of approximately three-fold over never-tobacco users from mortality associated with malignant neoplasms (Table 6.1-6). In contrast, neither dataset indicated an increased mortality risk from malignant neoplasms among ST users. The malignant neoplasms included digestive organs (ICD codes C00-C16, C18-C22, C25); esophagus only (C15); pancreas only (ICD code C25); colon, rectum, and anus only (ICD codes C18-C21); oral cavity, lip, and pharynx (ICD codes C00-C14); trachea, bronchus, and lung (ICD codes C33-C34); and genitourinary system (ICD codes C61, C64-C65, C67).

Table 6.1-6: Mortality from Malignant Neoplasms: Adjusted Hazard Ratio Estimates[1] for Smokeless Tobacco Users (Exclusive) and Adult Cigarette Smokers (Exclusive) Compared to Never-Tobacco Users

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
All Respondents	NLMS	1,863	8	0.805 (0.385-1.682)	38,076	520	2.880 (2.520-3.291)
	NHIS[2]	1,561	71	1.079 (0.791-1.471)	36,071	2,262	2.951 (2.726-3.195)
Males	NLMS	1,646	1	0.124 (0.017-0.887)	16,597	233	2.469 (2.017-3.022)
	NHIS	1,219	29	1.124 (0.705-1.792)	13,517	843	3.126 (2.710-3.607)
White Males	NLMS	1,545	1	0.153 (0.021-1.097)	13,893	190	2.549 (2.039-3.186)
	NHIS	1,119	24	1.135 (0.672-	10,585	640	3.125

[6] Centers for Disease Control and Prevention: Smoking and Tobacco Use, Tobacco-Related Mortality. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
				1.916)			(2.677-3.647)
Females	NLMS	217	7	1.974 (0.883-4.410)	21,479	287	3.063 (2.572-3.649)
	NHIS	342	42	1.102 (0.740-1.640)	22,554	1,419	2.773 (2.512-3.060)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs. NTU).
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). Note: The analysis was conducted on all respondents (P4 analysis) with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from analyses of the restricted access data file.

We focus our proposed modified risk claim on lung cancer since cigarette smoking is a known risk factor for lung cancer and is the leading fatal disease among smokers. More people in the U.S. die from lung cancer than any other type of cancer. In fact, smoking is directly responsible for more than 80% of lung cancer deaths [Surgeon General Report (2014)]. Prognosis of lung cancer is poor; around 7% of patients survive for five years (Parsons, Daley, Begh, & Aveyard, 2010). Our analysis of the NHIS and NLMS data confirms a high rate of lung cancer mortality in cigarette smokers, but neither dataset yielded many reports of lung cancer mortality in ST users.

Among current exclusive smokers in the NLMS dataset, lung cancer (malignant neoplasms of trachea, bronchus, and lung) mortality risk approached a 12-fold increase over never use of tobacco (Table 6.1-7). In contrast, among individuals in this dataset who did not smoke, but were current users of ST, the incidence of lung cancer mortality was quite low (three out of 1,863 respondents). All three recorded deaths occurred among females, with no deaths recorded in males.

The number of mortalities in the NHIS data for some sub-groups used in the model that incorporated all tobacco use groups (P4) did not exceed the reportable number of deaths allowed by NCHS[7] for some groups. We calculated an estimate for lung cancer mortality based on NHIS data, using a slightly different model comparing only exclusive ST users to never-tobacco users (P0 analysis, Table 6.1-1). Under these model conditions, eight lung cancer cases were recorded in the NHIS dataset among 1,561 observations, yielding a HR of 2.090 and 95 percent CI of 0.804-5.432.

[7] Due to privacy concerns, the NCHS requested that we not present data when less than five deaths were present.

Table 6.1-7: Mortality from Neoplasms of the Trachea, Bronchus, and Lung: Adjusted Hazard Ratio Estimates[1] for Various Tobacco Use Practices Compared to Never-Tobacco Users (Data Obtained from NLMS)

Tobacco use	Observations	Deaths	HR[1] (95% CI)
Never smoker, Current ST user	1,863	3	2.979 (0.910-9.756)
Current smoker, Never ST user	38,076	247	11.522 (8.740-15.190)

Source: NLMS = National Longitudinal Mortality Study
ST = smokeless tobacco; CI = Confidence Interval; HR = Hazard Ratio; NLMS = National Longitudinal Mortality Study
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, education, family income, health status, and tobacco use). The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters) (Section 7.4.1).

Previous epidemiology studies have reported a possible association between ST use and lung cancer which was minimally significant in some cases (Table 6.1-8; Section 6.1.3). A meta-analysis of data specific to studies among the U.S. population, which was available at the time of analysis, suggested no association between ST use and lung cancer (Lee & Hamling, 2009a). Subsequent to the analysis by Lee and Hamling, Andreotti et al. (2016) provided lung cancer estimates using data from the Agricultural Health Study for ST users (Table 6.1-8). The authors stated that the prevalence of ST use in the study was higher than the general U.S. population, while cigarette smoking prevalence was lower, and they considered the study to have "sufficient statistical power to evaluate cancer incidence in relation to exclusive and dual use of multiple types of tobacco products." Although the authors report increased risk for lung cancer in ST users when compared to non-tobacco users, this risk was still lower than that observed for smokers – the basis for our proposed modified risk claim.

Table 6.1-8: Summary of Lung Cancer Risk Estimates from U.S. Epidemiology Studies

Cohort Studies						
Author	***Gen-der***	***Tobacco use***		***Cases***	***Estimate (RR or OR (95% CI))***	***Adjustment factors***
		ST	***Cig***			
Winn et al. (1981)	M	Ever	Never	NA	0.60 (NA)	Age
Accortt et al. (2005) (NHANES I)	F	Ever	Never	4	6.80 (1.60–28.5)	Age, PIR, Race
Henley et al. (2005) (CPS-I)	M	Current	Never	18	1.08 (0.64–1.83)	Age, Alcohol, Asp, BMI, diet, Edu, Exercise, Occ, Race
Henley et al. (2005) (CPS-II)	M	Current	Never	18	2.00 (1.23–3.24)	Age, Alcohol, Asp, BMI, diet,
		Former		4	1.17 (0.43–3.14)	

Cohort Studies						
Author	***Gender***	***Tobacco use***		***Cases***	***Estimate (RR or OR (95% CI))***	***Adjustment factors***
		ST	***Cig***			
		Ever		22	1.77 (1.14–2.74)	Edu, Exercise, Occ, Race
		Chew only		12	1.97 (1.10–3.54)	
		Snuff only		2	2.08 (0.51–8.46)	
Andreotti et al. (2016) Agricultural Health Study	NR	ST	NR	10	2.21 (1.11-4.42)	Age, Alcohol, Gender, Race, Edu, State of Res.
		Chew		7	2.20 (0.98-4.97)	
		Snuff		3	-	
Williams and Horm (1977)	M	Ever	Ever	36	0.69 (0.47–1.00)	Age, Race, Smoking
	F			1	0.38 (0.05–2.80)	None
Wynder and Stellman (1977)	M	Chew	Ever	117	1.26 (0.99–1.59)	None
		Snuff		35	1.25 (0.83–1.89)	
		ST		152	1.27 (1.03–1.57)	
Meta-Analysis						
Author	***Gender***	***Group***		***Studies***	***Random Effect (RR (95%CI))***	***Adjustment factors***
Lee and Hamling (2009b)	M & F	Overall		6	1.22 (0.82–1.83)	Individual study dependent
		Smoking adjusted		4	1.38 (0.72–2.64)	
		Never smokers		3	1.79 (0.91–3.51)	

ASP = Aspirin; BMI = Body Mass Index; CI = Confidence Interval; Edu = Education; NR = Not Reported; Occ = Occupation; OR = Odds Ratio; PIR = Poverty Index Ratio; RR = Relative Risk; ST = Smokeless Tobacco

Andreotti et al. (2016) also report lung cancer risk associated with certain behaviors related to cigarette smoking (Table 6.1-9). Consistent with many previous studies, cigarette smoking in the study had a significant adverse impact on health by increasing lung cancer risk in smokers by 15 times over the levels found in non-tobacco users. The impact of smoking cessation is evident in the data where former smokers demonstrated a reduced, but still significantly elevated, risk of lung cancer over the non-tobacco use control group. The study data also suggested some relationship between risk and smoking intensity. Point estimates for shorter duration and fewer cigarettes per day were generally less than those for the higher intensity values; however, the differences were not statistically significant.

Table 6.1-9: Lung Cancer Risk for Exclusive Use of Cigarettes Compared to Non-tobacco Users

Cigarette Use Characteristics		Cases	HR (95% CI)
Status	Ever	401	15.48 (11.95- 20.06)
	Current	262	23.03 (17.34- 30.59)
	Former	139	9.30 (6.56- 13.18)
Duration	≤15yrs	49	21.56 (2.80- 66.29)
	>15 yrs	338	22.57 (17.16- 29.69)
Frequency	≤15/day	208	22.49 (16.10- 31.40)
	>15/day	182	29.25 (21.25- 40.26)

Source: Andreotti et al. (2016) Table 2. Study of 29,913 male and 8,897 female tobacco users.
HR = Hazard Ratio

Even if one assumes a relevant association between ST use and excess lung cancer mortality risk, considering the risk estimates illustrated in Table 6.1-7, Table 6.1-8 and Table 6.1-9, such risk is far lower than that observed for cigarette smoking.

In addition to information related to lung cancer mortality, the Linked Mortality datasets contained mortality data related to other types of cancers. ST use was not associated with excess risk for any cause of mortality in the NLMS dataset. Table 6.1-10 presents adjusted HR calculated for other neoplasms among exclusive ST users in the NLMS (never smokers) compared to current smokers who never used ST. There is evidence that cigarette smokers, but not ST users, have an increased mortality risk from malignant neoplasms of the esophagus, oral cavity, and genitourinary system. In the case of oral cavity, lip, and pharyngeal cancers, cigarette smoking mortality risk increased six-fold relative to never-tobacco use. We do not present NHIS study data in this analysis, since some groups in the NHIS dataset contained incidences for these cancers below the reportable range of five per group.

Table 6.1-10: Mortality from Malignant Neoplasms of Esophagus, Pancreas, Colon, Oral Cavity, or Genitourinary System: Adjusted Hazard Ratio Estimates for Various Tobacco Usage Compared to Never-Tobacco Users (Data obtained from NLMS)

Site	Tobacco use		Observations	Deaths	HR (95% CI)[1]
	Smoking	ST			
Esophagus	Never	Current	1,863	1	2.439 (0.312-19.052)
	Current	Never	38,076	16	2.312 (1.101-4.853)
Pancreas	Never	Current	1,863	1	1.364 (0.186-9.976)
	Current	Never	38,076	24	1.483 (0.858-2.562)
Colon, rectum, anus	Never	Current	1,863	0	NE
	Current	Never	38,076	30	1.465 (0.912-2.353)

Site	Tobacco use		Observations	Deaths	HR (95% CI)[1]
	Smoking	ST			
Oral cavity, lip, pharynx	Never	Current	1,863	0	NE
	Current	Never	38,076	9	6.325 (1.461-27.377)
Genitourinary	Never	Current	1,863	1	0.513 (0.070-3.778)
	Current	Never	38,076	37	2.104 (1.338-3.309)

Source: NLMS = Linked Mortality Analysis appendix (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs. NTU)
CI = Confidence Interval; HR = Hazard Ratio; NE = Not Estimated; ST = Smokeless tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, education, family income, health status, and tobacco use). The analysis was conducted on all respondents (P4 analysis) with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

Our analysis of the NLMS and NHIS datasets finds that the malignant neoplasm mortality risks among ST users relative to never tobacco users are substantially lower than those of current smokers relative to never tobacco use. This holds true even for diseases that public health authorities have causally associated with ST use, including oral, esophageal, and pancreatic cancers. Inferences made from the NLMS and NHIS datasets are consistent with previously published investigations of lung cancer mortality risks in smokers compared to people who only use ST.

6.1.2.1.3. Mortality from Diseases of the Heart

The CDC has identified heart disease as a major mortality risk among AS,[8] and some published literature (Gupta, Gupta, Sharma, Sinha, & Mehrotra, 2018; Timberlake et al., 2017) suggests a possible association between ST use and heart disease (Section 6.1.3). Our analysis of NHIS and NLMS datasets (all-respondents, males, white males, or females) clearly indicated excess mortality risk from diseases of the heart in AS compared to never-tobacco users; however, for this broad category of diseases of the heart, no such excess risk was identified among ST users compared to never tobacco users (Table 6.1-11).

Table 6.1-11: Mortality from Diseases of the Heart: Adjusted Hazard Ratio Estimates for Smokeless Tobacco Users (Exclusive) and Adult Cigarette Smokers (Exclusive) Compared to Never-Tobacco Users

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
All Respondents	NLMS	1,863	22	1.073 (0.656-1.754)	38,076	378	1.613 (1.404-1.853)

[8] Centers for Disease Control and Prevention: Smoking and Tobacco Use, Tobacco-Related Mortality. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm

Group	Study	ST Users (Exclusive)			Cigarette Smoking (Exclusive)		
		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
	NHIS[2]	1,561	114	1.176 (0.895-1.547)	36,071	1,796	1.951 (1.812-2.100)
Males	NLMS	1,646	13	1.113 (0.575-2.155)	16,597	194	1.570 (1.282-1.923)
	NHIS	1,219	48	1.408 (0.905-2.191)	13,517	733	2.152 (1.887-2.456)
White Males	NLMS	1,545	12	1.391 (0.699-2.769)	13,893	163	1.765 (1.415-2.202)
	NHIS	1,119	38	1.531 (0.942-2.489)	10,585	567	2.334 (2.019-2.698)
Females	NLMS	217	9	0.963 (0.464-2.000)	21,479	184	1.668 (1.378-2.018)
	NHIS[3]	399	44	0.816 (0.552-1.208)	22,554	829	1.929 (1.745-2.132)

Source: NLMS = Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs. NTU).
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco

[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, tobacco use). Note: The analysis was conducted on all respondents (P4 analysis) with the reference group comprising individuals who never used tobacco (according to survey defined parameters). The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

[2] NHIS data obtained from analyses of the restricted access data file.

[3] The number of deaths in one tobacco use category in the NHIS restricted file was <5. We show here instead an estimate based on the NHIS Public Use Full Follow-up data which reasonably approximates the numbers of observations and deaths for the restricted access file.

6.1.2.1.4. Nonclinical and Clinical Studies

In addition to the epidemiological evidence described above, we include several additional lines of nonclinical and clinical evidence that inform the health risks of ST products and cigarettes. We assign significant weight to the epidemiological studies in the hierarchy of evidence, as they provide health outcomes from long-term product use behavior under real-world conditions. Nonclinical and clinical studies are also important and provide additional information regarding the likelihood of health outcomes and the mechanistic basis for the epidemiological findings.

- Nonclinical Studies
  - Analysis of harmful and potentially harmful constituents (HPHC)
  - In-vitro toxicological assessments
  - Animal studies
- Clinical Studies
  - Biomarkers of exposure to select combustion related and tobacco specific HPHC
  - Biomarkers of potential harm related to inflammation that provide insights to smoking-related disease mechanisms

6.1.2.1.4.1.Nonclinical Studies

We summarize here many of the findings related to pre-clinical testing of ST products and compare those with findings from studies with cigarette smoke. Not unexpectedly, given the interest in tobacco product toxicity over the years (particularly cigarette smoke), there is a large body of evidence regarding nonclinical studies with tobacco products. Since many of these studies provide consistent information, corroborating the fundamental observations that tobacco products perturb biological systems, we summarize here only the key findings. We provide an expanded discussion of publications and a summary evidence table describing preclinical testing related to ST products in Section 7.5.6-1 and 7.5.6-2.

HPHC Analysis

Establishing the presence and levels of chemical constituents in cigarette smoke and ST, particularly those identified as HPHCs, provides insight into potential chemical exposure and disease risks. ST is non-combustible. As such, many of the combustion-related constituents found in cigarette smoke (e.g. “tar”) are absent or present at significantly lower levels. In their 2009 review, the Life Sciences Research Office (LSRO)[9] noted that the absence of tobacco combustion results in the obvious major chemical differences between cigarettes and ST products [LSRO (2008)]. Current epidemiology clearly establishes that the use of ST, compared with cigarette smoking, results in vastly lower risk of virtually all tobacco-related diseases. The biological basis for this risk differential, particularly lower lung cancer risk, is likely associated with the route of exposure, oral vs. pulmonary, combined with lower overall tobacco constituent exposure.

Burning of the cigarette (tobacco and paper) during smoking transfers chemical constituents of tobacco and products of combustion to cigarette smoke that comprise the “vapor phase”

[9]The Life Sciences Research Office, Inc. (LSRO) convened an Expert Panel of scientists and physicians in 2009 to conduct an independent, comprehensive scientific literature evaluation comparing the risks of ST product use to smoking cigarettes, to identify the critical characteristics that contribute to an evaluation of risk, and to determine whether there is sufficient evidence to categorize ST products according to risk. The project was funded by Philip Morris USA. The Differentiating Tobacco Risks (DTR) project is a case study of LSRO's Reduced Risk Review Project (RRRP), and utilized the risk assessment framework developed from the RRRP. http://www.lsro.org/articles/dtr_0209 html

and "particulate phase" (Baker, 1999; Hoffmann, Hoffmann, & El-Bayoumy, 2001). Cigarettes and cigarette smoke chemistry have been repeatedly analyzed, and the potential health impacts of exposure to smoke constituents have been well established (Dube & Green, 1982); (Hoffmann & Hoffmann, 1997); [Surgeon General Report (2014)]. Close to 8,700 individual constituents of tobacco smoke have been identified (Rodgman & Perfetti, 2009), and according to IARC's classification system for carcinogens, cigarette smoke contains more than 70 carcinogens (Hoffmann et al., 2001).

In contrast to the chemical complexity of cigarette smoke, ST contains a simpler chemical matrix, and many of the combustion-related constituents found in cigarette smoke are absent or present at significantly lower levels in ST. Chemical analysis of ST and ST products has concentrated on a relatively small number of ST constituents that are also present in cigarette smoke, focused specifically on the chemicals reportedly believed to have carcinogenic potential (Brunnemann & Hoffmann, 1992; Hoffmann & Hoffmann, 1997; International Agency on Research for Cancer (IARC), 2007; Oldham, DeSoi, Rimmer, Wagner, & Morton, 2014; Pappas, Stanfill, Watson, & Ashley, 2008; Richter, Hodge, Stanfill, Zhang, & Watson, 2008; Richter & Spierto, 2003; Rodu & Jansson, 2004; Stepanov et al., 2008).

Nicotine is a tobacco component common to both cigarette smoke and ST. Other constituents generally identified in both cigarette smoke and ST include carcinogens such as TSNA, polycyclic aromatic hydrocarbons (PAH), volatile aldehydes, heavy metals, and polonium-210. Regarding the toxicological relevance of constituents in tobacco products, Hecht (2006) has suggested that "the most important, based on their carcinogenic potency and levels in cigarette smoke are probably PAH, N-nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes, and ethylene oxide." Hecht notes, however, that "although difficult to prove, data from certain carcinogenicity studies, product analyses, and biochemical and molecular biological investigations do support a significant role for certain carcinogens in specific types of cancer."

Like cigarette smoke, ST products deliver pharmacologically active doses of nicotine. Nicotine is not considered carcinogenic (Hecht, 2006), but has been associated with certain cardiovascular effects that may contribute to cardiovascular risks from smoking Surgeon General Report (2004). However, the U.S. Surgeon General's report (2014) noted that studies of nicotine replacement therapy demonstrating no increase in cardiovascular risk suggest that chemicals other than nicotine in cigarette smoke may contribute to the elevated CVD risk associated with smoking.

TSNAs (N_-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N_-nitrosoanabasine (NAB), and N_-nitrosoanatabine (NAT)) are considered by many researchers to be the most important carcinogens in ST products and cigarette smoke, and are, therefore, among their most frequently analyzed constituents (Hoffmann & Hoffmann, 1997; Stepanov, Jensen, Hatsukami, & Hecht, 2006; Wu, Ashley, & Watson, 2003). NNN and NNK are considered by IARC to be Group 1 carcinogens (carcinogenic to humans), while NAB is a weak rodent carcinogen and NAT lacks carcinogenic activity (Hecht, 1998). Stepanov et al. (2008) estimated potential exposures for ST product constituents on a "per portion" basis and noted that if portion sizes were similar for conventional and "new" ST products, the toxicant and carcinogen intakes, including intakes

of TSNAs, would be somewhat similar (Stepanov et al., 2008). As discussed elsewhere in this application (Section 2.3.3.4 and Figure 2.3-8), USSTC implemented procedures in the manufacturing process more than a decade ago that limit TSNA formation from the time of purchase of tobacco leaf from farmers through the end of retail shelf life of the product. Djordjevic et al. (1993) observed general TSNA reductions in the marketplace, reporting that, over the time period of 1980 to 1992, TSNA content was reduced by 70-90% for two "leading U.S. snuff brands." We note that during this period the candidate product had approximately 40% of the MST market share (Figure 2.3-7). Since full implementation of process refinements by USSTC in 2005, TSNA levels have measured consistently about 10 µg/g or lower (Fisher et al., 2012) from the time tobacco is purchased from farmers through the end of product retail shelf life.

The role of PAHs in health risks associated with ST use, if any, remains unclear. Some PAHs (e.g., benzo(a)pyrene (B[a]P) are considered probable human carcinogens (International Agency on Research for Cancer (IARC), 2010) or co-carcinogens (Stepanov et al., 2010). PAHs are environmental chemicals commonly formed through incomplete combustion of organic matter. PAHs may appear in some ST products as a result of deposition of wood smoke particulates during the fire-curing step for some tobaccos. In their 2010 study, Stepanov et al. analyzed levels of various PAHs in extracts of a selection of 23 moist snuff products and 17 "spit-free" tobacco pouches (snus) marketed in the U.S. The authors found high levels of PAHs in some ST extracts (including Copenhagen Snuff), noting that the possible exposure to 14 PAHs (5.41 µg/1g sample of moist snuff) exceeded a similar total PAH exposure of 1.15 – 1.29 µg/cigarette provided by Ding et al. (2007). However, Stepanov et al., (2010) noted that the high levels of PAHs in MST comprised PAHs that were not listed as established carcinogens. Furthermore, the reported high levels of PAHs are not manifested in human exposure studies. As we note below in Section 6.1.2.1.4.2, the levels of urinary 1-hydroxypyrene, a well-established human biomarker of PAH exposure, are not significantly different in ST users (181.4±238 ng/24H) compared to non-tobacco users (113.4 ± 113.8 ng/24H) and significantly lower compared to smokers (369.3±345.2 ng/24H) (Prasad, Jones, Chen, & Gregg, 2016).

Heavy metals such as arsenic, cadmium, beryllium, chromium, and nickel are found in varying amounts in tobacco as a result of soil composition, tobacco variety, growing conditions, air pollution, and other environmental factors. Relatively few studies have reported the presence of metals in ST products (Borgerding, Bodnar, Curtin, & Swauger, 2012; Hoffmann, Adams, Lisk, Fisenne, & Brunnemann, 1987; Pappas et al., 2008). Hoffmann et al. (1987) measured lead, cadmium and selenium in five samples of moist snuff and three samples of dry snuff (none identified by brand) from the 1985-86 U.S. market and the estimated daily intake of these elements by a ST user. They concluded that "the trace amounts of these three elements in snuff will not make a significant contribution to its toxicity or carcinogenicity."

Several other chemical constituents have been measured in cigarette tobacco, cigarette smoke and/or ST products including volatile aldehydes (formaldehyde, acetaldehyde); radionuclides (polonium-210); and the volatile nitrosamine, NDMA (Stepanov et al., 2008). The potential

health effects of many of these substances in ST products relative to cigarettes have not been directly evaluated.

Because ST products are not combusted and do not produce mainstream or sidestream smoke, users and nonusers are not exposed to the combustion products associated with many of the health risks of smoking. In contrast to the chemical complexity of cigarette smoke, ST appears to be a simpler chemical matrix, and many of the combustion-related constituents found in cigarette smoke are absent or present at significantly lower levels in ST. Adult tobacco consumers, therefore, should experience significant reductions in exposure to such HPHCS.

In vitro toxicological assessments

A number of *in vitro* assays have been used to assess perturbations in biological systems including cytotoxicity, cell proliferation, cell cycle control, apoptosis, and genotoxicity. Given the strong causal association between cigarette smoking and human disease, considerable research has focused on identifying underlying potential mechanisms. Several reviews (Andreoli, Gigante, & Nunziata, 2003; DeMarini, 2004; Johnson, Schilz, Djordjevic, Rice, & Shields, 2009) have discussed *in vitro* methods for assessing tobacco products, and FDA recently conducted a workshop on this topic (Behrsing et al., 2017). As stated in the 2012 MRTPA Draft Guidance, *in vitro* studies "[m]ay offer useful information about the health risks," and "[a]lso provide context for data obtained from other types of studies, such as product analyses and human studies." We summarize the numerous nonclinical studies related to U.S. ST products that appear in the published literature (Section 7.5.6-1 and 7.5.6-2).

Despite differences in extraction and testing conditions, ST products have consistently been shown to be less genotoxic and cytotoxic than cigarette smoke. While mainstream cigarette smoke and cigarette smoke condensate are genotoxic in nearly all systems in which they have been tested (e.g., bacterial mutagenicity, sister chromatid exchanges, micronuclei in bone marrow and lung cells, DNA adduct, and other genetic abnormalities), ST products exhibit substantially lower perturbations in similar assays (Jansson, Romert, Magnusson, & Jenssen, 1991; Rickert, Wright, Trivedi, Momin, & Lauterbach, 2007). These results were also corroborated in a human study by Benowitz et al., (1989) where the urine mutagenicity was significantly ($p<0.05$) lower in ST users compared to cigarette smokers. Urine mutagenicity of MST users was not increased compared to nonusers and urine mutagenicity in users of chewing tobacco "tended to be increased" when compared to that of nonusers, but this increase was not statistically significant ($p < 0.05$).

Genotoxicity and cytotoxicity assays, while useful as screening tools, also provide mechanistic insights regarding smoking-related disease mechanisms. Test systems like a bacterial mutagenesis assay, evaluating induction of mutations in target genes, provide insights regarding genotoxic potential, one of the mechanisms for carcinogenesis. In a recent *in vitro* air-liquid interface study by Thorne et al., (2017), the gas/vapor phase constituents of cigarette smoke were shown to account for the majority of cytotoxicity (~65%) from cigarette smoke. The absence of combustion related constituents in ST, along with lack of direct pulmonary exposure, therefore, provide plausible rationale explaining the differential lung cancer risk between cigarettes and ST.

In addition to cell-based assays, recent advances in methods to assess proteins and genes at the cellular level have provided additional mechanistic insights regarding the differential risks between ST and cigarettes. Exposure to cigarette smoke is a major risk factor for oral squamous cell carcinoma (OSCC) of the head and neck, with cigarette smokers having 7–10 times greater risk than never smokers (Jha et al., 2013; Lee & Hamling, 2009b). Woo et al. (2017) performed microarray-based gene expression profiling in normal, non-metastatic, and metastatic OSSC human cell lines exposed to cigarette smoke total particulate matter preparations, whole-smoke conditioned media, smokeless tobacco extract in complete artificial saliva, or nicotine. Xenobiotic metabolism and steroid biosynthesis were the two major pathways upregulated by combustible tobacco preparations, but not by non-combustible tobacco preparations. Aldo-keto reductase enzymes, AKR1C1 and AKR1C2 were statistically upregulated more than eight-fold by combustible TPPs. Overexpression of AKR1C1/2 has been found in buccal oral samples of smokers (Boyle et al., 2010; Gumus et al., 2008), and observed in non-small cell lung carcinoma (Fukumoto et al., 2005; Hsu et al., 2001). In bronchial epithelial cell brushes of smokers, AKR1C1 and AKR1C2 were two of the most upregulated genes, but their expressions were downregulated in smokers who quit (L. Zhang et al., 2008; X. Zhang et al., 2010).

To summarize, based on HPHC analysis, ST is less likely to illicit a biological effect compared to cigarette smoke. The reduced effects observed in the *in vitro* test systems with ST preparations compared to cigarette smoke preparations are consistent with the expected reductions in exposure to combustion-related HPHCs from ST use compared to cigarette smoking. Further, we note that the differential effects between ST products and cigarettes in the nonclinical studies are also consistent with current epidemiology presented in this application (Section 6.1.2) showing lower lung cancer risk for ST users compared to cigarette smoking.

Animal studies

There are no animal studies with a head-to-head comparison of ST product extracts vs. cigarette smoke. Most animal models used for testing the carcinogenic potential of ST products are designed to investigate questions of oral cancer and use a cheek pouch assay method (either naturally occurring as for hamsters or surgically created for rodents). The animal models summarized in this section are highly artificial, using oral pouches formed surgically which are then sewn shut to retain the test material, neither adequately represents human ST user behavior. Refinement of the cheek pouch assay (natural pouch in hamsters) led to creation of a method using an artificial lip canal surgically created in the lower lip of rats and intended to hold the ST product (Hirsch & Thilander, 1981). In their studies, no oral tumors resulted from long-term administration of ST using this technique, but evidence of epithelial hyperplasia and dysplasia were observed. Hecht et al. (1986) used a similar “lip canal” technique in rats to investigate effects of snuff, snuff extracts, pure preparations of the nitrosamines NNN and NNK, and a mixture of snuff extract plus nitrosamines. Although oral tumor incidence in rats treated with snuff was greater than controls, it was not statistically significant. The pattern of tumor response in other groups led the authors to speculate that snuff extract may actually contain inhibitors of NNN and NNK activation (Hecht, Trushin, et al., 1986). Johansson and colleagues (Johansson, Hirsch, Larsson, Saidi, & Osterdahl, 1989;

Johansson, Saidi, Osterdahl, & Smith, 1991) also used the lip canal technique to study tumor occurrence and promotion potential of snuff, concluding that the presence of squamous lesions in some experimental groups suggests that snuff has a weak carcinogenic potential with regard to squamous lesions. Despite individual studies showing possible exposure-related effects, Grasso and Mann (1998) concluded that the sum total of experimental work in animal models regarding ST and oral cancer suggests that "snuff" (types not specified, but both moist and dry snuff described) is not carcinogenic to the oral mucosa of hamsters or rats.

The potential role of tobacco constituents, such as NNK, in lung cancer has also been investigated in animal models through different routes of exposure including intravenous, intraperitoneal, subcutaneous etc., (Ge, Xu, & Chen, 2015). Hecht and Hoffmann (1988) hypothesized that exposure to NNN or NNK, found in ST, could promote lung cancer development. The authors report NNK to be particularly organ specific for the lung in rat, mouse, and hamster animal models. Exposures via subcutaneous injection, oral swabbing, or topical application have all produced increased numbers of animals with lung tumors, with DNA adduct formation providing a potential mechanistic explanation for this phenomena.

We found the research conducted by Rivenson et al, in which they administered NNK in drinking water (i.e. oral route exposure), to be applicable in assessing health risks of ST products. Rivenson et al. (1988) administered 0.5, 1.0, or 5.0 ppm of NNK to male F344 rat via drinking water for a lifetime and noted a statistically significant dose-related trend toward increased incidence of lung tumors. The authors also noted an increased incidence of pancreatic tumors in some NNK groups. Earlier studies of NNK using subcutaneous injections also increased lung cancer response, but did not increase pancreatic cancer incidence (Hecht, Rivenson, et al., 1986; Lijinsky & Taylor, 1976). The oral exposure study by Rivenson is directly applicable to an examination of the health risks of oral ST product use; nonetheless, the relevance of these findings should be assessed in the context of estimated actual human exposure levels of NNK. While these animal studies suggest that NNK plays a possible mechanistic role in lung cancer, the doses of NNK required to induce lung tumor in the drinking water study were ~60 times higher than the typical estimated amount of NNK exposure over a 20-year period of ST use (Hecht et al., 2008).

Evaluation of MST acting as a modulator of carcinogenicity also provides mixed outcomes, which appear to depend on the initiating agent used in the study. For example, evidence suggests that when using 7, 12-dimethyl(a)anthracene or ethanol as initiating agents, MST does not modulate carcinogenesis (Johansson et al., 1989; Johansson, Hirsch, Larsson, Saidi, & Osterdahl, 1991; Summerlin, Dunipace, & Potter, 1992). There is sufficient evidence to suggest that MST may promote viral-mediated carcinogenesis; in contrast, however, there is sufficient evidence to suggest that MST does not promote TSNA-induced tumor formation (Brunnemann, Genoble, & Hoffmann, 1987; Hecht, Rivenson, et al., 1986). In fact, the evidence suggests that MST may even inhibit TSNA-induced carcinogenesis (Prokopczyk, Adams, LaVoie, & Hoffmann, 1987).

A critical unknown factor regarding *in vitro* and *in viv*o studies is the relevance of the ST exposure regimen and preparation of study product compared with the ST exposure conditions encountered by humans. Oral cancer studies in animal models are exceedingly

difficult to conduct without creating some unique exposure system or dosing regimen that does not fit the human situation. Similarly, chemical extraction of ST before conducting *in vitro* experiments may or may not actually represent human exposure situations. The relevance of the nonclinical research methods with ST to actual human exposure, as related to use behavior, has not been established.

In summary, while there are reports of an association between TSNA and carcinogenesis in nonclinical studies, the causal role of TSNA in the potential health effects of ST in humans is still open to question. Current human epidemiology among ST users does not confirm the observations reported in animals.

6.1.2.1.4.2.Clinical Studies

Biomarkers of exposure to select combustion-related and tobacco-specific HPHC

Biomarkers of exposure undoubtedly provide more reliable estimates of HPHC exposure compared to product chemistry analysis, since these studies incorporate actual human use of tobacco products and account for factors that cannot be replicated in *in vitro* studies, including differences in routes of administration, absorption, distribution, metabolism, and excretion. Biomarker measurements represent a constituent or metabolite present in biological fluid or tissue after it has interacted with critical subcellular, cellular, or target tissues and may either be direct measurement of a chemical (e.g., cadmium levels in blood or serum), or indirect (e.g., total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in urine as an estimate of NNK exposure (Hatsukami, Benowitz, Rennard, Oncken, & Hecht, 2006).

Biomarker studies with ST users have primarily focused on traditional smoking-related endpoints, including measurements of nicotine, cotinine, TSNAs, other tobacco toxicants, and their metabolites in serum, urine, and saliva. Some comparative BOEs measured in cigarette smokers and ST users indicate that exclusive ST users may have exposure to nicotine or TSNAs comparable to, or even higher than, in smokers (Carmella, Han, Fristad, Yang, & Hecht, 2003; Rostron, Chang, van Bemmel, Xia, & Blount, 2015; Stepanov & Hecht, 2005). In contrast, other biomarker studies of ST consumers confirm that exposures to most of the constituents associated with tobacco combustion are lower than in smokers and are similar to those of non–tobacco users (Campbell, Brown, Jones, Marano, & Borgerding, 2015; Naufal, Marano, Kathman, & Wilson, 2011; Prasad et al., 2016; Sarkar et al., 2010).

In general, cigarettes contain about 15-18 mg of nicotine per gram of unburned tobacco, or an average of 10-12 mg of nicotine in the unburned tobacco per cigarette. ST, by contrast, contains lower levels of nicotine per gram of tobacco (range 10-12 mg/g - (Oldham et al., 2014). While cigarettes are combusted, and only a small fraction (~10%) remains in the mainstream smoke that is inhaled into the lungs, the amount of nicotine delivered depends on individual smoking behaviors, such as puff frequency, puff volume, and inhalation behavior. ST, however, is ingested orally and numerous tobacco, product, and behavior characteristics influence the absorption of nicotine, including types and amounts of tobacco, tobacco cuts, particle size, and behavioral characteristics of the ST user (use frequency, how long it is held in the mouth, the amount of salivation, etc.). ST users generally maintain similar daily

plasma nicotine levels (Foulds, Ramstrom, Burke, & Fagerstrom, 2003). Benowitz (1997) found that the systemic absorption and levels of nicotine are similar in ST users and cigarette smokers. ST users have higher plasma cotinine levels, but this may reflect more rapid metabolism of orally ingested nicotine than occurs in smokers (Ebbert et al., 2004). We present a comparison of the nicotine plasma levels from the candidate product relative to own brand cigarette in Section 6.3.8.1.1; Figure 6.3.5,. Nicotine plasma levels were lower by ~12% on average, although not statistically significantly different, between the candidate product and own brand cigarettes.

Some researchers consider TSNAs (NNN, NNK, NAB, and NAT) to be the most important carcinogens in tobacco because of a possible link to lung cancer (Hecht et al., 2008); however, the causal association between TSNAs from cigarette products and induction of lung cancer or other cancers in humans is not known with certainty. NNAL and glucuronide conjugates of this metabolite in urine have frequently been used to estimate NNK uptake in smokers and ST users. Yuan et al. (2009) measured urinary levels of total NNAL in smokers and found a statistical association with lung cancer risk in a dose-dependent manner. Watanabe et al. (2009), however, evaluated the relationship between NNK in cigarette smoke and incremental lifetime cancer risks noting that NNK would likely only account for a small proportion of the lung cancer risk derived from epidemiological data. Watanabe et al. (2009) also suggested that complete removal of NNK, NNN, and B(a)P from the smoke of cigarettes would bring little to no reduction in cancer risks due to smoking. Hecht et al. (2008) reported a 14-17% conversion rate of NNK to total NNAL in ST users. Based on this rate, the authors estimated "…that the dose of NNK to a daily user of smokeless tobacco will be ~44 mg in 20 years of use or 0.6 mg/kg (0.003 mmol/kg)." The authors note that this amount is ~60 times less than the total dose of NNK that induced a significant incidence of lung and pancreatic tumors in rats upon chronic administration in drinking water (Rivenson et al., 1988).

Some studies report that the levels of NNAL, analyzed as total urinary NNAL (NNAL + glucuronides) or hemoglobin adducts of the TSNA 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) in blood, are greater in ST users than those found in smokers. Rostron and colleagues (2015) observe higher levels of total urinary NNAL in ST users compared to smokers in adult participants of the National Health and Nutrition and Examination Survey (NHANES). Rostron and colleagues (2015) also noted that, based on limited sample sizes, the estimated NNAL concentrations for ST users substantially decreased from 1013.7 pg/mg creatinine (95% CI = 738.9, 1390.8) in the 2007-2008 sample to 325.7 pg/mg creatinine (95% CI = 159.6, 664.9) in the 2011-2012 sample. Cotinine concentrations for ST users during this time were relatively steady, as were mean NNAL concentrations for smokers. The authors suggest that product use changes do not appear to account for the reduction in NNAL, since ST product use was stable (about 4.3 to 4.5 days each week in either time period). However, ST products showed a general reduction in TSNA levels during the biomarker study period, as indicated by published product analysis studies (Borgerding et al., 2012; Fisher et al., 2012).

There is a vast body of research on cellular DNA damage associated with TSNA constituents found in tobacco and tobacco smoke (Nilsson, 2011, 2017). DNA adducts can provide an integrated measurement of carcinogen intake, metabolic activation (α-hydroxylation catalyzed by cytochrome P450s), and delivery to the target macromolecule in target tissues

(Phillips, 2005). Based on several studies in animal models, DNA adducts have been linked to the carcinogenesis mechanisms (Hecht, 2003). The formation of DNA adducts has the potential to cause miscoding and mutations and affect growth control genes, a critical step in carcinogenesis by NNK and NNAL. Ma et al., (2018) reported finding 160 different, structurally unique DNA phosphate adducts in tissues of rats treated with NNK via drinking water. The presence of adducts is consistent with a carcinogenic hazard, but there is currently no established relationship between adduct levels and the level of disease risk (Phillips, 2005). Measurable levels of DNA adducts with oral administration of NNK in rodents has lead to the hypothesis that similar DNA adduct formation could result in ST users exposed to NNK. However, Nilsson (2017) argues that inhibited adduct repair efficacy at high TSNA doses used in rodent bioassays could result in exaggerated risk estimates for humans.

When assessing biomarkers of exposure it is important to recognize that many smoke constituents are ubiquitous, non-specific to cigarette smoke, and arise from other sources of exposure. ST users can show some cigarette HPHC levels similar to non-tobacco users because of environmental sources. For example, the biomarker of exposure to PAHs (found in cigarette smoke), 1-hydroxypyrene, also appears at relatively high levels in non-smokers due to dietary or environmental exposure (Strickland & Kang, 1999; Strickland, Kang, & Sithisarankul, 1996). The levels of urinary 1-hydroxypyrene in ST users (181.4$\pm$238 ng/24H) have been reported (Prasad et al., 2016) to be not significantly different than non-tobacco users (113.4 $\pm$ 113.8 ng/24H) and significantly lower than smokers (369.3$\pm$345.2 ng/24H). Similar results were reported by the authors for other PAHs (1- and 9-hydroxyphenanthrene, 2- and 3-hydroxyphenathrene, 1-naphthol, 2-naphthol and 2- and 3-hydroxyphenathrene) (Prasad et al., 2016).

In a large sample based on NHANES data, biomarkers of exposure to many of the other HPHCs (blood cadmium, blood mercury and urinary arsenic) were not elevated among ST users compared with non-tobacco users (Rostron et al., 2015). Prasad et. al corroborated similar observations related to cadmium (Prasad et al., 2016). Additional trace metals like chromium, nickel, tin, and selenium were also found to be not significantly different in ST users compared to non-tobacco users (Prasad et al., 2016).

Tobacco smoke, which comprises an aerosol (a mixture of solid and liquid particles) and gases, has thousands of chemical components, including many well-characterized toxins and carcinogens [IARC (2007)], many of which are present in the gas phase. The pulmonary toxicity of many of the gas phase constituents found in cigarette smoke are well established; for example, acrolein is an established pulmonary irritant and cilia toxicant, and it impairs lung defenses. The 2010 U.S. Surgeon General Report provides a compilation of the mechanistic studies related to pulmonary toxicity. Therefore, this MRTPA does not include a detailed discussion on this topic. The candidate product is non-combustible, and, therefore, ST users are not exposed to any of the gas phase HPHC, providing the mechanistic basis for lack of pulmonary effects in ST users compared to cigarette smokers.

Prasad et al., confirmed the lack of exposure to gas phase HPHC in a study (Prasad et al., 2016) where biomarkers of exposure to 1,3-butadiene, acrolein, crotonaldehyde, benzene, and acrylamide were observed to be statistically significantly lower in ST users compared to cigarette smokers and not statistically different compared to non-tobacco users. The urinary

levels of the mercapturic acid (MA) metabolite of 1,3-butadiene (monohydroxy butenyl MA) were 70±99.1 ng/24H in ST users compared to 195.6 ± 106.4 ng/24H in smokers; urinary levels of MA metabolite of acrolein (3-hydroxy propyl MA) were 746 ± 648.1 ng/24H in ST users compared to 3747 ± 1663.9 ng/24H in smokers; urinary levels of MA metabolite of crotonaldehyde (hydroxy methyl MA) were 333 ± 212.5 ng/24H in ST users compared to 1782.9 ± 894.6 ng/24H in smokers; urinary levels of MA metabolite of acrylamide (N-acetyl-S-(2-carbamoylethy)-cysteine and N-acetyl-S-(2-carbamoyl-2-hydroxyethl)-cysteine) respectively were 172.8 ± 93.2 and 23.2 ± 10.9 ng/24H in ST users compared to 388.1 ± 166.6 and 51.7 ± 25.3 ng/24H in smokers. These results were confirmed in another study (Campbell et al., 2015), where the authors report no significant differences in biomarkers of acrolein, benzene, pyrene, carbon monoxide, and 1,3-butadiene between MST users and non-tobacco users and significantly lower levels in MST users relative to cigarette smokers. Further, Rostron et al., (2015) report that levels of N-Acetyl-S-(2-cyanoethyl)-L-cysteine, a biomarker of exposure to tobacco smoke, were significantly lower among ST users (2.21 ng/mg creatinine, 95% CI, 1.11–4.39) compared to cigarette smokers (117.3 ng/mg creatinine, 95% CI, 103.1–133.4), but not different compared to non-tobacco users (1.47 ng/mg creatinine, 95% CI, 1.37–1.58).

In addition, other BOEs (e.g. urinary aromatic amines) have also been reported (Prasad et al., 2016) to be significantly lower in ST users compared to smokers and not significantly different compared to non-tobacco users. Levels of 2-aminonaphthalene, 4-aminobiphenyl and o-toluidine were significantly lower in ST users (7.4 ± 5.9; 4.6 ± 2.4; 84.3 ± 48.8 ng/24H respectively) than that observed in smokers (45.9 ± 37.9; 23 ± 11.3; 245.1 ± 115.5 ng/24H respectively) and not different than non-tobacco users (7 ± 5.7; 5.5 ± 2.8; 65.5 ± 35.8 ng/24H respectively).

In summary, measuring BOEs can provide a more accurate estimate of HPHC exposure compared to product chemistry analysis, since BOEs incorporate actual human use and account for absorption, distribution, metabolism, and excretion factors. BOEs reflecting exposure to combustion-related HPHC are either absent or present at levels not different than non-tobacco users and significantly lower than cigarette smokers, providing bioplausible evidence regarding the lower risk of pulmonary damage in ST users compared to cigarette smokers. Human biomarker studies report higher levels of urinary metabolites of NNK in ST users compared to smokers; yet, contrary to the hypothesis regarding a causal link between TSNA at levels in most current U.S ST products and lung cancer development, epidemiological evidence clearly demonstrates that lung cancer risks are lower with ST products than cigarettes.

Biomarkers of potential harm (BOPH) related to inflammation that provide insights into smoking-related disease mechanisms

The relationship between tobacco exposure and disease is complicated by the stochastic and multifactorial nature of tobacco-related diseases. Nevertheless, biomarkers based on our current understanding of disease mechanisms can be useful in assessing the health impacts of potential of MRTPs. In a recent review, Mattes et al. (2014) stated that “biomarkers that can

monitor tobacco exposure and health effects can play a critical role in tobacco product regulation and public health policy."

BOPHs (sometimes referred to as Biomarkers of Biological Effect or Biomarkers of Effect or Biomarkers of Clinical Risk End-points) represent changes in the biological systems resulting from exposure to HPHC, but relatively few of these biomarkers have been "validated" as definitive end-points for health outcomes from tobacco-related diseases. BOPH assessments in cigarette smokers focus on changes in processes related to chronic inflammation since there is substantial evidence of a common mechanistic thread between the three major smoking-related diseases: lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). Importantly, the 2010 Surgeon General's report concluded that "Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation, and oxidative stress." Specifically for CVD, the Surgeon General states that "Cigarette smoking produces a chronic inflammatory state that contributes to the atherogenic disease processes and elevates levels of biomarkers of inflammation, known powerful predictors of cardiovascular events." [Surgeon General Report (2010)].

Separate cross-sectional studies have analyzed BOPHs in ST users relative to non-tobacco users and cigarette smokers (Nordskog et al., 2015; Prasad et al., 2016). Through principal component analysis, Nordskog et al. (2015) identified three biomarkers, IL-12(p70), sICAM-1, and IL-8, that provided the best differentiation between tobacco use groups. The authors report significantly higher levels of these three BOPHs, suggesting that inflammation and immune response are elevated in smokers compared to ST users and no significant differences were observed between ST users and non-tobacco users. Since chronic inflammatory response in the lungs is highly associated with cigarette smoke [Surgeon General Report (2010)], the lower levels of the three BOPHs reported by Nordskog et al. (2015) indicate that MST users appear to have reduced inflammation compared to cigarette smokers.

Other measured BOPHs related to inflammatory disease also suggest a fundamentally different response in cigarette smokers compared to ST users. Statistically significantly higher levels of hs-CRP (60–90%), fibrinogen (7-8%), white blood cells (15–25%), monocytes (10–15%), and lymphocytes (20%) have been observed in smokers compared to ST users (Marano et al., 2015). Similarly, significantly higher levels of white blood cells (WBC), neutrophils, lymphocytes, monocytes, and fibrinogen in cigarette smokers compared to ST users and no differences compared to non-tobacco users were reported by Prasad et al. (2016). Lipid profiles of ST users resemble those of nonusers of tobacco rather than those of smokers (Asplund, Nasic, Janlert, & Stegmayr, 2003; Siegel, Benowitz, Ernster, Grady, & Hauck, 1992). These observations were corroborated by Prasad et al (2016) who found biomarkers for the lipid metabolism pathways (oxidized low-density lipoprotein and apolipoprotein B-100) to be comparable between ST users and non-tobacco users and significantly lower compared to smokers. Additionally, ST use does not appear to elevate hemoglobin or hematocrit levels; increase leukocyte counts or high sensitivity C-reactive protein (two important markers of systemic inflammation that are elevated in smokers);

impair the fibrinolytic system; or reduce circulating antioxidant vitamins (Asplund et al., 2003).

Significant reductions in inflammatory responses provide further mechanistic insights into the epidemiological evidence regarding the differential risks between ST and cigarettes. For example, changes in WBC have been mechanistically linked with both CVD and pulmonary diseases (Barnes, 2000; Tamakoshi et al., 2007). Adhesion of circulating WBC to the endothelium is one of the first steps in the initiation of atherosclerosis, followed by directed migration of the bound WBC into the intima, maturation of the WBC into macrophages, and their uptake of lipid, yielding foam cells. Furthermore, the role of WBC, particularly alveolar macrophages in pulmonary inflammation has also been well established (Barnes, 2000). A decrease of WBC count of 1,000/µL has been reportedly associated with a 14% decrease in risk of cardiovascular disease death (Margolis et al., 2005).

Overall, the studies with BOPHs provide relevant mechanistic basis for the reduction in risks from ST use compared to cigarette smoking. Ultimately, well conducted, prospective, epidemiological data provide a more informed understanding of the potential health risks associated with long-term use of tobacco products.

6.1.2.1.4.3.Summary

HPHC measurements in tobacco products (e.g., aldehydes, PAHs, TSNAs, and metals) are informative and can provide mechanistic insights into possible health risks. However, in most cases, these endpoints as measured in a tobacco product matrix are not necessarily confirmatory for human disease outcomes. Additionally, because of the inherent variability of this agricultural product, many constituents, such as PAHs, TSNAs, and metals present in the candidate product or any tobacco product, will vary over time. Thus, theoretical risk estimates based on analytical results may be unreliable. Current literature provides a variety of analytical estimates for the HPHC composition of cigarette tobacco, cigarette smoke, and ST. Together, this literature suggests some critical differences between ST and cigarette smoke. ST lacks, or has considerably lower concentrations of, many of the carcinogens and other toxicants formed during the combustion of tobacco, including PAHs, aldehydes, ethylene oxide, benzene, and acrolein.

Compared to cigarettes, ST products have a significantly lower risk of lung cancer in humans. It is clear that cigarette smoke contains thousands of combustion products that carry a significant toxicological burden, and are found in substantially lower levels in ST. Because ST is not combusted, it does not produce mainstream smoke or environmental tobacco smoke. Users (and non-users) avoid exposure to many of the combustion products found in cigarette smoke. The differences in product chemistry, combined with the different route of exposure in ST users, limit direct exposure of lung tissues to many of the harmful constituents of cigarette smoke.

Pre-clinical studies using *in vitro* or animal models demonstrate that ST products convey some potential biological activity. However, in comparative assays assessing bacterial mutagenicity, clastogenic activity, and cytotoxicity, ST appears to have less than 10% of the biological activity relative to extracts of mainstream cigarette smoke condensate. Animal

studies with ST that have investigated oral cancer development suggest, in aggregate, that "snuff" is not carcinogenic to the oral mucosa of hamsters or rats (Grasso & Mann, 1998).

Biomarkers of exposure are consistent with the lower levels of harmful chemical constituents present in ST products compared to cigarette smoke, confirming that exposure to many HPHC is significantly lower in ST users. However, studies have shown urinary NNAL levels in MST users to be generally greater than those found in cigarette smokers, suggestive of greater exposure to TSNA with ST (Naufal et al., 2011). As we show in this application, epidemiology studies confirm a demonstrable lower risk for lung cancer and overall malignant neoplasms with ST exposure compared to cigarette smoking (Section 6.1.2.1.2). Thus, despite higher levels of urinary metabolites of NNK in ST users, the reported carcinogenic effects associated with NNK in animal studies do not seem to match current epidemiology evidence on malignant neoplasms with ST. Moreover, a growing body of scientific evidence shows that markers reflective of biological harm in humans are less affected by ST exposure than by cigarette smoke exposure. This is particularly relevant for indicators of inflammatory changes associated with pulmonary diseases or cardiovascular diseases.

Health outcomes resulting from actual use of ST (e.g., epidemiology) provide the most definitive and direct evidence showing a lower health risk compared to cigarette smoking. Current evidence, including chemical analysis of toxic constituents in the product, preclinical studies in animals or cell cultures, biomarkers of exposure, and biomarkers of potential harm in humans are supportive of the accuracy of this conclusion.

6.1.2.1.4.4.Overall Summary

Our analysis of health datasets representing users of current ST products (e.g., Linked Mortality Analysis) identified no significant increased risk of all-cause mortality, diseases of the heart, or malignant neoplasms, including lung cancer, relative to cigarette smoking. This analysis provides a stark contrast to the increased risk for these fatal diseases associated with cigarette smoking, which was evident in participants in both the NHIS and NLMS studies.

6.1.2.2. MST Compared to Other ST Products

MST and loose leaf chewing tobacco are the dominant forms of ST in the U.S. and provide the basis for most of the comparative epidemiology data among ST users. We recognize "Swedish Snus type products" are currently in the U.S. market; however, epidemiology evidence with these Swedish Snus type products is insufficient in the U.S. population. Nevertheless, it is worth noting that in Sweden, male lung cancer death rates have continued to decline, which may relate to the decline in cigarette consumption and switching to ST among Swedish males. For this analysis, we compare MST and chewing tobacco, historically the most predominant ST products in the U.S. market (Brad Rodu & Cole, 2009). The available published evidence does not support a significant mortality risk differential between these two ST product types.

Timberlake and colleagues (2017) used data from the NLMS TUS-CPS study to compare estimated mortality risks by ST type (defined by the authors as snuff or chewing tobacco). Table 6.1-12 presents mortality risk estimates for all-causes, all-cancers, and coronary heart

disease (CHD) among respondents in the study. Ever users of snuff or chewing tobacco did not have an excess mortality risk from all-causes, all-cancers, or CHD compared to never-tobacco users (reference group). Use of both snuff and chewing tobacco resulted in a small, but statistically significant, excess risk for mortality from all-causes and CHD. Additionally, current users who used snuff alone had an excess mortality risk from CHD. The authors noted that the absence of known, potentially confounding CHD risk factors in the data was a study limitation that raises the possibility of a non-causal association. Use of either type of ST did not result in increased mortality risk from all-cancers.

Table 6.1-12: Mortality from All-causes, All-Cancers, and Coronary Heart Disease by Smokeless Tobacco Type (Snuff/Chewing Tobacco)

Mortality	ST Use	Deaths	Adjusted HR (95% CI)	
			Ever ST use (n=349,282)	Current ST Use[1] (n=345,541)
All-cause	Snuff only	355	1.10 (0.99-1.22)	1.01 (0.90-1.1.4)
	Chew only	371	0.98 (0.88-1.09)	0.97 (0.86-1.10)
	Snuff and Chew	50	1.05 (0.81-1.37)	1.49 (1.05-2.13)[2]
All-cancer	Snuff only	49	0.88 (0.67-1.15)	0.83 (0.61-1.14)
	Chew only	76	1.11 (0.89-1.39)	1.08 (0.83-1.41)
	Snuff and Chew	10	0.92 (0.49-1.75)	1.83 (0.87-3.82)
CHD	Snuff only	86	1.22 (0.99-1.52)	1.30 (1.03-1.63)[2]
	Chew only	86	1.12 (0.91-1.38)	1.11 (0.88-1.42)
	Snuff and Chew	8	1.18 (0.66-2.09)	2.35 (1.24-4.46)[3]

Source: Data from Timberlake et al. (2017)
CI = Confidence Interval; HR = Hazard Ratio (Hazard ratio adjusted for age, gender, race/ethnicity, education, and family income); ST = Smokeless Tobacco
[1] Excludes former ST users
[2] $p<0.05$
[3] $p<0.01$

Henley et al (2005) analyzed the American Cancer Society's CPS-II data to compare mortality risks for exclusive snuff[10] users and exclusive chewing tobacco[11] users. These results show some increased risks among current chewing tobacco users that were not apparent for current snuff users (Table 6.1-13). However, the differences noted between ST

[10] Snuff is generally synonymous with MST. However, snuff could also include dry snuff, which differs from MST. However, prevalence of dry snuff use has generally been low and is now almost non-existent. Therefore, we consider data related to snuff use to be relevant to MST unless information is available to indicate otherwise.
[11] Chewing tobacco that is coarsely shredded and sold in pocket sized packs of loose tobacco leaves.

product types were relatively small and probably do not indicate major biologically relevant differences in the health risks between snuff and chewing tobacco.

Table 6.1-13: Relative Risks among Moist Smokeless Tobacco Users and Chewing Tobacco Users

Cause of Death	Group	Number of Deaths	HR (95% CI)
All causes	Current snuff	70	1.25 (0.98-1.58)
	Current chew	366	1.16 (1.05-1.29)
All cancers	Current snuff	14	0.93 (0.55-1.57)
	Current chew	113	1.23 (1.02-1.49)
Lung cancer	Current snuff	2	2.08 (0.51-8.46)
	Current chew	12	1.97 (1.10-3.54)
Cardiovascular disease	Current snuff	36	1.38 (0.99-1.92)
	Current chew	186	1.26 (1.09-1.46)
Coronary heart disease	Current snuff	24	1.59 (1.06-2.39)
	Current chew	111	1.25 (1.03-1.51)

Source: Data from Henley et al. (2005)
HR = Hazard Ratio; CI = Confidence Interval

Rodu and Cole (2002) reported the results of a meta-analysis comparing head and neck cancer risks between MST and chewing tobacco. These authors found no relevant statistically significant differences between the two types of ST (Table 6.1-14).

Table 6.1-14: Relative Risks for Head and Neck Cancer among Moist Smokeless Tobacco Users and Chewing Tobacco Users

Cancer Site(s)	Group	Cases/Controls	RR (95% CI)
Oral cavity	MST	283/296	0.6 (0.3-1.3)
	Chewing Tobacco	482/995	1.1 (0.8-1.6)
Oropharynx	MST	2113/4454	1.1 (0.8-1.6)
	Chewing Tobacco	1682/3931	0.7 (0.4-1.2)
Larynx	MST	387/2560	1.3 (0.9-1.8)
	Chewing Tobacco	544/3201	1.2 (0.9-1.7)
All sites	MST	3145/5245	1.2 (1.0-1.4)
	Chewing Tobacco	2846/4926	1.0 (0.8-1.2)

Source: Data from Rodu and Cole (2002)

CI = Confidence Interval; MST = Moist Smokeless Tobacco; RR = Relative Risk

6.1.2.2.1. Summary

The currently available scientific information does not support a conclusion of a noteworthy difference in health outcomes between MST and chewing tobacco, which are the predominant forms of ST used in the U.S.

6.1.2.3. Consumer Reported Adverse Events (AE)

The AE information presented in this section is from two sources:

- AE data collected during a clinical study (Study# ALCS-RA-17-02-MST; Appendix 7.3.1-1) on the candidate product, and
- AE data collected by ALCS on similar products to the candidate product.

We summarize the AEs as follows:

1. The AEs observed in the clinical study demonstrate that the candidate product is well tolerated and no deaths or serious AEs were reported. Furthermore, the Principal Investigator of the study considered the AEs reported during the use of the candidate product as "unlikely related" or "not related" to the product. The AEs resolved quickly after candidate product use and are similar to the AEs reported with the use of nicotine polacrilex gum in the clinical study (Section 7.3.1).
2. The AE data collected on similar products from the Consumer Call Center shows that, relative to the billions of U.S. Smokeless Tobacco Company (USSTC) cans of MST sold, the numbers of AEs reported by consumers are relatively few and are mostly mild in severity.

6.1.2.3.1. AE Data on the Candidate Product

ALCS conducted a single Clinical Study[12] using a crossover study design (Appendix 7.3.1-1) on the candidate product to measure nicotine pharmacokinetics and subjective effects from use of the candidate product compared to nicotine polacrilex gum and the subject's own brand cigarettes. Section 6.3 includes a brief summary of the results of this study.

Overall, 14 (58%) subjects experienced a total of 22 AEs in this study. Most AEs occurred following use of the subject's own brand cigarette or nicotine gum. The AEs reported by the study participants for the candidate product were similar in nature to those reported for nicotine polacrilex gum. There were relatively few subjects reporting AEs either for the candidate product (one subject over a four-hour *ad lib* use and two subjects with single use)

[12] The clinical study (Moist Snuff Tobacco Product, Study No. ALCS-RA-17-02-MST [Appendix 7.3.1-1]) was conducted in compliance with FDA regulations as described in the Code of Federal Regulations (CFR) 21 Parts 50 and 56; Department of Health and Human Services regulations as described in 45 CFR 46; guidelines resulting from the International Council for Harmonisation (ICH); and Good Clinical Practice (GCP). The clinical study involved collection and measurement in biospecimens (e.g. plasma nicotine measurements).

or for nicotine gum (four subjects over a four-hour *ad lib* use and two subjects with single use) (Appendix 7.3.1-1; Table 23). Each of the subjects had only one AE to report, none of the AEs were considered by the PI to be related to the product, and all the AEs resolved quickly.

6.1.2.3.2. ALCS AE Data on Similar Products to the Candidate Product

ALCS uses an established and documented AE collection system to capture and classify spontaneous calls[13] of unsolicited consumer complaints and unverified AEs temporally associated with the use of USSTC's MST products sold in the marketplace. The similarity of the candidate product to the other MST products marketed by USSTC allows us to draw insights regarding likely AEs that will be observed for the candidate product.

We summarize the consumer call AE data for the MST products marketed by USSTC during the period January 2012 through June 2017.[14] ALCS does not have coded AE data for consumer calls prior to January 1, 2012.

During this period, USSTC sold over 4.4 billion cans of MST products and recorded 1,353 calls from consumers with AEs. Gastrointestinal disorders, comprising upset stomach, nausea, and vomiting, were the most frequently reported health risk complaints for ST products, followed by lip and oral injuries. The majority of cases were coded as mild (1,140 cases: 84.3%), or moderate (203 cases: 14.9%), with only seven cases (0.5%) coded as severe. Three cases (0.3%) were coded as serious AEs involving hospitalization with symptoms like coughing or vomiting of blood and high blood pressure. Section 7.4.3, Table 7.4.3-4 describes additional details regarding the SAE. There were two cases reported as tobacco poisoning.

When examined on a monthly basis, over the time period monitored, we received about 20 calls per month, with an average of 38.5 AE symptoms reported per month. This number may be somewhat inflated, however, due to a product tampering incident that prompted a product recall (FDA Recall Tracking Number: RES-76382) during early 2017. Symptoms reported during the recall period were mostly due to a foreign body, with injuries to the lip, gingiva, and mouth.

The number of AEs reported by consumers of USSTC MST products is significantly low relative to the over 4.4 billion cans sold. The rate of AEs among consumers of USSTC MST products is less than one per million (0.6/1M) cans sold during a period of five and a half years. Overall, the vast majority of the AEs reported over a five and a half year period were mostly mild and non-life threatening.

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[13] Consumers report complaints and potential adverse events (AE) through the ALCS Consumer Call Center by using information found on the product packaging or the "Contact Us" option found on the company and branded websites. The ALCS Consumer Call Center currently uses the term alleged physical effect (APE) rather than AE. APE is defined by ALCS as any complaint that alleges symptoms, illness or injury.

[14] Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

These data demonstrate that the candidate product will be well-tolerated. Generally, AEs associated with the candidate product and other USSTC MST products resolve quickly after product use. The infrequent number of consumer AE calls received for USSTC MST products, and the general lack of severe symptoms reported, indicates a very low risk for AEs associated with the candidate product use.

6.1.2.4. Conclusion

We present here the conclusions regarding the health risks associated with use of the candidate product as compared to cigarettes and chewing tobacco. Cigarette smoking remains the predominant form of tobacco use in the U.S., and is the most likely tobacco form currently used by the consumer who may adopt the candidate product. Although a variety of tobacco product types are available in the U.S. market, we concentrate comparisons of the health risks of the candidate product to those we believe are most relevant: cigarette smoking and chewing tobacco, another form of oral tobacco. The currently available scientific information does not support a conclusion of a noteworthy difference in health outcomes between MST and chewing tobacco, which are the principal forms of ST used in the U.S.

Scientific studies have consistently and clearly shown that cigarette smoking is the greatest preventable risk factor for lung cancer and other respiratory diseases. Studies with ST users demonstrate a far lower risk for many serious fatal diseases, including lung cancer, compared to cigarette smoking. While there are some limitations to comparison of the risk estimates across independent studies due to variability in data sources and differences in measurement periods, the existing information related to this comparative mortality risk differential is consistent.

Reducing the risk of lung cancer among smokers is the primary purpose of our proposed health claim. ST use is not risk-free, but from a comparative standpoint, scientific data demonstrates that the mortality risk from cigarette smoking far exceeds the mortality risk from ST use. Together, the epidemiology evidence clearly shows that ST is a viable alternative for AS who want to lower their risk of smoking-related disease while still using tobacco.

6.1.3. The Health Risks Associated with Initiating Product Use Compared to Never Using Tobacco Products

The CDC[15] warns that ST can lead to addiction; causes cancers of the mouth, esophagus and pancreas; leads to diseases of the mouth; increases risk of early delivery and stillbirth; causes nicotine poisoning in children; and may increase the risk of heart disease and stroke. Published scientific studies and reviews have addressed the potential health risks associated with ST use compared to never-tobacco use [IARC (2007)]. Based on this literature, federally mandated warnings for ST products address gum disease, tooth loss, mouth cancer,

[15] Centers for Disease Control and Prevention: Smoking and Tobacco Use, Smokeless Tobacco Health Effects http://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/health_effects/#cancer

and addiction. The candidate product will include these federally mandated health warnings.[16]

We base much of our discussion here on our Linked Mortality Analysis of the NHIS and NLMS datasets using a model that compares current ST users with never-tobacco users (P0 analysis, Table 6.1-1). Additionally, we provide relevant findings from the literature, where appropriate. We focus most of our discussion on the major mortality risks, including all-cause mortality, diseases of the heart, and malignant neoplasms. These health endpoints embrace the major specific diseases attributed to tobacco use (especially cigarettes) by the CDC[17], and are those most frequently measured and reported in published literature. Where possible, we present data for individual neoplasms or diseases, recognizing that the low number of actual cases recorded in the studies often limits analysis. Additionally, we include a brief analysis of the possible impact of ST use on several of the leading causes of mortality identified by the CDC.[18] An expanded review of the literature is in Section 7.5.6-1 and 7.5.6-2.

Our recent analysis of these two datasets (i.e., Linked Mortality Analysis) linking specific diseases with mortality incidence in various tobacco use and non-use groups demonstrates no statistically significant association between ST use and excess mortality risk, compared to never tobacco use, from all-causes, diseases of the heart, or malignant neoplasms such as lung cancer. Additionally, we note that within these datasets, mortality risks for other cancers, such as those of the oral cavity, esophagus, or pancreas are not elevated in ST users compared to never-tobacco users. In some cases, there were insufficient mortality events from specific diseases among ST users to derive a reliable risk estimate. The lack of evaluable data specific to certain diseases is not taken as evidence that ST does not cause these diseases. Nonetheless, it bears noting that mortality among ST users for certain diseases associated with ST use was low.

As summarized in this section and discussed in greater detail in Section 7.4.1, the literature generally provides evidence regarding the association between ST use and all-cause mortality, risk of all cancers, oropharyngeal cancer, lung cancer, esophageal cancer, digestive cancers, kidney cancer, prostate cancer, and various cardiovascular disease (CVD) endpoints. However, for many of these endpoints, the available U.S. epidemiology data demonstrate low relative risk (RR) or HR estimates for mortality, wide confidence intervals (CIs),

[16] Since July 22, 2010, smokeless tobacco product packaging and advertising must bear one of the following federally mandated warning statements, per section 3 of the Comprehensive Smokeless Tobacco Health Education Act (CSTHEA), as amended by section 204 of the Tobacco Control Act, in accordance with an FDA approved warning plan:

- **WARNING**: This product can cause mouth cancer.
- **WARNING**: This product can cause gum disease and tooth loss.
- **WARNING**: This product is not a safe alternative to cigarettes.
- **WARNING**: Smokeless tobacco is addictive.

These required warning statements must also meet certain requirements, with respect to font, text, size, placement and formatting of the warning statements on the package labels and advertisements.

[17] Centers for Disease Control and Prevention: Smoking and Tobacco Use, Smokeless Tobacco Health Effects https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm

[18] The ten causes of death are: diseases of the heart mortality, malignant neoplasms mortality, chronic lower respiratory diseases mortality, accidents (unintentional injuries) mortality, cerebrovascular diseases mortality, Alzheimer's disease mortality, diabetes mellitus mortality, influenza and pneumonia mortality, nephritis mortality, and all other causes (residual) mortality.

inconsistency between studies, and lack of adequate adjustment for known confounding factors.

6.1.3.1. Mortality from All Causes

The category of all-cause mortality incorporates the widest collection of possible fatal outcomes and provides the most fundamental platform for absolute overall risk evaluation of ST use compared to never-tobacco use. Our analyses of the NHIS and NLMS mortality linkages indicate that the all-cause mortality risk of current ST users is not different from that of never-ST users (Table 6.1-15).

Table 6.1-15: Mortality from All-causes: Adjusted Hazard Ratio Estimates for Smokeless Tobacco Users Compared to Never-tobacco Users

Group	Study	Observations	Deaths	HR[1](95% CI)
All Respondents	NLMS	1,863	48	0.794 (0.577-1.093)
	NHIS[2]	1,562	347	1.125 (0.970-1.305)
Males	NLMS	1,646	25	0.630 (0.393-1.010)
	NHIS	1,219	142	1.140 (0.900-1.444)
White Males	NLMS	1,545	22	0.721 (0.436-1.194)
	NHIS	1,119	110	1.171 (0.895-1.533)
Females	NLMS	217	23	1.019 (0.656-1.583)
	NHIS	343	205	1.070 (0.900-1.272)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never).
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from the restricted access data file.

Across both studies, no excess all-cause mortality risk was indicated among males, white males, or females compared to respective never-tobacco groups. The NHIS and NLMS studies contain gender assignments, which allow calculation of gender-specific risk estimates useful in determining if there is a disproportionate risk between genders or across special use groups (Table 6.1-15). Males, specifically white males, are currently the predominant consumers of ST products, and both datasets represented this tobacco product use pattern (about 70-80% of either study). Although the data for females are less robust compared to males, the datasets do provide a reasonably large number of female respondents for calculation of risk estimates.

Timberlake et al. (2017) recently published an analysis of the NLMS study and arrived at a similar conclusion to ours regarding the lack of an association between ST use and excess all-cause mortality risk. Timberlake reported that the unadjusted all-cause mortality HR estimates for current ST users were significantly greater than for never users. Adjustment for covariates (age, sex, race/ethnicity, education, and family income), however, produced an all-cause mortality estimate for ST users that did not significantly differ from never-tobacco users (HR = 1.01 (95 percent CI: 0.93-1.10)). There were some minor differences between the model used by Timberlake et al. and the model we used to evaluate NLMS data. Timberlake et al. included a wider timeframe and did not include self-assessed health status. Nonetheless, the consistency of the conclusions is compelling; ST use is not associated with an increased risk for overall mortality.

We compare the results of our NHIS and NLMS analyses with the two studies available in the published literature (Accortt et al., 2002; Henley et al., 2005). Accortt et al. reported no statistically significant increased risk for all-cause mortality among male or female ever-users of ST compared to never tobacco use in the nationally representative First National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study. In this study, 817 males and 251 females (1,068 total) age 45 years or older at baseline (1971-1975), who reported ever use of ST, were evaluated with a 20 year follow-up in 1992. The adjusted HR for all-cause mortality for male ever ST users was 1.0 (95 percent CI: 0.8-1.3), and the adjusted HR for all-cause mortality for female ever ST users was 1.3 (95 percent CI: 0.9-1.7).[19]

Henley et al. (2005) reported slightly elevated all-cause mortality risks among current male ST users from two cohort studies, CPS-I and CPS-II. In both studies, men who currently used snuff or chewing tobacco had "higher rates of death from all causes" than men who did not use tobacco products. The CPS-I included 7,745 men enrolled in 1959, with follow up 12 years later in 1971, who reported current exclusive use of snuff or chewing tobacco. The adjusted HR for death from all causes among current ST users was 1.17 (95 percent CI: 1.11-1.23).[20] The CPS-II included 3,327 men who reported exclusive use of snuff or chewing tobacco. Respondents for the CPS-II were enrolled in 1982, with follow up 18 years later in 2000. The adjusted HR for all-cause mortality among current ST users was 1.18 (95 percent CI: 1.08-1.29).[21]

The reason for the discrepancy between the results reported in CPS-I and CPS-II and those reported by Accortt et al. (2002), as well as from our own analysis, may possibly be due to misclassification of cigarette smokers among the current ST user population. Current ST users in both cohorts included in the Henley study had excess mortality risks for smoking-related diseases, specifically lung cancer (HR: 2.00, 95% confidence interval [CI]: 1.23-3.24

[19] Cox proportional hazard model adjusted for age, race and poverty index ratio.
[20] Cox proportional hazard model adjusted for age, race, education level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use.
[21] Cox proportional hazard model adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.

in the Cancer Prevention Study II[22] cohort) and COPD (HR: 1.86, 95% CI: 1.12-3.06 in the Cancer Prevention Study I cohort). Both COPD and lung cancer are well-established risk factors for cigarette smoking, but are not typically associated with ST use.

Overall, the Linked Mortality Analysis of the NLMS and NHIS datasets indicates that the risk of mortality from all causes among ST users is not statistically different from that of never-tobacco users and is far lower than the all-cause mortality risks associated with cigarette smoking.

6.1.3.2. Mortality from Malignant Neoplasms (All-Cancer)

The measure of mortality, or incidence, from all types of malignant neoplasms (all-cancer) provides a broad measure of the carcinogenic risk associated with ST use. Data from our NHIS and NLMS examination provide recent statistics regarding cancer mortality among tobacco product users (Section 7.4.1). Published epidemiology studies and meta-analyses further inform the possible association between the use of ST products in the U.S. and the risk of mortality from malignant neoplasms. However, it is important to place any assessment of the absolute risk of the candidate product compared to never tobacco use in the context of the risk of cigarette smoking.

We detected no statistically significant excess hazard for mortality from all cancers among current ST users compared to never users in the NHIS and NLMS datasets (Table 6.1-16). The malignant neoplasms included digestive organs (ICD codes C00-C16, C18-C22, C25)[23]; esophagus only (C15); pancreas only (ICD code C25); colon, rectum, and anus only (ICD codes C18-C21); oral cavity, lip, and pharynx (ICD codes C00-C14); trachea, bronchus, and lung (ICD codes C33-C34); and genitourinary system (ICD codes C61, C64-C65, C67). These results are consistent across the demographic subgroups analyzed, although the number of cases was small in some instances limiting HR calculation.

Table 6.1-16: Mortality from Malignant Neoplasms: Adjusted Hazard Ratio Estimates for Smokeless Tobacco Users Compared to Never-tobacco Users

Group	Study	Observations	Deaths	HR[1] (95% CI)
All Respondents	NLMS	1,863	8	0.790 (0.376-1.659)
	NHIS[2]	1,561	71	1.113 (0.815-1.519)
Males	NLMS	1,646	1	0.121 (0.017-0.868)
	NHIS	1,219	29	1.139 (0.716-1.811)
White Males	NLMS	1,545	1	0.151 (0.021-1.078)
	NHIS	1,119	24	1.135 (0.673-1.913)

[22] The Henley study included analyses of the American Cancer Society's Cancer Prevention Study I and Cancer Prevention Study II cohorts.

[23] Here and throughout this section, ICD codes refer to the code used to classify mortality data from death certificates. http://www.who.int/classifications/icd/en/ The ICD-10 replaced ICD-9 for this purpose as of January 1, 1999.

Group	Study	Observations	Deaths	HR[1] (95% CI)
Females	NLMS	217	7	2.163 (0.962-4.863)
	NHIS	342	42	1.155 (0.775-1.721)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never)
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from the restricted access data file.

The mortality risk estimates from malignant neoplasms derived from the NHIS and NLMS datasets for ST users compared to never-tobacco users are in general agreement with previous published studies of ST.

Accortt et al. (2002) calculated an all-cancer mortality HR of 0.9 (95 percent CI 0.3-2.3) among male ST users and 1.7 (95 percent CI 1.0-2.8) among females. In the First National Health and Nutrition Examination Survey (NHEFS), Sterling et al. (1992) examined data from the 1986 National Mortality Followback Survey and calculated a RR of 0.88 (95 percent CI 0.69-1.12) among those who had used ST more than 10,000 times. Henley et al. (2005) estimated the relationship between current ST use and all-cancer mortality among males who currently use ST and never used other tobacco products in the CPS-I and the CPS-II. Data from CPS I showed no statistically significant association (adjusted HR = 1.07 [95 percent CI: 0.95-1.20]), while data from CPS-II suggested some association (adjusted HR = 1.19 [95 percent CI 1.02-1.40]).

Accortt et al. (2002) used the NHEFS dataset to examine cancer incidence among ST users and reported that ST use was not associated with an excess all-cancer risk (male: HR = 0.8 (95 percent CI 0.4-1.6), female: HR = 1.2 (0.7-2.1).

Lee and Hamling (2009a) conducted a systematic review and meta-analysis evaluating all-cancer mortality among ST users. On the basis of risk estimates from five U.S. studies (not including our NHIS and NLMS analysis), these authors calculated the RR of all-cancer mortality for ST users to be 0.95 (95 percent CI: 0.74-1.22). The authors noted that studies included in the meta-analysis generally do not fully characterize exposure (frequency or duration of use) or ST product type.

Table 6.1-17 separates the total malignant neoplasm data in the NLMS and NHIS datasets into the more prevalent cancer sites attributed to tobacco exposure. In some cases, the low numbers of deaths attributable to malignant neoplasms recorded within the datasets for specific cancers prevented calculation of reliable adjusted HR estimates. Low case numbers generally lead to statistical uncertainty. To maximize statistical robustness, we only show data for all respondents and do not further differentiate by gender. Additionally, the analysis was suppressed by National Center for Health Statistics when fewer than five deaths were present, to protect respondent confidentiality.

Table 6.1-17: Mortality Risk Estimates for Specific Malignant Neoplasms Among Smokeless Tobacco Users (All Respondents) Compared to Never-Tobacco Users

Neoplasm	Study	Observations	Deaths	HR[1] (95% CI)
Trachea, bronchus, lung	NLMS	1,863	3	2.529 (0.742-8.623)
	NHIS[2]	1,561	8	2.090 (0.804-5.432)
Oral cavity, lip, pharynx	NLMS	1,863	0	NE
	NHIS	1,561	<5	NR
Digestive organs	NLMS	1,863	3	1.040 (0.328-3.300)
	NHIS	1,561	24	1.309 (0.750-2.286)
Esophagus	NLMS	1,863	1	2.898 (0.371-22.643)
	NHIS	1,561	<5	NR
Pancreas	NLMS	1,863	1	1.219 (0.165-9.014)
	NHIS	1,561	5	2.263 (0.737-6.951)
Colon, rectum, anus	NLMS	1,863	0	NE
	NHIS	1,561	14	1.177 (0.637-2.178)
Genitourinary system	NLMS	1,863	1	0.435 (0.058-3.238)
	NHIS	1,561	5	0.699 (0.250-1.952)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never)
NE = Not estimated; NR = Not reported. Number of deaths was <5; CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from analyses of the restricted access data file.

Public health authorities have not identified lung cancer as a risk for ST use (Table 6.1-2). Consistent with this lack of association of lung cancer with ST use, mortalities due to cancer of the trachea, bronchus, and lung in ST users were rarely noted among exclusive ST users in either the NLMS or NHIS datasets (Table 6.1-17). The HR estimates derived for all respondents in both studies were not significantly elevated compared to never tobacco users. Within the NLMS dataset only three lung cancers were noted among ST users; however, all three appeared in females. Limiting the analysis to only females, a relatively small base size, resulted in an elevated HR with corresponding wide confidence intervals (HR: 7.092; 95% C.I. 1.929-26.071). While this increase cannot be totally dismissed, we attach little practical relevance to the finding, considering the small sample size and large variability. The suggested excess risk for lung cancer among exclusive female ST users in the one dataset is

likely incidental given the overall negative association between ST use and lung cancer found among all respondents in both datasets. The findings from our Linked Mortality Analysis are consistent with the published epidemiology, which have shown mixed results regarding a possible association between ST use and respiratory cancer mortality (Andreotti et al., 2016). Published epidemiology studies have shown mixed results regarding a possible association between ST use and respiratory cancer mortality. Andreotti et al. (2016) recently reported cancer incidence in relation to exclusive use of cigarettes, pipes, cigars, cigarillos, and smokeless tobacco (chewing tobacco, snuff) in the Agricultural Health Study.[24] The HR for ST users was 2.21 (95 percent CI: 1.11-4.42). Henley et al. (2005) estimated an adjusted HR of 1.08 (95 percent CI: 0.64-1.83)[25] for death from lung cancer among current male ST users in the CPS-I study. However, using CPS-II data, the estimated HR for lung cancer mortality among current ST users compared to never-tobacco users increased to 2.00 (95 percent CI: 1.23-3.24).[26] For context, lung cancer HR in exclusive cigarette smokers is greater than 10.

Many ST users report experience with past or current cigarette smoking (Section 3.2.3). Given the strong association between smoking and lung cancer risk, it is possible, if not likely, that an increased number of respiratory cancers noted in ST users in some studies could be related to smoking history. Further, the fact that many ST users have been, or are smokers, suggest that recall bias by respondents could have a potential confounding effect on the outcomes of these studies. Accortt et al. (2002) suggested misclassification, or uncontrolled confounding as the reason for an "unexpected" presence of four cases of lung cancer among 189 female exclusive ST users in their evaluation of NHEFS. These four cases resulted in an adjusted HR for lung cancer, compared with that of female never-tobacco users, of 6.8 (95 percent CI: 1.6-28.5).[27] No lung cancer cases were reported among males, the primary users of ST. In another study of male ST users, (Zahm et al., 1989) reported no significant association between ST use and lung cancer risk.

Lee and Hamling (2009a) conducted a systematic review and meta-analysis evaluating lung cancer risk among ST users and calculated the RR of lung cancer mortality for ST users to be 1.22 (95 percent CI: 0.82-1.83). Limiting the analyses to smoking-adjusted data or to never smokers resulted in only slightly greater RR estimates of 1.38 (95 percent CI: 0.72-2.64) and 1.79 (95 percent CI: 0.91-3.51), respectively. The authors noted that the studies included in the meta-analysis generally do not fully characterize exposure (frequency or duration of use) or ST product type.

The International Agency for Research on Cancer (IARC) published a review of ST carcinogenic risks as part of a review of personnel habits and indoor combustions [IARC (2012)]. This review did not identify ST as a risk factor for lung cancer.

[24] AHS is a prospective cohort study of 89,655 participants, including licensed private pesticide applicators and their spouses recruited in Iowa and North Carolina.
[25] Adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use
[26] Adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.
[27] Adjusted for age, race, and poverty index ratio.

Overall, we find that there is insufficient evidence to conclude that the use of ST conveys any relevant excess risk for cancers of the trachea, bronchus, or lung. However, even if we accept the results of previous epidemiology as suggestive of an association between ST and lung cancer risk, this risk is far lower than that established for the cigarette smoker.

The U.S. Surgeon General (1986) has concluded a causal association between ST use and cancer of the oropharynx. Both evaluations included studies conducted outside of the U.S. Neither the NHIS nor NLMS datasets indicated a high incidence of oropharyngeal cancer mortality among current ST users, with fewer than five or zero deaths seen in these datasets, respectively (Table 6.1-17).

The incidence of cancers of the digestive organs (combined: esophagus, stomach, colon, rectum and anus, liver, and pancreas) among ST users was not significantly different from never-tobacco users in either the NHIS and NLMS datasets (Table 6.1-17).

Our analysis of the NHIS and NLMS mortality linkages indicated that mortality from esophageal cancer was rare among current ST users, and HR estimates were not significantly different from never-tobacco users. The CDC has concluded that ST use causes esophageal cancer, citing the World Health Organization, IARC evaluation of the carcinogenicity of ST (2007). IARC (2012) in its evaluation of international ST products has concluded that there is sufficient evidence that ST causes cancer of the esophagus. However, the inferences drawn from international products, which may have vastly different constituent levels compared to U.S. ST products, should be interpreted with caution.

The published scientific literature includes four studies evaluating esophageal cancer risk among ST users (Brown et al., 1988; Martinez, 1969; Williams & Horm, 1977; Wynder & Stellman, 1977). The risk estimates provided in these studies are generally not statistically significantly elevated; however, a meta-analysis including these data derived an esophageal cancer risk estimate for ST users of 1.56 (95% CI: 1.11-2.19) (Lee & Hamling, 2009a).[28]

The IARC (2012) has concluded a causal association between ST use and pancreatic cancer.[29] However, these conclusions are generally based on studies of international ST products, which may or may not reflect the risks of U.S. ST products. Recently published pooled analyses of independent studies have shown inconclusive or lack of significant associations (Araghi et al., 2017; Burkey et al., 2014).

We did not detect a statistically significant excess risk for pancreatic cancer mortality among current ST users in the NHIS mortality linkage (Table 6.1-17). Our findings are consistent with meta-analyses conducted on U.S. and Canadian ST products (Lee & Hamling, 2009a). Based on risk estimates from five U.S. studies, these authors calculated the relative risk of pancreatic cancer for ST users to be 0.86 (95% CI: 0.47-1.57). Limiting the analysis to studies which adjusted for smoking produced a risk estimate of 0.99 (95% CI: 0.51-1.91). Three studies included pancreatic cancer risk estimates for never-smoking ST users; a meta-

[28] This analysis included risk estimates derived by the authors from information contained in the underlying publications. We have not included these derived data in our summary of published risk estimates because they did not appear in the original publication. The inclusion of derived risk estimates in the meta-analysis accounts for the overall increased risk estimate.
[29] IARC's conclusion was based on international smokeless tobacco product data and not U.S. data.

analysis of these results yielded an estimate of 1.09 (95% CI: 0.44-2.67). Another meta-analysis from the same group and using much of the same published data calculated the risk for pancreatic cancer among U.S. and Canadian ST users to be 0.92 (95% CI: 0.65-1.29) using a fixed-effect model and to be 0.89 (95% CI: 0.50-1.60) using a random-effect model (Sponsiello-Wang, Weitkunat, & Lee, 2008). For both meta-analyses, the authors note various issues with the underlying study data including small sample sizes, limited adjustment for potential confounders, and use of surrogates to identify potential pancreatic cancer risk factors. Overall, the body of U.S.-specific evidence does not support an association between ST use and pancreatic cancer.

Data from the NHIS mortality linkage indicated no excess risk among ST users for genitourinary cancer of the colon, rectum, or anus compared to never-tobacco users (Table 6.1-17). A single publication evaluated colon and rectal cancer risk among ST users and reported an association for rectal, but not colon cancer (Heineman, Zahm, McLaughlin, & Vaught, 1994).

6.1.3.3. Mortality From Diseases of the Heart

Diseases of the heart comprise a wide variety of coronary diseases such as, but not limited to, rheumatic heart disease, ischemic heart disease, acute myocardial infarction, and atherosclerotic cardiovascular disease. The NLMS and NHIS datasets both contained a high incidence of mortalities attributed to diseases of the heart. The robustness of these datasets allowed for separation of 'all respondents' into specific demographic populations, including male and female ST users, while still obtaining reasonably narrow confidence intervals (Table 6.1-18). We identified no relevant excess mortality risk from diseases of the heart among all respondents, nor among the subsets of males, white males, or females.

Table 6.1-18: Mortality from Diseases of the Heart: Adjusted Hazard Ratio Estimates for Smokeless Tobacco Users Compared to Never-Tobacco Users

Group	Study	Observations	Deaths	HR[1] (95% CI)
All Respondents	NLMS	1,863	22	1.065 (0.649-1.747)
	NHIS[2]	1,561	114	1.195 (0.906-1.577)
Males	NLMS	1,646	13	1.112 (0.572-2.162)
	NHIS	1,219	48	1.356 (0.865-2.125)
White Males	NLMS	1,545	12	1.437 (0.722-2.861)
	NHIS	1,119	38	1.500 (0.916-2.457)
Females	NLMS	217	9	0.980 (0.471-2.041)
	NHIS	342	66	1.063 (0.764-1.479)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never)
CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey. NHIS data shown is obtained from the restricted access data file. NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco

[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from analyses of the restricted access data file.

Because of the relatively large number of deaths included in this broad category, we attempted to further investigate a possible association between ST use and cardiovascular disease by analyzing the NLMS and NHIS datasets specifically for individual diseases, such as diseases of the circulatory system (ICD codes I00-I99), ischemic heart disease (ICD codes I20-I25), and cerebrovascular disease using (ICD codes I60-I69). (Table 6.1-19). We identified no excess mortality risk for diseases of the circulatory system, ischemic heart disease, or cerebrovascular disease among ST users (all respondents) compared to never-tobacco users in either dataset. Subgroup analysis of males, white males, and females yielded similar results (data not shown).

Table 6.1-19: Mortality from Circulatory Diseases, Ischemic Heart Disease, and Cerebrovascular Disease Adjusted Hazard Ratio Estimates: Smokeless Tobacco Users Compared to Never-Tobacco Users

Disease	Study	Observations	Deaths	HR[1] (95% CI)
Diseases of the Circulatory System	NLMS	1,863	25	0.903 (0.570-1.430)
	NHIS[2]	1,561	153	1.152 (0.908-1.460)
Ischemic Heart Disease	NLMS	1,863	14	0.945 (0.490-1.825)
	NHIS	1,561	68	0.872 (0.628-1.211)
Cerebrovascular Disease	NLMS	1,863	3	0.611 (0.191-1.954)
	NHIS	1,561	28	1.108 (0.699-1.758)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never).
CI = Confidence Interval; HR = Hazard Ratio; NE = Not estimated due to low incidence rate and resultant wide CI; NHIS = National Health Interview Survey. NHIS data shown is obtained from the restricted access data file. NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters)
[2] NHIS data obtained from analyses of the restricted access data file.

Recently, Timberlake et al. (2017) identified coronary heart disease (CHD) as associated with ST use within the NLMS dataset noting "…current SLT [smokeless tobacco] users had a higher mortality risk for coronary heart disease (CHD) (HR(95% C.I.)=1.24 (1.05, 1.46)) relative to never tobacco users." Timberlake and colleagues also provided a separate analysis comparing MST use with chewing tobacco use and noted some difference between ST types "…the elevated risk for CHD mortality corresponded to the use of moist snuff (HR (95% C.I.) =1.30 (1.03, 1.63))."

In discussing the significance of a possible association between ST use and heart disease, Timberlake et al. noted that "…the associations with CHD mortality could be attributed to long-term nicotine exposure, other SLT constituents (e.g., metals), or the confounding effects of CHD risk factors not accounted for in this study." The authors acknowledged that their estimate could be inflated relative to other estimates due to the residual confounding of lack of exercise and fruit/vegetable intake.

Gupta et al (2018) conducted a meta-analysis of twenty studies from four WHO regions to analyze for a possible association between ST use and coronary heart disease (CHD). The authors reported "CHD in SLT users was not significantly positive (1.05, 95% CI 0.96-1.15) although a higher risk of fatal CHD was seen (1.10, 95% CI 1.00-1.20)." An assessment by geographical region identified a significant risk for fatal CHD among ST users in the European Region (1.30, 95% CI 1.14-1.47), but not in the American region (1.04, 95% CI 0.83- 1.24). The fraction of fatal CHD attributable to ST was calculated as 0.30% for the entire international dataset, 5% for Sweden, and 0.014% in the U.S, noting close agreement with previous estimates of Boffetta & Straif (2009) (attributable fraction of myocardial infarction deaths 0.5% in U.S. and 5.6% in Sweden). American region estimates in the Gupta study included data from Accortt et al. (2002) and Henley et al. (2005), and did not use recent estimates of Timberlake et al. (2017) or our unpublished examination of the NLMS and NHIS datasets.

Identification of an excess risk for CHD among ST users in the Timberlake study is consistent with findings of both CPS studies (I and II) (Henley et al., 2005), and the Atherosclerosis Risk Communities study conducted by (Yatsuya & Folsom Aaron, 2010). In contrast, Accortt et al. (2002) analyzed the longitudinal NHANES I Follow-up Study and found no significant risk for CHD.

Exclusion criteria used to select the sample for analysis can also meaningfully impact epidemiology study findings. Timberlake et al. (2017) excluded pipe, cigar, and AS from their sample population, but did not account for self-reported health status (included in the survey). Similarly, we also excluded pipe and cigar smokers from our sample, but our Linked Mortality Analysis included self-perceived health status in our data selection criteria. We believe our approach adjusting for self-reported health status may account for dietary and lifestyle confounders, which can adversely affect cardiovascular health.

Two published studies evaluated ischemic heart disease (IHD) and cerebrovascular disease (stroke) risk among ST users (Accortt et al., 2002; Henley et al., 2005). Accortt et al. did not detect a statistically significant risk elevation in male or female ST users for IHD or cerebrovascular disease. Henley et al., however, found that IHD risk and cerebrovascular disease were significantly elevated in both male cohorts evaluated. Two independent, published meta-analyses derived relatively modest, but statistically elevated, pooled risk estimates for IHD or cerebrovascular disease (Boffetta & Straif, 2009; Lee & Hamling, 2009a).

Current data reflect somewhat contradictory results regarding an association between ST use and the risk for cardiovascular disease. The possibility of an increased risk of cardiovascular disease with ST use cannot be totally dismissed, because nicotine has been reportedly

suggested as a contributing factor related to CVD risk (Benowitz & Burbank, 2016). Yet, the residual effects of smoking could also account for the identified risk increase. Given the strong association between cigarette smoking and CVD risk, inclusion of current or former AS within samples of never-smoking ST users could unduly influence results, particularly when relatively low excess risk is indicated.

6.1.3.4. Other Health Risk Endpoints

Our analysis of the NLMS and NHIS studies also examined several other major causes of death as identified by the CDC, including chronic lower respiratory diseases; Alzheimer's disease; diabetes mellitus; influenza and pneumonia; and nephritis/nephrosis. As shown in Table 6.1-20, based on NLMS or NHIS study data, ST use does not appear to have any significant association with an excess risk for these major mortality causes.

Table 6.1-20: Mortality Risk Estimates for Selected Causes of Death among Smokeless Tobacco Users (All Respondents) Compared to Never-Tobacco Users

Cause of Death	Study	Observations	Deaths	HR[1] (95% CI)
Chronic Lower Respiratory Diseases	NLMS	1,863	0	NE
	NHIS[2]	1,561	<5	NR
Alzheimer's Disease	NLMS	1,863	1	2.206 (0.313-15.564)
	NHIS	1,561	8	1.539 (0.629-3.761)
Diabetes mellitus	NLMS	1,863	2	1.509 (0.375-6.075)
	NHIS	1,561	14	1.310 (0.659-2.605)
Influenza and pneumonia	NLMS	1,863	0	NE
	NHIS	1,561	10	1.013 (0.531-1.933)
Nephritis / Nephrosis	NLMS	1,863	0	NE
	NHIS	1,561	10	0.974 (0.471-2.011)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P0-CSLT vs Never)
CI = Confidence Interval; HR = Hazard Ratio; NE = Not estimated; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; NR = Not reported. Number of deaths was <5; ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on never smokers excluding former ST users (P0 analysis) with the reference group comprising individuals who never used tobacco (according to survey defined parameters).
[2] NHIS data obtained from analyses of the restricted access data file.

Diseases of the respiratory system include chronic lower respiratory diseases and infectious diseases. The NLMS and NHIS datasets offered no evidence of an association between ST use and respiratory disease mortality or with specific respiratory disease endpoints, including chronic lower respiratory disease. Two publications evaluate the association between ST use and respiratory diseases (Accortt et al., 2002; Henley et al., 2005). Respiratory disease risk

was not elevated among ST users in the Accortt et al. study, or in one of the cohorts (CPS-II) evaluated by Henley et al. However, Henley et al. did detect significantly elevated risks for respiratory diseases and COPD in CPS-I. As discussed previously, the finding of increase COPD, a disease strongly associated with cigarette smoking risk, among purported never-smoking ST users suggests possible misclassification.

The U.S. Surgeon General established a causal association between ST use and leukoplakia in 1986 (U.S. Dept. Health Human Services, 1986). ST products marketed in the U.S. carry federally mandated labels warning of the oral health consequences associated with ST use. (Note: In this MRTPA, we request no change to existing warning labels.)

Kallischnigg et al. (2008) conducted an exhaustive review of the published literature investigating the relationship between ST use and non-neoplastic oral diseases. This review addressed experimental and epidemiological studies published from 1963–2007 related to the risk of oral lesions associated with ST use and assessed data separately for oral mucosal lesions; periodontal and gingival diseases; dental caries and tooth loss; and oral pain. The authors concluded that the current scientific evidence supports an association between ST use and oral mucosal lesions and suggests an association between snuff use and gingival recession.

6.1.3.5. Maternal and Fetal Effects

Males are the primary consumers of ST in the U.S., with relatively few females adopting the use of this type of tobacco product. In a recent study conducted by England et al. (2016); however, women in focus groups who were generally unfamiliar with ST products like snus[30] did find some potential advantages of these products, raising a concern that pregnant women may be attracted to such products.

Studies of possible maternal or fetal effects of ST use in humans are relatively sparse. England et al. (2012) examined the medical records of a small sample of Alaskan women and "…found a modest but non-significant reduction in the birthweight of infants of smokeless tobacco users compared with infants of tobacco non-users."

Although we have not generally relied on data for Swedish products in this application, we include some here due to the paucity of U.S. information. England et al. (2003) examined birth weight, preterm delivery, and pre-eclampsia (considering these "outcomes that have been shown consistently to be affected by cigarette smoking") among Swedish women. Compared with nonusers, adjusted mean birth weight was reduced in ST users by 39 g (95% CI, 6-72 g), and in smokers by 190 g (CI, 178-202 g). Both ST users and smokers showed a significant increase in pre-term delivery (defined as <37 completed weeks of gestation), when compared with non-users. More modest reductions in gestation-adjusted birth weight compared with cigarette smoking led the authors to suggest that "carbon monoxide plays a more prominent role in fetal growth restriction than does nicotine in smokers." Pre-eclampsia

[30] The authors defined snus as moist snuff packaged in pouches that resemble small tea bags. Study participants were shown Camel and Marlboro snus products in addition to other emerging non-combustible tobacco products. The applicability of the results obtained with these snus products to the candidate product is unknown.

was significantly reduced in the smokers, but was significantly increased in ST users, when both groups were compared with non-users.

A series of nonclinical studies have evaluated the effects of aqueous ST extracts (gastric intubation three times daily during gestation) on pregnant rodents (Paulson, Shanfeld, Mullet, Cole, & Paulson, 1994; Paulson, Shanfeld, Sachs, Price, & Paulson, 1989; Paulson, Shanfeld, Vorhees, et al., 1994). Very high plasma nicotine concentrations (up to 869 ng/ml) were noted in the higher dose groups, resulting in large numbers (up to 31%) of maternal deaths. The lowest ST dosage produced negligible effects on the offspring, in each of the three experiments.

6.1.3.6. Conclusion

ST products, including the candidate product, are not risk-free. Previous literature reports have indicated potential increased mortality risks from certain diseases from ST use relative to never tobacco use. However, our analysis of recent linked mortality datasets, which we believe represent modern products, generally does not corroborate the older published epidemiology. Importantly, the health risks associated with the candidate product compared to never using tobacco products should be considered in the context of the lower mortality risks compared to cigarette smoking.

6.1.4. Health Risk Changes to Users Who Switch from Using Another Tobacco Product to Using the Candidate Product, including Tobacco Products within the Same Class of Products

The current U.S. tobacco market comprises a variety of products such as cigarettes, cigars, Swedish-style snus, chewing tobacco, and e-cigarettes. Consequently, the phrase “another tobacco product” could mean any, or all, of these products. However, we believe that consumers most likely to switch to the candidate product are cigarette smokers (consumers of the most predominant and most harmful tobacco product in the current U.S. population), consumers who currently use both cigarettes and ST (dual users), or consumers who currently use other ST products such as chewing tobacco. Additionally, the proposed claim language is intended to draw the attention of adult smokers by emphasizing “IF YOU SMOKE, CONSIDER THIS.”

In a 2009 review of the relative risk of ST products, the Life Sciences Research Organization (LSRO) (2009)[9] concluded that “Swedish snus (moist snuff tobacco) poses the lowest risk of smokeless tobacco products, traditional American smokeless tobacco products (U.S. smokeless tobacco products other than those recently developed) pose an intermediate risk, and international smokeless tobacco products (products other than those primarily used in the U.S. and Sweden) pose the greatest health risk.” Additionally, LSRO concluded that “considerable additional research on smokeless tobacco products that involves application of standardized methods is needed to better characterize risk of smokeless tobacco products.” We believe there is sufficient evidence showing a risk differential between smoking and ST product use; however, insufficient evidence exists to suggest that, despite some physical or chemical differences between ST products, switching between ST products would result in discernible overall changes in health risk.

Existing scientific data demonstrate a substantial difference in the health risks between ST use and cigarette smoking and show that AS who quit smoking can significantly reduce their risk for serious diseases. Although, depending on smoking history, this reduction may not return to the risk levels of never-tobacco users. The use of ST by former smokers does not have a significant adverse effect on this risk reduction and preserves the benefit obtained from smoking cessation.

6.1.4.1. Switching from Cigarette Smoking to ST Use

We use the NHIS and NLMS datasets to estimate adjusted HR for mortality from all causes, diseases of the heart, and malignant neoplasms between never-tobacco users and current smokers who do not use ST, former smokers who do not use ST, and former smokers who stopped smoking at some point and switched[31] to ST (Table 6.1-21).

Current smokers had an excess risk for all three endpoints. In the case of malignant neoplasms, both datasets indicated about a three-fold increase in risk compared to never-tobacco users.

Former smokers who stopped smoking (cessation time unmeasured) had a significantly lower mortality risk compared to current smokers, but an elevated risk remained compared to never-tobacco users. Although the available sample size for former smokers who switched to ST is less than that available for current or former smokers in both datasets, the use of ST by former AS does not appear to have a meaningfully adverse effect on the results of smoking cessation.

Table 6.1-21: Effect of Switching from Cigarette to Smokeless Tobacco: Adjusted Hazard Ratio Estimates for Current and Former Adult Cigarette Smokers Compared to Never-Tobacco Users

Tobacco Use		Mortality Cause	NLMS			NHIS		
Cigarettes	ST		Observations	Deaths	HR[1] (95% CI)	Observations	Deaths	HR (95% CI)
Current	Never	All Causes	38,076	1,505	1.878 (1.744-2.023)	36,112	7,525	2.130 (2.048-2.215)
		HD	38,076	378	1.613 (1.404-1.853)	36,071	1,796	1.951 (1.812-2.100)
		MN	38,076	520	2.880 (2.520-3.291)	36,071	2262	2.951 (2.726-3.195)

[31] Participants stopped smoking at some point prior to the survey and started using ST prior to the survey. Neither dataset allows us to determine whether these participants switched to ST use from smoking; or stopped smoking, were tobacco free for some period of time, and then started ST.

Tobacco Use		Mortality Cause	NLMS			NHIS		
Cigarettes	**ST**		**Observations**	**Deaths**	**HR[1] (95% CI)**	**Observations**	**Deaths**	**HR (95% CI)**
Former	Never	All Causes	39,401	2,703	1.416 (1.334-1.503)	28,552	7,415	1.301 (1.255-1.348)
		HD	39,401	749	1.162 (1.042-1.296)	28,524	2,148	1.161 (1.084-1.243)
		MN	39,401	758	1.953 (1.733-2.201)	28,524	1,740	1.577 (1.458-1.705)
Former	Current	All Causes	972	59	1.317 (0.963-1.802)	744	204	1.331 (1.093-1.619)
		HD	972	14	0.828 (0.461-1.488)	742	72	1.471 (1.049-2.063)
		MN	972	19	2.040 (1.173-3.548)	742	49	1.572 (1.098-2.250)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs NTU)
CI = Confidence Interval; HD = Diseases of the heart; HR = Hazard Ratio; MN = Malignant neoplasms; NLMS = National Longitudinal Mortality Study; NHIS = National Health Interview Survey (NHIS data obtained from the restricted access data file); ST = Smokeless Tobacco
[1] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

Henley et al. (2007) noted that participants in the CPS-II study who switched from cigarettes to chew, snuff, or a combination of both ST products generally had a higher risk of mortality from all-causes, or lung cancer compared to those who stopped all tobacco use. As we have discussed previously, the finding that two diseases strongly associated with cigarette smoking are elevated among ST users may suggest differences in past smoking intensity or continued smoking among these purported switchers.

Previous investigations have established the adverse impact of cigarette smoking on lung cancer associated mortality and other respiratory diseases, as well as the impact of smoking cessation [Surgeon General Report (2014)]. Data from the NLMS and NHIS studies illustrate the effect of smoking cessation and show that the use of ST following smoking cessation does not adversely impact the expected reductions in risk for mortality from neoplasms of the trachea, bronchus, and lung and other respiratory diseases (Table 6.1-22). Based on the NLMS dataset, current smokers had significantly increased mortality risk from respiratory tract cancer. Former smokers who did not use ST had a marked reduction in the risk of

mortality from neoplasms of the trachea, bronchus, and lung (about 50%) compared to current smokers. Former smokers who switched to ST use (current use) also demonstrated this marked reduction in mortality from neoplasms of the trachea, bronchus, and lung. The NHIS dataset contained a low incidence of mortality from respiratory tract cancers. As discussed previously, given that NCHS suppresses low incidence data, we were unable to complete an analysis of the NHIS dataset with the all-respondent model.

Table 6.1-22: Mortality from Neoplasms of the Trachea, Bronchus and Lung, and Other Respiratory Diseases: Adjusted Hazard Ratio Estimates for Various Tobacco Use Practices Compared to Never-Tobacco Users

Tobacco Use		Study	Neoplasms[1]			Respiratory Diseases[2]		
Cigarettes	**ST**		**Observations**	**Deaths**	**HR[3] (95% CI)**	**Observations**	**Deaths**	**HR (95% CI)**
Current	Never	NLMS	38,076	247	11.522 (8.740-15.190)	38,076	151	2.728 (2.133-3.489)
		NHIS[4]	36,071	1,079	NR	36,071	1,003	5.268 (4.678-5.931)
Former	Never	NLMS	39,401	254	5.650 (4.329-7.376)	39,401	361	2.441 (2.025-2.941)
		NHIS[4]	28,524	452	NR	28,524	918	2.755 (2.422-3.135)
Former	Current	NLMS	972	6	5.341 (2.035-14.016)	972	4	0.89 (0.309-2.562)
		NHIS[4]	742	17	NR	742	26	2.735 (1.632-4.583)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs NTU)
NR = Not reported; CI = Confidence Interval; HR = Hazard Ratio; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco

[1] ICD Codes C33-C34

[2] ICD Codes J00-J98

[3] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

[4] NHIS data shown is obtained from analyses of the restricted access data file. The P4 model for this analysis included current and former ST user groups who never smoked cigarettes. Both groups had fewer than 5 lung cancer mortality events.

Both datasets showed the impact of smoking cessation on reducing the risk of respiratory diseases. The response was, however, less dramatic than that seen for neoplasms. Importantly, the use of ST by former smokers did not appear to adversely impact the effects of smoking cessation. In the NLMS dataset, former smokers who used ST did not have a greater risk for respiratory diseases compared to never-tobacco users, although the low incidence rate limits the power to detect a statistically significant finding.

6.1.4.2. Switching from Chewing Tobacco Use to MST Use

Few studies in the published literature address the changes in health risk related to switching among ST products. Further, the existing data primarily relate to males, because females have not widely adopted MST use.

Henley et al. (2005) investigated the relationship between snuff or chewing tobacco use and mortality among men enrolled in the CPS-II in 1982. The CPS-II dataset included mortality information related to exclusive use of either ST product, as well as to switching between products. Men using chewing tobacco exclusively had an excess mortality risk for several endpoints compared with non-tobacco users (Table 6.1-23). In contrast, male snuff users who never used chewing tobacco showed an excess mortality risk only for CHD as compared with male non-tobacco users. Although tobacco chewers who switched to snuff were found to have a greater risk of lung cancer mortality, very wide confidence intervals limit the reliability of the point estimate (95 percent CI: 3.58-26.7). None of the causes of death reported in the analysis reached statistical significance for snuff users who switched to chewing tobacco.

Table 6.1-23: Mortality HRs and 95% CI for Men Who Used ST Products Exclusively (CPS-II, 1982-2000)

Cause of death	Multivariate-adjusted HR (95% CI) listed by tobacco use type[1]			
	Chewing tobacco users		Snuff users	
	Never used snuff	Switched to snuff	Never used chew	Switched to chew
All causes[2]	1.16 (1.05-1.29)	1.01 (0.69-1.47)	1.25 (0.98-1.58)	0.96 (0.61-1.50)
All cancers[3]	1.23 (1.02-1.49)	1.58 (0.87-2.87)	0.93 (0.55-1.57)	1.30 (0.58-2.89)
Lung cancer[3]	1.97 (1.10-3.54)	9.78 (3.58-26.7)	2.08 (0.51-8.46)	NP
Cardiovascular disease[4]	1.26 (1.09-1.46)	0.64 (0.33-1.24)	1.38 (0.99-1.92)	0.87 (0.45-1.70)
Coronary heart disease[5]	1.25 (1.03-1.51)	0.80 (0.37-1.70)	1.59 (1.06-2.39)	1.02 (0.45-2.30)
Cerebrovascular disease[6]	1.38 (1.02-1.86)	0.68 (0.17-2.75)	0.62 (0.23-1.67)	1.24 (0.39-3.91)
Other causes	1.07 (0.92-1.25)	1.20 (0.73-1.97)	1.07 (0.74-1.54)	1.00 (0.53-1.87)

Source: Data extracted from (Henley et al., 2005)
CI = Confidence Interval; CPS-II = Cancer Prevention Study II; HR = Hazard Ratio; NP = Not Presented; ST = Smokeless Tobacco
[1] Cox models adjusted for age, race, education level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.

[2] Analysis for all causes excludes men who reported prevalent cancer, heart disease, diabetes, or stroke in 1982 (due to disease exclusions the number of all cause deaths differs from the summed total of specific causes of death).
[3] Analyses for cancers exclude men who reported prevalent cancer in 1982.
[4] Analysis for cardiovascular disease excludes men who reported prevalent heart disease, diabetes, or stroke in 1982.
[5] Analysis for coronary heart disease excludes men who reported prevalent heart disease or diabetes in 1982.
[6] Analysis for stroke excludes men who reported prevalent stroke in 1982.

Due to the considerable statistical uncertainty in the CPS-II data (the single study that provides switching data for ST products), we do not draw any definitive conclusions regarding the health risk implications of switching from chewing tobacco to the candidate product. However, we find most of the risk estimates calculated from the CPS-II to be relatively low and generally consistent between the sub-categories of ST products.

6.1.4.3. Switching from Other MST Products to the Candidate Product

Some investigators have suggested that different chemical composition among MST products could lead to differences in health risk (Borgida et al., 2015). There is, however, insufficient product-specific, human epidemiological evidence in the literature comparing the health risks of individual MST products to accurately assess a possible change in health risk among MST users who switch between products.

Based on the current state of knowledge, switching between MST products would not substantially alter the established profile of the major tobacco-associated health outcomes associated with ST use. Given the results of the Henley et al. study (2005) where switching between two fundamentally different ST products such as chewing tobacco and snuff failed to produce a substantial impact on health risk, we conclude that the chemical composition differences between MST products, although measurable, would be largely inconsequential to major health risk outcomes measured by current epidemiology methods.

6.1.4.4. Conclusion

We would expect that, for those ST users who switch to the candidate product, there would be no measurable, or substantial, change in health risk. Rather, the major change in health risk related to ST use remains with AS who stop smoking and adopt MST use exclusively.

We believe the scientific evidence showing a clear difference between AS and ST users fully supports our proposed claim. Providing the proposed accurate health risk information to adult tobacco consumers could encourage exclusive AS and dual users to stop smoking and substantially reduce their mortality risk from lung cancer and other fatal diseases. As we demonstrate, for those who wish to continue tobacco use, switching to the candidate product does not measurably impact the established reduction in health risk associated with smoking cessation.

6.1.5. The Health Risks Associated with Using the Product in Conjunction with Other Tobacco Products

An evaluation of the potential health risks of the concomitant use of cigarettes and the candidate product is necessary because many exclusive smokers who decide to try the candidate product will likely undergo some undetermined period of combined tobacco product use before complete transition. We note that approximately 2.3 million of the 4.3 million current adult ST users also smoke cigarettes[32]. Communicating relative tobacco product health risk could persuade some individuals who are unable or unwilling to quit all tobacco use to switch to exclusive use of the candidate product. Since smoking is a risk factor for many diseases, we concentrate our analysis of the possible health effects of dual use on the most prevalent diseases associated with cigarette smoking, including mortality from all-causes, disease of the heart and malignant neoplasm, and non-fatal oral diseases such as leukoplakia or gingival effects.

We assess the synergistic effects of ST use and cigarette smoking by comparing the disease risks of dual users with those of exclusive AS in the NHIS and NLMS mortality linkages. Additionally, we review the published literature where several studies have investigated the potential for synergistic relationships between tobacco types.

Previous studies have assessed dual use of ST products and cigarettes from the perspective of smoking prevention, dependence, and gateway issues (Foulds et al., 2003; Tomar, 2002). We find no compelling evidence based on the NLMS or NHIS datasets, nor from our review of published literature, that the use of ST (including the candidate product) in conjunction with cigarettes results in an increased risk for serious health effects associated with cigarette smoking.

6.1.5.1. Effect of ST Use and Cigarette Smoking on Selected Health Risk Endpoints

First, the NLMS and NHIS datasets provide relevant information to examine the potential synergistic risk for AS who also use ST products; however, many of the more specific patterns of dual use (e.g., mix and magnitude of tobacco products use) are unknown. Table 6.1-24 presents adjusted HR for mortalities related to all-causes, diseases of the heart and malignant neoplasms among dual users compared to exclusive AS. Neither dataset indicated a significant excess mortality risk for dual users compared to exclusive AS (male and female respondents). Further analysis of the data by gender showed no excess risk for all-cause mortality, although the numbers of recorded deaths limited analysis (data not shown). The adjusted hazard ratios for respiratory disease, individual neoplasms and other causes of death are not shown, since the low incidence rates for these endpoints generally provided unreliable statistical results.

[32] Based on ALCS analysis of PATH Wave 1 data Sep 12, 2013 – Dec 14, 2014. We refer to the population of ST consumers that also smokes cigarettes as “Dual Users.” This population is heterogeneous and we do not differentiate between levels of dual usage, which may consist of regular smokers that occasionally use ST or regular ST users that smoke cigarettes occasionally.

Table 6.1-24: Dual Use of Smokeless Tobacco and Cigarette Smoking: Adjusted Hazard Ratio Estimates for Current Adult Cigarette Smokers Who Also Used ST Compared to Adult Cigarette Smokers Who Never Used ST

Mortality Cause	NLMS			NHIS[1]		
	Observations	Deaths	HR[2] (95% CI)	Observations	Deaths	HR (95% CI)
All Causes	657	22	1.156 (0.687-1.948)	673	91	1.009 (0.769-1.322)
HD	657	5	1.095 (0.416-2.888)	673	17	0.578 (0.340-0.982)
MN	657	7	1.516 (0.633-3.631)	673	26	0.870 (0.570-1.330)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P2-CSLT vs Never)
CI = Confidence Interval; HR = Hazard Ratio; HD = Diseases of the heart; MN = Malignant neoplasms; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] NHIS data obtained from analyses of the restricted access data file.
[2] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data , not available in the NLMS data], education, family income, health status, tobacco use, and cigarettes per day [only for the NHIS data]). The analysis compared male and female respondents who were dual users to current smokers never using ST (P2 analysis).

Second, several published studies have assessed the implications of dual use on health risk. Accortt et al. (2002) used the results of the NHANES I and a 20-year mortality follow-up of subjects who took part in the original survey to compare the effects of combined dual use of ST and cigarettes. The authors compared the smoking groups with respect to mortality up to 1992 (by which time almost a third of subjects had died) from major causes, with RR estimates adjusted for age, race, an index of poverty, and, in some analyses, also for alcohol, exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol, and body mass index. The authors noted that the proportion of males was considerably higher (92.7 percent) in dual users than in exclusive ST users (56 percent) and exclusive smokers (55.7 percent). Also, physical activity and dietary fat intake were higher in dual users.

Accort et al. (2002) found that dual users did not experience increased mortality for ischemic heart disease, although exclusive smokers had a statistically significant increase in mortality (HR = 1.6; 95 percent CI: 1.3, 1.9). The authors also noted that "…the lung cancer mortality among combined users was nearly twice that of exclusive smokers (HRs = 22.6 and 13.2, respectively)." In male smokers who never used ST, the reported lung cancer HRs were, as expected (and consistent with many other studies), clearly increased both in ever smokers and in subgroups of current and former smokers. HRs were about three times higher in current smokers than in former smokers, and were roughly in between the two estimates in ever smokers. The same pattern of smoking-associated lung cancer HRs occurred in smokers who were ever users of ST; this time, however, the ratios were increased by a factor of around 1.3 to 1.7, depending on the classification of the smoking status.

Despite the statistically significant findings, Accortt et al. (2002) rejected the notion of an interactive effect of dual use stating, "Although the mortality rate among combined users was higher than that expected from the individual rates, this result is not likely due to a synergistic effect between smokeless tobacco and cigarettes (Accortt et al., 2002). The combined users smoked more than exclusive smokers did (42.3 and 35.1 mean pack-years, respectively). The higher cigarette smoking dose, not the use of smokeless tobacco, is likely leading to the increased lung cancer mortality among combined users."

In a subsequent analysis, Accortt et al. (2005) reviewed cancer incidence, instead of mortality from chronic diseases, using the same data analyzed in their 2002 publication. With respect to the question of adverse health effects related to dual use of ST and cigarettes, the authors concluded that "No synergistic effect was observed between ST and cigarette smoking among male combined users (females were not analyzed for combined use) for the major cancers."

Together, the analyses of data from NHANES I collected from 1971 to 1975 suggest no relevant synergistic effect of ST use and cigarette smoking for major health risks associated with tobacco. In both studies, the authors rejected the notion of an interactive effect of dual use on lung cancer incidence/mortality.

Other studies of the concomitant use of ST with cigarette smoking have found no evidence of an association between ST use and increased risk of serious and potentially fatal diseases. Hassan et al. (2007) evaluated the associations with pancreatic cancer noting "…there was no significant association between ever-use or heavy intake (>20 total times/years) of chewing tobacco, snuff, pipes, or cigars and the risk of pancreatic cancer among adult cigarette smokers." Zahm et al. (1992) found an association between cigarette smoking and soft tissue sarcoma (RR = 1.8; 95 percent CI = 1.1-2.9) among military veterans, but no statistically significant increased risk for ST use only (RR = 1.4; 95 percent CI = 0.8-2.6) or ST use with other tobacco products (RR = 1.5; 95 percent CI = 0.8-2.7). However, the authors only described dual use as ST and other tobacco products and dual use exposure is assumed to ST and cigarettes. Yatsuya and colleagues (2010) assessed the possible relationship of dual use of ST and cigarettes with CVD reporting a HR of 1.09; (95 percent CI: 0.74-1.60) for those ST users who also reported cigarette smoking. Finally, Andreotti and colleagues (2016) assessed exclusive and dual tobacco product use among participants in the Agricultural Health Study and reported that "Cigarette smokers who additionally ever used smokeless tobacco had cancer risks similar to exclusive cigarette smokers."

Studies of oral disease risk associated with dual use have provided mixed results. Andrews et al. (1998) sampled over 34,000 dental patients noting that AS had a greater incidence of gingival bleeding and mouth sores than nonusers, and those who reported dual use of ST and cigarette smoking had a higher incidence of gingival bleeding and mouth sores than either AS or tobacco non-users. The subset of dual users in this study was exceedingly small, as compared with that in other prevalence reports (only 100 dual users out of >34,000 subjects). Grady et al. (1990) reports finding that the "Severity of leukoplakic lesions did not vary by age, race, cigarette smoking, alcohol consumption or dental hygiene practices." Finally, Wolfe and Carlos (1987) investigated the association between ST, cigarettes, or alcohol and oral disease. While duration and frequency of ST use were highly significant factors

associated with leukoplakia, the concomitant use of ST with alcohol or cigarettes did not appear to increase the prevalence of these lesions.

6.1.5.2. Conclusion

Many ST users are dual tobacco product users who also smoke cigarettes. Additionally, it is reasonable to expect that exclusive AS who decide to use the candidate product instead of smoking will experience a period of dual product exposure before complete transition to smoking cessation.

Dual use is currently not an accepted[33] pathway for smoking cessation; quitting smoking completely remains the best way to protect an individual's health. However, the data do not suggest that dual use of the candidate product by AS exacerbates the serious health consequences associated with smoking. We compared the disease risks of dual users with those of exclusive AS in the NHIS and NLMS mortality linkages. Additionally, we reviewed several scientific publications containing health risk information related to the concomitant use of ST and cigarettes. In aggregate, we find no compelling evidence that the use of ST, including the candidate product, in conjunction with cigarettes increases risks to health beyond those associated with exclusive cigarette smoking.

Thus, dual use by AS during a transition to smoking cessation or full adoption of the candidate product should not be a barrier to authorization of the proposed modified risk claim. On the contrary, this application provides an opportunity to reduce the mortality hazards risk by encouraging dual users to switch to exclusive use of the candidate product.

6.1.6. The Health Risks Associated with Switching to the Product as Compared with Quitting Tobacco Product Use

Our proposed modified risk claim provides accurate information to ATC, permitting dual users or exclusive AS to make the informed decision to exclusively use the candidate product instead of smoking. In this section, we address the health risk from switching to the candidate product relative to stopping cigarette smoking and find that smokers who quit all tobacco use are not likely to experience substantively different mortality risks than smokers who switch to the candidate product.

6.1.6.1. Effect of Switching to ST Use on Selected Health Risk Endpoints in Former Adult Cigarette Smokers

Using the NLMS and NHIS mortality linkages, we compare the adjusted HRs for all-cause mortality and major groups of diseases among former AS who never used ST (quitters) and who currently use ST (switchers) to never tobacco users (Table 6.1-25). Former cigarette smokers retain residual risks from their active smoking [Surgeon General Report (1990)]. Consistent with this effect, both groups (quitters and switchers) had statistically elevated risks for mortality from all-causes, diseases of the heart, and malignant neoplasms compared to never-tobacco users. The adjusted HRs for other causes of death measured in the NLMS

[33] https://www.cdc.gov/tobacco/campaign/tips/diseases/dual-tobacco-use html

and NHIS datasets are not shown, since the low incidence rates for these endpoints using the all-respondents model generally provided unreliable statistical results. Notably, the adjusted HRs for quitters are reasonably consistent with those of switchers, suggesting a relatively small and probably non-relevant risk differential between switching to ST compared with quitting tobacco use altogether.

Table 6.1-25: Effect of Switching from Cigarette Smoking to Smokeless Tobacco Use: Adjusted Hazard Ratio Estimates[1] for Former Adult Cigarette Smokers Who Never Used ST (Quitters) and Former Adult Cigarette Smokers Who Currently Use ST (Switchers) Compared with Never-Tobacco Users

Mortality Cause	Tobacco Use		NLMS			NHIS[1]		
	Cigarettes	ST	Observations	Deaths	HR[2] (95% CI)	Observations	Deaths	HR (95% CI)
All Causes	Former	Never	39,401	2,703	1.416 (1.334-1.503)	28,552	7,415	1.301 (1.255-1.348)
	Former	Current	972	59	1.317 (0.963-1.802)	744	204	1.331 (1.093-1.619)
Disease of the heart	Former	Never	39,401	749	1.162 (1.042-1.296)	28,524	2,148	1.161 (1.084-1.243)
	Former	Current	972	14	0.828 (0.461-1.488)	742	72	1.471 (1.049-2.063)
Malignant neoplasms	Former	Never	39,401	758	1.953 (1.733-2.201)	28,524	1,740	1.577 (1.458-1.705)
	Former	Current	972	19	2.040 (1.173-3.548)	742	49	1.572 (1.098-2.250)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P4 - TUGs vs NTU)
CI = Confidence Interval; HR = Hazard Ratio; HD = Diseases of the heart; MN = Malignant neoplasms; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] NHIS data obtained from analyses of the restricted access data file.
[2] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, and tobacco use). The analysis was conducted on all respondents (P4 analysis), with the reference group comprising individuals who never used tobacco (according to survey defined parameters).

To further confirm that the health risks of switchers are not different from quitters, we conducted an additional analysis of the NHIS and NLMS mortality linkages using a model limited to only former AS. In this model, we calculated adjusted HRs for mortality from all-

causes, diseases of the heart, and malignant neoplasms among former smokers who switched to ST use and former smokers who did not use tobacco at survey baseline (Table 6.1-26). No differences were noted in the calculated adjusted HRs for switchers compared to quitters. Deaths attributed to other diseases measured in the two studies were insufficient and limited reliable statistical calculations.

Table 6.1-26: Switching from Cigarette Smoking to Smokeless Tobacco Use: Adjusted Hazard Ratio Estimates for Former Adult Cigarette Smokers Comparing ST Users (Switchers) to Tobacco Quitters

Mortality Cause	NLMS Current ST, Former Smoker			NHIS1 Current ST, Former Smoker		
	Observations	Deaths	HR2 (95% CI)	Observations	Deaths	HR (95% CI)
All Causes	972	59	0.939 (0.685-1.289)	165	61	1.123 (0.863-1.463)
HD	972	14	0.713 (0.396-1.284)	165	18	0.880 (0.488-1.589)
MN	972	19	1.044 (0.600-1.818)	165	17	1.451 (0.935-2.250)

Source: Linked Mortality Analysis (Appendix 7.4.1-2; Sheet tab: P3-CSLT-Never)
CI = Confidence Interval; HR = Hazard Ratio; HD = Diseases of the heart; MN = Malignant neoplasm; NHIS = National Health Interview Survey; NLMS = National Longitudinal Mortality Study; ST = Smokeless Tobacco
[1] NHIS data for this analysis were specifically limited to the 1987 restricted access data which was the only file showing cigarettes per day data for all former smokers.
[2] Estimates derived from Cox proportional hazards analysis with covariate adjustments (gender, race [white, non-white], age, BMI [only for the NHIS data, not available in the NLMS data], education, family income, health status, tobacco use, and cigarettes per day [only for the NHIS data]). The analysis compared male and female respondents who were former smokers (dual use unknown) to individuals who stopped smoking and never used ST (P3 analysis).

The results of our NHIS and NLMS analyses contrast with findings from the single study published in the scientific literature that also compared the health outcomes of switchers with those of quitters. Henley et al. (2007) reported statistically elevated hazards for all-cause mortality and mortality from lung cancer, coronary heart disease, and stroke for switchers, as compared with quitters.

6.1.6.2. Conclusion

The results of our NHIS and NLMS analyses provide evidence that the health risks of former smokers who stop smoking and switch to ST use are not different from those of former smokers who stop smoking and do not use any tobacco products. Our analyses provides convincing evidence supporting our proposed modified risk claim, that switching completely to the candidate product from cigarettes reduces risk of lung cancer.

6.1.7. The Health Risks Associated with Switching to the Product as Compared with Using FDA-Approved Tobacco-Cessation Medication

Meaningful comparisons of the risks of ST use, as described in the previous sections, compared to FDA-approved tobacco-cessation medications present a significant challenge due to the vastly different contexts and circumstances associated with their respective uses. A full review of the health risks of tobacco cessation therapies is beyond the scope of this application. However, we briefly summarize some relevant review articles for three FDA-approved tobacco-cessation medications; nicotine replacement therapies (NRTs), bupropion, and varenicline (Section 7.5.6-1 and 7.5.6-2).

The candidate product is a tobacco product and is not safe. FDA-approved tobacco-cessation medications have met the legal standard of being safe and effective for their intended uses. The candidate product is not intended as a substitute for FDA-approved tobacco-cessation medications.

The candidate product contains measurable amounts of some HPHCs, while tobacco cessation medications are either free of such compounds or contain trace amounts of TSNA (i.e., NRTs) (Stepanov et al., 2006). It is plausible that the candidate product presents a greater risk for some diseases compared to tobacco cessation therapies due to the impact of differences in product formulation. However, we are aware of no specific comparative information, or study, using ST products and tobacco cessation medications that appropriately measures the long-term health risk (i.e., epidemiology) outcomes for smokers switching to either ST or cessation medications.

6.1.7.1. Health Risks of Nicotine Replacement Therapies (NRT)

Nicotine is a common component of the candidate product and many commercial replacement therapies used to aid smoking cessation. As a component of a cessation therapy, nicotine is generally considered to be safe for its intended use, since the benefits of the use outweigh the potential health risks (Apelberg, Onicescu, Avila-Tang, & Samet, 2010). Nicotine is not without some possible health consequences, and within the context of use under prescribed conditions for tobacco cessation medication, noted health effects have focused primarily on ASs, CV effects, and reproductive health outcomes (Benowitz, 1997). Two meta-analyses have investigated the cardiovascular effects of NRTs. Mills et al. (2014) conducted a review of 63 randomized clinical trials of smoking-cessation aids, including NRTs, to assess possible associations with CV events. On the basis of findings from 21 randomized clinical trials of NRTs, the authors concluded that “Smoking cessation therapies do not appear to raise the risk of serious cardiovascular disease events.” Greenland et al. (1998) conducted a meta-analysis of AE data from 47 reports of 35 clinical trials of subjects using the nicotine patch. There were no statistically significant increases in myocardial infarction, stroke, tachycardia, arrhythmia, or angina.

Mills et al. (2010) conducted a systematic review and meta-analysis of 120 studies and found no statistically significant increase in anxiety or depressive symptoms associated with NRT

use. The investigators concluded that use of NRTs is associated with a variety of acute adverse effects that may be discomforting, but that are not life-threatening.

Tobacco-cessation medications can help some people quit tobacco use altogether, and the potential health risks of these products have been extensively assessed by the FDA. In general, these medications are only used for a relatively short time period (e.g., the current label indication on these products is limited to use for 12 weeks), often in conjunction with behavioral modifications. ST, on the other hand, is not a product specifically indicated for smoking cessation. Rather, it is a consumer product used for enjoyment and intended for adult use *ad libitum*, including potentially individuals who use ST products for years.

The Lung Health study provides the longest documented use of NRT, in which participants used nicotine gum for up to five years (Murray et al., 1996). According to the investigators, "NP (nicotine polacrilex), as used in the Lung Health Study, appears to be safe and unrelated to any cardiovascular illnesses or other serious side effects." As noted by the Royal College of Physicians (2007), "evidence on the safety of long-term use of NRT is lacking, but there are no grounds to suspect appreciable long-term adverse effects on health."

Due to the large number of adult females who smoke cigarettes and as a result may use NRT as a cessation method, the potential adverse effects of NRT on maternal and fetal outcomes have been thoroughly assessed.

In a 2011 review, Coleman et al. (2011) conducted a systematic search of the literature in several electronic databases, as well as the Cochrane Pregnancy and Childbirth Group Trial Register. In addition to smoking-cessation efficacy, this literature review evaluated a number of pregnancy outcomes, including birth weight, low birth weight (<2,500 g), preterm birth (<37 weeks gestation), neonatal intensive care unit admissions, and fetal demise. The investigators reported that five of the seven safety outcomes were more positive among infants born to women who had used NRT; however, none of the observed differences between trial groups reached statistical significance. The investigators concluded the following: "We found that there is currently insufficient evidence to demonstrate that NRT, used by pregnant women for smoking cessation, is either effective or safe."

The same research group published a Cochrane Review of the safety of NRT related to pregnancy outcomes (Coleman, Chamberlain, Davey, Cooper, & Leonardi-Bee, 2012). Similar to the 2011 review, the authors concluded: "There is currently insufficient evidence to support either the efficacy or safety of nicotine replacement therapy (NRT) used with behavioral support by pregnant women for smoking cessation."

Based on the available evidence we conclude that the candidate product is likely to have greater health risks than NRT products, due to the differences in product formulation and the longer duration of ST product use.

6.1.7.2. Health Risks of Other Tobacco Cessation Medications

Published systematic reviews have summarized tolerability and AEs associated with use of bupropion as a smoking-cessation aid (Ferry & Johnston, 2003). Bupropion appears to be generally well tolerated, but may cause insomnia, headache, dry mouth, nausea, and anxiety.

Some trials have reported the occurrence of allergic reactions (Cahill, Stevens, Perera, & Lancaster, 2013).

Serious neuropsychiatric events, such as depression, suicidal ideation, suicide attempt, and completed suicide, have been reported in patients taking the prescription smoking cessation aid Chantix® (varenicline). However, recently, Hughes (2016) reviewed data from several placebo-controlled trials and uncontrolled observational studies and concluded that "…there is consistent evidence that varenicline either does not cause increased suicide outcomes, or if it does, the effect is very small." Studies have also assessed the cardiovascular effects of varenicline. Singh et al. (2011) conducted a systematic review and meta-analysis of studies of varenicline and reported a significantly increased risk of adverse CV events associated with varenicline, as compared to placebo. However, Mills et al. (2014) conducted a review of randomized clinical trials and reported no association between use of varenicline for smoking cessation and CVD events.

According to Coleman et al. (2012), studies of pregnancy outcomes have not been conducted on varenicline or bupropion. These investigators state that "There are no studies of either varenicline or bupropion and neither can be recommended for use in pregnancy."

6.1.7.3. Conclusion

For those who succeed in smoking cessation, the major health risk to the individual former smoker appears to be a result of the residual and lasting effects of smoking. For those who do not succeed in quitting, their health risk logically reverts to that of continued smoking.

We described the health risks of ST, and the candidate product, throughout Section 6.1 of this application. It is plausible that ST presents a higher risk for some diseases compared to cessation medications due to the differences in product formulation or the period of use (a few weeks for cessation medications vs. potentially years for ST use). However, we are aware of no specific comparative information, or study, using ST products and tobacco cessation medications that appropriately measures the long-term health risk (i.e., epidemiology) outcomes for smokers switching to either ST or cessation medications.

6.1.8. Overall Health Risk Conclusions

We conclude from several converging lines of evidence that ST is less risky than cigarettes and switching completely to the candidate product from cigarettes reduces risk of lung cancer. We assign significant weight to the epidemiological studies in the hierarchy of evidence, as they provide health outcomes from long-term product use behavior under real-world conditions. Nonclinical and clinical studies are also important and provide additional information regarding the likelihood of health outcomes and the mechanistic basis for the epidemiological findings.

1. Epidemiological evidence provides the ultimate proof that ST product use presents substantially lower morbidity and mortality risks compared to cigarette smoking, particularly as it relates to lung cancer. This evidence is further substantiated by the following conclusions from the nonclinical and clinical evidence.

2. Combustion related HPHCs are either absent or present at significantly lower levels in ST compared to cigarettes
3. The biological effect of ST is far lower than cigarettes, as demonstrated by a number of *in vitro* assays assessing perturbations in biological systems, including cytotoxicity, cell proliferation, cell cycle control, apoptosis, and genotoxicity.
4. Animals studies conducted under exaggerated exposure conditions that are not reflective of human use level do indicate perturbations in biological systems; however, the epidemiological evidence does not support the relevance of these changes in disease manifestation.
5. Biomarkers of exposure to combustion-related HPHCs in ST users are similar to those observed in non-tobacco users and significantly lower than cigarette smokers, confirming the product chemistry analyses observations.
6. Significant reductions in biomarkers related to chronic inflammation have been observed in ST users compared to smokers, further confirming that the reductions in exposure to many of the HPHCs are likely related to reductions in underlying smoking-related disease mechanisms

Our analysis of the health risks associated with the candidate product also incorporates two sets of epidemiology data comprising the most current risks for U.S. marketed products, including MST products such as the candidate product. We supplement this analysis with results from various published studies of U.S. ST products to arrive at the following conclusions regarding the absolute and comparative health risks of the candidate product:

- The health risks associated with use of the product as compared with those associated with using other tobacco products on the market, including tobacco products within the same class of products:
  - The current evidence demonstrates that ST conveys substantially lower individual health risk compared to conventional cigarettes. Mortality risks from all-causes, disease of the heart, and malignant neoplasms are significantly greater in AS compared to never-tobacco users. In contrast, ST users have mortality risks for all cancers, diseases of heart, and malignant neoplasms generally comparable to never-tobacco users.
  - Scientific studies have consistently and clearly shown that cigarette smoking is the greatest preventable risk factor for lung cancer and other respiratory diseases. Studies with ST users demonstrate a far lower risk for many serious fatal diseases, including lung cancer, compared to cigarette smoking. Even if one accepts the potential for an increased risk of lung cancer with ST use, the HR estimates presented in the literature to date show a far lower overall risk for lung cancer for ST use compared to cigarette smoking.
  - Currently available scientific information does not conclude a notable difference in health outcomes between MST (including the candidate product) and chewing tobacco, which are the dominant forms of ST used in the U.S.

- The health risks associated with initiating use of the product as compared with those associated with never using tobacco products:
  - ST products, including the candidate product, are not risk free as evidenced by the current federally mandated health warnings and many scientific investigations.
  - ST products, including the candidate product, contain and potentially expose consumers to chemical constituents considered to be harmful. Some of these constituents are considered animal or human carcinogens. While many epidemiology studies suggest no substantial increase in disease risk between ST users and never tobacco users, exposure to the harmful chemicals in ST is considered a health risk.
  - AS have more than ten times greater mortality risk for lung cancer than never-tobacco users. While some published literature suggests a possible association between ST use and lung cancer, our analysis of two recent, nationally representative, linked mortality datasets suggests that the lung cancer mortality risk of current ST users is not different from never-tobacco users
- 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 currently available scientific evidence demonstrates that switching to exclusive ST use from cigarette smoking reduces overall risk of mortality compared to continued smoking.
  - We would expect that, for current MST users who switch to the candidate product, there would be no measurable or substantial change in health risk. The major change in health risk will be observed with AS who adopt and use the candidate product exclusively instead of smoking and with dual users who switch to exclusive use of the candidate product.
- The health risks associated with using the product in conjunction with other tobacco products:
  - The current evidence demonstrates that mortality risks for dual users (AS who also use ST) are greater than those for exclusive ST users, but not substantially different than for exclusive smokers. Dual users do not have different risks for mortality from all-causes, diseases of the heart, or malignant neoplasms compared to exclusive AS.
- The health risks associated with switching to the product as compared with those associated with quitting the use of tobacco products:
  - The mortality risk from malignant neoplasms of the trachea, bronchus, and lung is markedly reduced (by about 50%) in former smokers who do not use ST compared to current smokers. The reduction in mortality risks does not change if former smokers are using ST products.

  - Mortality risks from all-causes, disease of the heart, or malignant neoplasms will be reduced by switching completely from cigarettes to ST. Quitting all tobacco use completely is the best way to protect an individual's health. However, for those unable or unwilling to quit, the current evidence suggests that use of the candidate product instead of cigarette smoking would not diminish the benefits of smoking cessation.

- The health risks associated with switching to the candidate product as compared with using an FDA-approved tobacco-cessation medication:
  - The candidate product is a tobacco product and is not safe. FDA-approved tobacco-cessation medications have met the legal standard of being safe and effective for their intended uses. The candidate product is not intended as a substitute for FDA-approved tobacco-cessation medications.
  - It is plausible that ST presents a higher risk for some diseases compared to cessation medications due to the differences in product formulation or the period of use (a few weeks for cessation medications vs. potentially years for ST use).

ST products, including the candidate product, are not risk free. However, there is extensive scientific evidence showing that MST products, such as the candidate product, present significantly lower risks for serious and fatal diseases compared to smoking cigarettes. Based on our analysis of public, nationally representative data sets, NHIS and NLMS, and our evaluation of published epidemiological studies, we conclude:

- Compared to cigarette smokers, ST users have significantly lower risks for mortality from all-causes, disease of the heart, and malignant neoplasms.
- Specific to malignant neoplasms of the trachea, bronchus and lung, information in the NLMS and NHIS data sets is consistent with previous published investigations of mortality risk in ST users and AS, showing substantially greater risk for mortality from lung cancer in smokers compared to people who only use ST.

The data provided and reviewed show clear differences in mortality risks between cigarette smokers and ST users that substantiates our modified risk claim that switching completely from cigarettes to the candidate product reduces risk of lung cancer. As we demonstrate, for those who stop smoking but continue using tobacco, switching to the candidate product does not adversely impact the established reduction in health risk associated with smoking cessation. Providing accurate health risk information to ATC could encourage exclusive AS and dual users to stop smoking cigarettes and substantially reduce their mortality risk from lung cancer, and other fatal diseases.

6.1.9. Literature Cited

Accortt, N. A., Waterbor, J. W., Beall, C., & Howard, G. (2002). Chronic disease mortality in a cohort of smokeless tobacco users. *American journal of epidemiology, 156*(8), 730-737.

Accortt, N. A., Waterbor, J. W., Beall, C., & Howard, G. (2005). Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer causes & control, 16*(9), 1107-1115.

Andreoli, C., Gigante, D., & Nunziata, A. (2003). A review of in vitro methods to assess the biological activity of tobacco smoke with the aim of reducing the toxicity of smoke. *Toxicol In Vitro, 17*(5-6), 587-594.

Andreotti, G., Freedman, N. D., Silverman, D. T., Lerro, C. C., Koutros, S., Hartge, P., . . . Sandler, D. P. (2016). Tobacco use and cancer risk in the Agricultural Health Study. *Cancer Epidemiology, Biomarkers & Prevention, 29*(29), 1538-7755. doi:10.1158/1055-9965.epi-16-0748

Andrews, J. A., Severson, H. H., Lichtenstein, E., & Gordon, J. S. (1998). Relationship between tobacco use and self-reported oral hygiene habits. *Journal of the American Dental Association, 129*(3), 313-320.

Apelberg, B. J., Onicescu, G., Avila-Tang, E., & Samet, J. M. (2010). Estimating the risks and benefits of nicotine replacement therapy for smoking cessation in the United States. *Am J Public Health, 100*(2), 341-348. doi:10.2105/ajph.2008.147223

Araghi, M., Rosaria Galanti, M., Lundberg, M., Lager, A., Engstrom, G., Alfredsson, L., . . . Magnusson, C. (2017). Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies. *Int J Cancer, 141*(4), 687-693. doi:10.1002/ijc.30773

Asplund, K., Nasic, S., Janlert, U., & Stegmayr, B. (2003). Smokeless tobacco as a possible risk factor for stroke in men: a nested case-control study. *Stroke, 34*(7), 1754-1759. doi:10.1161/01.str.0000076011.02935.a1

Baker, R. R. (1999). Smoke chemistry. In D. L. Davis & M. T. Nielsen (Eds.), *Tobacco. Production, Chemistry and Technology* (pp. 398-439). London, England: CORESTA, Blackwell Science, Ltd.

Barnes, P. J. (2000). Mechanisms in COPD: differences from asthma. *Chest, 117*(2 Suppl), 10s-14s.

Behrsing, H., Hill, E., Raabe, H., Tice, R., Fitzpatrick, S., Devlin, R., . . . Curren, R. (2017). In vitro exposure systems and dosimetry assessment tools for inhaled tobacco products: Workshop proceedings, conclusions and paths forward for in vitro model use. *Altern Lab Anim, 45*(3), 117-158.

Benowitz, N. L. (1997). Systemic absorption and effects of nicotine from smokeless tobacco. *Advances in Dental Research, 11*(3), 336-341.

Benowitz, N. L., & Burbank, A. D. (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends in Cardiovascular Medicine, 26*(6), 515-523. doi:10.1016/j.tcm.2016.03.001

Benowitz, N. L., Jacob III, P., & Yu, L. (1989). Daily use of smokeless tobacco: systemic effects. *Ann Intern Med, 111*(2), 112-116.

Boffetta, P., & Straif, K. (2009). Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ, 339*, b3060.

Bopp, M., Braun, J., Gutzwiller, F., & Faeh, D. (2012). Health risk or resource? Gradual and independent association between self-rated health and mortality persists over 30 years. *PloS One, 7*(2), e30795. doi:10.1371/journal.pone.0030795

Borgerding, M. F., Bodnar, J. A., Curtin, G. M., & Swauger, J. E. (2012). The chemical composition of smokeless tobacco: a survey of products sold in the United States in 2006 and 2007. *Regulatory Toxicology and Pharmacology, 64*(3), 367-387.

Borgida, E., Williams, A. L., Vitriol, J., Loken, B., Stepanov, I., & Hatsukami, D. (2015). Assessing Constituent Levels in Smokeless Tobacco Products: A New Approach to Engaging and Educating the Public. *Nicotine &Tobacco Research, 17*(11), 1354-1361. doi:10.1093/ntr/ntv007

Boyle, J. O., Gumus, Z. H., Kacker, A., Choksi, V. L., Bocker, J. M., Zhou, X. K., . . . Dannenberg, A. J. (2010). Effects of cigarette smoke on the human oral mucosal transcriptome. *Cancer Prev Res (Phila), 3*(3), 266-278. doi:10.1158/1940-6207.capr-09-0192

Brown, L. M., Blot, W. J., Schuman, S. H., Smith, V. M., Ershow, A. G., Marks, R. D., & Fraumeni, J. F., Jr. (1988). Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *Journal of the National Cancer Institute, 80*(20), 1620-1625.

Brunnemann, K. D., Genoble, L., & Hoffmann, D. (1987). Identification and analysis of a new tobacco-specific N-nitrosamine, 4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol. *Carcinogenesis, 8*(3), 465-469.

Brunnemann, K. D., & Hoffmann, D. (1992). Chemical composition of smokeless tobacco products. In D. R. Shopland, R. C. Stotts, K. L. Shroeder, & D. M. Burns (Eds.), *Monograph 2: Smokeless Tobacco or Health: An International Perspective* (pp. 109-118). Bethesda, MD: National Institutes of Health, National Cancer Institute.

Burkey, M. D., Feirman, S., Wang, H., Choudhury, S. R., Grover, S., & Johnston, F. M. (2014). The association between smokeless tobacco use and pancreatic adenocarcinoma: A systematic review. *Cancer epidemiology, 38*(6), 647-653.

Cahill, K., Stevens, S., Perera, R., & Lancaster, T. (2013). Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *The Cochrane Database of Systematic Reviews*(5), CD009329.

Campbell, L. R., Brown, B. G., Jones, B. A., Marano, K. M., & Borgerding, M. F. (2015). Study of cardiovascular disease biomarkers among tobacco consumers, part 1: biomarkers of exposure. *Inhalation Toxicology, 27*(3), 149-156.

Carmella, S. G., Han, S., Fristad, A., Yang, Y., & Hecht, S. S. (2003). Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. *Cancer epidemiology, 12*(11 Pt 1), 1257-1261.

Carter, B. D., Abnet, C. C., Feskanich, D., Freedman, N. D., Hartge, P., Lewis, C. E., . . . Jacobs, E. J. (2015). Smoking and mortality--beyond established causes. *N Engl J Med, 372*(7), 631-640. doi:10.1056/NEJMsa1407211

Coleman, T., Chamberlain, C., Cooper, S., & Leonardi-Bee, J. (2011). Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. *Addiction (Abingdon, England), 106*(1), 52-61.

Coleman, T., Chamberlain, C., Davey, M. A., Cooper, S. E., & Leonardi-Bee, J. (2012). Pharmacological interventions for promoting smoking cessation during pregnancy. *The Cochrane Database of Systematic Reviews, 9*, CD010078.

DeMarini, D. M. (2004). Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. *Mutat Res, 567*(2-3), 447-474. doi:10.1016/j.mrrev.2004.02.001

Ding, Y. S., Ashley, D. L., & Watson, C. H. (2007). Determination of 10 carcinogenic polycyclic aromatic hydrocarbons in mainstream cigarette smoke. *J Agric Food Chem, 55*(15), 5966-5973. doi:10.1021/jf070649o

Djordjevic, M. V., Brunnemann, K. D., & Hoffmann, D. (1993). The need for regulation of carcinogenic N-nitrosamines in oral snuff. *Food and Chemical Toxicology, 31*(7), 497-501.

Dube, M., & Green, C. (1982). Methods of collection of smoke for analytical purposes. *Recent Advances in Tobacco Science, 8*, 42-102.

Ebbert, J. O., Dale, L. C., Nirelli, L. M., Schroeder, D. R., Moyer, T. P., & Hurt, R. D. (2004). Cotinine as a biomarker of systemic nicotine exposure in spit tobacco users. *Addictive Behaviors, 29*(2), 349-355.

England, L. J., Kim, S. Y., Shapiro-Mendoza, C. K., Wilson, H. G., Kendrick, J. S., Satten, G. A., . . . Callaghan, W. M. (2012). Maternal smokeless tobacco use in Alaska Native women and singleton infant birth size. *Acta Obstetricia et Gynecologica Scandinavica, 91*(1), 93-103.

England, L. J., Levine, R. J., Mills, J. L., Klebanoff, M. A., Yu, K. F., & Cnattingius, S. (2003). Adverse pregnancy outcomes in snuff users. *American Journal of Obstetrics and Gynecology, 189*(4), 939-943.

England, L. J., Tong, V. T., Koblitz, A., Kish-Doto, J., Lynch, M. M., & Southwell, B. G. (2016). Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Preventive Medicine Reports, 4*, 481-485. doi:10.1016/j.pmedr.2016.09.002

Ferry, L., & Johnston, J. A. (2003). Efficacy and safety of bupropion SR for smoking cessation: data from clinical trials and five years of postmarketing experience. *Int J Clin Pract, 57*(3), 224-230.

Fisher, M. T., Bennett, C. B., Hayes, A., Kargalioglu, Y., Knox, B. L., Xu, D., . . . Gaworski, C. L. (2012). Sources of and technical approaches for the abatement of tobacco specific nitrosamine formation in moist smokeless tobacco products. *Food and Chemical Toxicology, 50*(3-4), 942-948.

Ford, E. S., Greenlund, K. J., & Hong, Y. (2012). Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. *Circulation, 125*(8), 987-995. doi:10.1161/circulationaha.111.049122

Foulds, J., Ramstrom, L., Burke, M., & Fagerstrom, K. (2003). Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control, 12*(4), 349-359.

Fukumoto, S., Yamauchi, N., Moriguchi, H., Hippo, Y., Watanabe, A., Shibahara, J., . . . Aburatani, H. (2005). Overexpression of the aldo-keto reductase family protein AKR1B10 is highly correlated with smokers' non-small cell lung carcinomas. *Clin Cancer Res, 11*(5), 1776-1785. doi:10.1158/1078-0432.ccr-04-1238

Ge, G. Z., Xu, T. R., & Chen, C. (2015). Tobacco carcinogen NNK-induced lung cancer animal models and associated carcinogenic mechanisms. *Acta Biochim Biophys Sin (Shanghai), 47*(7), 477-487. doi:10.1093/abbs/gmv041

Grady, D., Greene, J., Daniels, T. E., Ernster, V. L., Robertson, P. B., Hauck, W., . . . Silverman, S., Jr. (1990). Oral mucosal lesions found in smokeless tobacco users. *Journal of the American Dental Association, 121*(1), 117-123.

Grasso, P., & Mann, A. H. (1998). Smokeless tobacco and oral cancer: an assessment of evidence derived from laboratory animals. *Food Chem Toxicol, 36*(11), 1015-1029.

Greenland, S., Satterfield, M. H., & Lanes, S. F. (1998). A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety, 18*(4), 297-308.

Gumus, Z. H., Du, B., Kacker, A., Boyle, J. O., Bocker, J. M., Mukherjee, P., . . . Weinstein, H. (2008). Effects of tobacco smoke on gene expression and cellular pathways in a cellular model of oral leukoplakia. *Cancer Prev Res (Phila), 1*(2), 100-111. doi:10.1158/1940-6207.capr-08-0007

Gupta, R., Gupta, S., Sharma, S., Sinha, D. N., & Mehrotra, R. (2018). Risk of coronary heart disease among smokeless tobacco users: results of systematic review and meta-analysis of global data. *Nicotine Tob Res*. doi:10.1093/ntr/nty002

Hassan, M. M., Abbruzzese, J. L., Bondy, M. L., Wolff, R. A., Vauthey, J., Pisters, P. W., . . . Li, D. (2007). Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. *Cancer, 109*(12), 2547-2556.

Hatsukami, D., Benowitz, N. L., Rennard, S. I., Oncken, C., & Hecht, S. S. (2006). Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine Tob Res, 8*(4), 600-622. doi:10.1080/14622200600858166

Hecht, S. S. (1998). Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem Res Toxicol, 11*(6), 559-603. doi:10.1021/tx980005y

Hecht, S. S. (2003). Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer, 3*(10), 733-744. doi:10.1038/nrc1190

Hecht, S. S. (2006). Cigarette smoking: cancer risks, carcinogens, and mechanisms. *Langenbecks Arch Surg, 391*(6), 603-613. doi:10.1007/s00423-006-0111-z

Hecht, S. S., Carmella, S. G., Stepanov, I., Jensen, J., Anderson, A., & Hatsukami, D. K. (2008). Metabolism of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone to its biomarker total NNAL in smokeless tobacco users. *Cancer Epidemiology, Biomarkers & Prevention, 17*(3), 732-735.

Hecht, S. S., & Hoffmann, D. (1988). Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis, 9*(6), 875-884.

Hecht, S. S., Rivenson, A., Braley, J., DiBello, J., Adams, J. D., & Hoffmann, D. (1986). Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. *Cancer Research, 46*(8), 4162-4166.

Hecht, S. S., Trushin, N., Castonguay, A., & Rivenson, A. (1986). Comparative tumorigenicity and DNA methylation in F344 rats by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosodimethylamine. *Cancer Res, 46*(2), 498-502.

Heineman, E. F., Zahm, S. H., McLaughlin, J. K., & Vaught, J. B. (1994). Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *International journal of cancer, 59*(6), 728-738.

Henley, J., Connell, C. J., Richter, P., Husten, C., Pechacek, T., Calle, E. E., & Thun, M. J. (2007). Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. *Tobacco Control, 16*(1), 22-28.

Henley, J., Thun, M. J., Connell, C., & Calle, E. E. (2005). Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer causes & control, 16*(4), 347-358.

Hirsch, J. M., & Thilander, H. (1981). Snuff-induced lesions of the oral mucosa - an experimental model in the rat. *J Oral Pathol, 10*(5), 342-353.

Hoffmann, D., Adams, J. D., Lisk, D., Fisenne, I., & Brunnemann, K. D. (1987). Toxic and carcinogenic agents in dry and moist snuff. *Journal of the National Cancer Institute, 79*(6), 1281-1286.

Hoffmann, D., & Hoffmann, I. (1997). The changing cigarette, 1950-1995. *J Toxicol Environ Health, 50*(4), 307-364. doi:10.1080/009841097160393

Hoffmann, D., Hoffmann, I., & El-Bayoumy, K. (2001). The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol, 14*(7), 767-790.

Hsu, N. Y., Ho, H. C., Chow, K. C., Lin, T. Y., Shih, C. S., Wang, L. S., & Tsai, C. M. (2001). Overexpression of dihydrodiol dehydrogenase as a prognostic marker of non-small cell lung cancer. *Cancer Res, 61*(6), 2727-2731.

Hughes, J. R. (2016). Varenicline as a cause of suicidal outcomes. *Nicotine & Tobacco Research, 18*(1), 2-9.

Inoue-Choi, M., Hartge, P., Liao, L. M., Caporaso, N., & Freedman, N. D. (2018). Association between long-term low-intensity cigarette smoking and incidence of smoking-related cancer in the national institutes of health-AARP cohort. *Int J Cancer, 142*(2), 271-280. doi:10.1002/ijc.31059

International Agency on Research for Cancer (IARC). (2007). *Smokeless tobacco and some tobacco-specific N-nitrosamines* (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans Ed. Vol. 89). Lyon, France: International Agency for Research on Cancer.

International Agency on Research for Cancer (IARC). (2010). *Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures* (Vol. 92). Lyon, France: International Agency for Research on Cancer.

International Agency on Research for Cancer (IARC). (2012). Personal habits and indoor combustions. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Vol. 100E). Lyon, France: International Agency on Research for Cancer.

Jansson, T., Romert, L., Magnusson, J., & Jenssen, D. (1991). Genotoxicity testing of extracts of a Swedish moist oral snuff. *Mutat Res, 261*(2), 101-115.

Jha, P., Ramasundarahettige, C., Landsman, V., Rostron, B., Thun, M., Anderson, R. N., . . . Peto, R. (2013). 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med, 368*(4), 341-350. doi:10.1056/NEJMsa1211128

Johansson, S. L., Hirsch, J. M., Larsson, P. A., Saidi, J., & Osterdahl, B. G. (1989). Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4-nitroquinoline N-oxide. *Cancer Research, 49*(11), 3063-3069.

Johansson, S. L., Hirsch, J. M., Larsson, P. A., Saidi, J., & Osterdahl, B. G. (1991). Lack of promoting ability of snuff in rats initiated with 4-nitroquinoline-N-oxide. *IARC scientific publications*(105), 507-509.

Johansson, S. L., Saidi, J., Osterdahl, B. G., & Smith, R. A. (1991). Promoting effect of snuff in rats initiated by 4-nitroquinoline-N-oxide or 7,12-dimethylbenz(a)anthracene. *Cancer Research, 51*(16), 4388-4394.

Johnson, M. D., Schilz, J., Djordjevic, M. V., Rice, J. R., & Shields, P. G. (2009). Evaluation of in vitro assays for assessing the toxicity of cigarette smoke and smokeless tobacco. *Cancer Epidemiol Biomarkers Prev, 18*(12), 3263-3304. doi:10.1158/1055-9965.epi-09-0965

Kallischnigg, G., Weitkunat, R., & Lee, P. N. (2008). Systematic review of the relation between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States. *BMC oral health, 8*, 13.

Lee, P. N. (2007). Circulatory disease and smokeless tobacco in Western populations: a review of the evidence. *International journal of epidemiology, 36*(4), 789-804.

Lee, P. N., & Hamling, J. (2009a). The relation between smokeless tobacco and cancer in Northern Europe and North America. A commentary on differences between the conclusions reached by two recent reviews. *BMC cancer, 9*, 256.

Lee, P. N., & Hamling, J. (2009b). Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC medicine, 7*, 36.

Lijinsky, W., & Taylor, H. W. (1976). Carcinogenicity test of two unstaurated derivatives of N-nitrosopiperdine in Sprague-Dawley rats. *J Natl Cancer Inst, 57*(6), 1315-1317.

LSRO. Life Sciences Research Organization Inc. (2008). Differentiating the health risks of categories of tobacco products. In K. D. Lewis (Ed.). Bethesda, MD: LSRO.

Ma, B., Zarth, A. T., Carlson, E. S., Villalta, P. W., Upadhyaya, P., Stepanov, I., & Hecht, S. S. (2018). Methyl DNA Phosphate Adduct Formation in Rats Treated Chronically with 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone and Enantiomers of Its Metabolite 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Chem Res Toxicol, 31*(1), 48-57. doi:10.1021/acs.chemrestox.7b00281

Marano, K. M., Kathman, S. J., Jones, B. A., Nordskog, B. K., Brown, B. G., & Borgerding, M. F. (2015). Study of cardiovascular disease biomarkers among tobacco consumers. Part 3: evaluation and comparison with the US National Health and Nutrition Examination Survey. *Inhalation Toxicology, 27*(3), 167-173.

Margolis, K. L., Manson, J. E., Greenland, P., Rodabough, R. J., Bray, P. F., Safford, M., . . . Prentice, R. (2005). Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Arch Intern Med, 165*(5), 500-508. doi:10.1001/archinte.165.5.500

Martinez, I. (1969). Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *Journal of the National Cancer Institute, 42*(6), 1069-1094.

Mattes, W., Yang, X., Orr, M. S., Richter, P., & Mendrick, D. L. (2014). Biomarkers of tobacco smoke exposure. *Adv Clin Chem, 67*, 1-45. doi:10.1016/bs.acc.2014.09.001

Mills, E. J., Thorlund, K., Eapen, S., Wu, P., & Prochaska, J. J. (2014). Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation, 129*(1), 28-41.

Mills, E. J., Wu, P., Lockhart, I., Wilson, K., & Ebbert, J. O. (2010). Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tobacco Induced Diseases, 8*, 8.

Murray, R. P., Bailey, W. C., Daniels, K., Bjornson, W. M., Kurnow, K., Connett, J. E., . . . Kiley, J. P. (1996). Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. *Chest, 109*(2), 438-445.

Naufal, Z. S., Marano, K. M., Kathman, S. J., & Wilson, C. L. (2011). Differential exposure biomarker levels among cigarette smokers and smokeless tobacco consumers in the National Health and Nutrition Examination Survey 1999-2008. *Biomarkers, 16*(3), 222-235.

Nilsson, R. (2011). The molecular basis for induction of human cancers by tobacco specific nitrosamines. *Regul Toxicol Pharmacol, 60*(2), 268-280. doi:10.1016/j.yrtph.2011.02.014

Nilsson, R. (2017). Use of rodent data for cancer risk assessment of smokeless tobacco in the regulatory context. *Regul Toxicol Pharmacol, 88*, 338-348. doi:10.1016/j.yrtph.2017.06.005

Nordskog, B. K., Brown, B. G., Marano, K. M., Campell, L. R., Jones, B. A., & Borgerding, M. F. (2015). Study of cardiovascular disease biomarkers among tobacco consumers, part 2: biomarkers of biological effect. *Inhalation Toxicology, 27*(3), 157-166. doi:10.3109/08958378.2015.1013227

Oldham, M. J., DeSoi, D. J., Rimmer, L. T., Wagner, K. A., & Morton, M. J. (2014). Insights from analysis for harmful and potentially harmful constituents (HPHCs) in tobacco products. *Regulatory Toxicology and Pharmacology, 70*(1), 138-148.

Pappas, R. S., Stanfill, S. B., Watson, C. H., & Ashley, D. L. (2008). Analysis of toxic metals in commercial moist snuff and Alaskan iqmik. *Journal of Analytical Toxicology, 32*(4), 281-291.

Parsons, A., Daley, A., Begh, R., & Aveyard, P. (2010). Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ, 340*. doi:10.1136/bmj.b5569

Paulson, R., Shanfeld, J., Mullet, D., Cole, J., & Paulson, J. O. (1994). Prenatal smokeless tobacco effects on the rat fetus. *Journal of Craniofacial Genetics and Developmental Biology, 14*(1), 16-25.

Paulson, R., Shanfeld, J., Sachs, L., Price, T., & Paulson, J. (1989). Effect of smokeless tobacco on the development of the CD-1 mouse fetus. *Teratology, 40*(5), 483-494.

Paulson, R., Shanfeld, J., Vorhees, C. V., Cole, J., Sweazy, A., & Paulson, J. O. (1994). Behavioral effects of smokeless tobacco on the neonate and young Sprague Dawley rat. *Teratology, 49*(4), 293-305.

Phillips, D. H. (2005). DNA adducts as markers of exposure and risk. *Mutat Res, 577*(1-2), 284-292. doi:10.1016/j.mrfmmm.2005.03.008

Prasad, G. L., Jones, B. A., Chen, P., & Gregg, E. O. (2016). A cross-sectional study of biomarkers of exposure and effect in smokers and moist snuff consumers. *Clinical Chemistry and Laboratory Medicine, 54*(4), 633-642. doi:10.1515/cclm-2015-0594

Prokopczyk, G., Adams, J. D., LaVoie, E. J., & Hoffmann, D. (1987). Effect of snuff and nicotine on DNA methylation by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Carcinogenesis, 8*(10), 1395-1397.

Richter, P., Hodge, K., Stanfill, S., Zhang, L., & Watson, C. (2008). Surveillance of moist snuff: total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. *Nicotine &Tobacco Research, 10*(11), 1645-1652.

Richter, P., & Spierto, F. W. (2003). Surveillance of smokeless tobacco nicotine, pH, moisture, and unprotonated nicotine content. *Nicotine &Tobacco Research, 5*(6), 885-889.

Rickert, W. S., Wright, W. G., Trivedi, A. H., Momin, R. A., & Lauterbach, J. H. (2007). A comparative study of the mutagenicity of various types of tobacco products. *Regulatory Toxicology and Pharmacology, 48*(3), 320-330.

Rivenson, A., Hoffmann, D., Prokopczyk, B., Amin, S., & Hecht, S. S. (1988). Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines. *Cancer Res, 48*(23), 6912-6917.

Robinson-Cohen, C., Hall, Y. N., Katz, R., Rivara, M. B., de Boer, I. H., Kestenbaum, B. R., & Himmelfarb, J. (2014). Self-rated health and adverse events in CKD. *Clin J Am Soc Nephrol, 9*(12), 2044-2051. doi:10.2215/cjn.03140314

Rodgman, A., & Perfetti, T. A. (2009). Alphabetical index to chemical components of tobacco, tobacco smoke, and tobacco substitute smoke. In *The Chemical Components Of Tobacco And Tobacco Smoke*. Boca Raton, FL: CRC Press.

Rodu, B., & Cole, P. (2002). Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, 93*(5), 511-515.

Rodu, B., & Cole, P. (2009). Lung cancer mortality: comparing Sweden with other countries in the European Union. *Scandinavian Journal of Public Health, 37*(5), 481-486.

Rodu, B., & Jansson, C. (2004). Smokeless tobacco and oral cancer: a review of the risks and determinants. *Crit Rev Oral Biol Med, 15*(5), 252-263.

Rostron, B. (2012a). Alcohol consumption and mortality risks in the USA. *Alcohol Alcohol, 47*(3), 334-339. doi:10.1093/alcalc/agr171

Rostron, B. (2012b). Lung cancer mortality risk for U.S. menthol cigarette smokers. *Nicotine Tob Res, 14*(10), 1140-1144. doi:10.1093/ntr/nts014

Rostron, B. (2013). Smoking-attributable mortality by cause in the United States: revising the CDC's data and estimates. *Nicotine &Tobacco Research, 15*(1), 238-246. doi:10.1093/ntr/nts120

Rostron, B., Chang, C. M., van Bemmel, D. M., Xia, Y., & Blount, B. C. (2015). Nicotine and Toxicant Exposure among U.S. Smokeless Tobacco Users: Results from 1999 to 2012 National Health and Nutrition Examination Survey Data. *Cancer Epidemiology, Biomarkers & Prevention, 24*(12), 1829-1837. doi:10.1158/1055-9965.epi-15-0376

Royal College of Physicians. (2007). *Harm reduction in nicotine addiction: Helping People Who Can't Quit*. London.

Sarkar, M., Liu, J., Koval, T., Wang, J., Feng, S., Serafin, R., . . . Roethig, H. J. (2010). Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. *Nicotine &Tobacco Research, 12*(2), 105-116.

Shavelle, R. M., Paculdo, D. R., Strauss, D. J., & Kush, S. J. (2008). Smoking habit and mortality: a meta-analysis. *Journal of Insurance Medicine, 40*(3-4), 170-178.

Siegel, D., Benowitz, N., Ernster, V. L., Grady, D. G., & Hauck, W. W. (1992). Smokeless tobacco, cardiovascular risk factors, and nicotine and cotinine levels in professional baseball players. *American journal of public health, 82*(3), 417-421.

Singh, S., Loke, Y. K., Spangler, J. G., & Furberg, C. D. (2011). Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *Canadian Medical Association journal, 183*(12), 1359-1366.

Sponsiello-Wang, Z., Weitkunat, R., & Lee, P. N. (2008). Systematic review of the relation between smokeless tobacco and cancer of the pancreas in Europe and North America. *BMC cancer, 8*, 356.

Stepanov, I., & Hecht, S. S. (2005). Tobacco-specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiology, Biomarkers & Prevention, 14*(4), 885-891.

Stepanov, I., Jensen, J., Hatsukami, D., & Hecht, S. S. (2006). Tobacco-specific nitrosamines in new tobacco products. *Nicotine & Tobacco Research, 8*(2), 309-313.

Stepanov, I., Jensen, J., Hatsukami, D., & Hecht, S. S. (2008). New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine & Tobacco Research, 10*(12), 1773-1782.

Stepanov, I., Villalta, P. W., Knezevich, A., Jensen, J., Hatsukami, D., & Hecht, S. S. (2010). Analysis of 23 polycyclic aromatic hydrocarbons in smokeless tobacco by gas chromatography-mass spectrometry. *Chemical Research in Toxicology, 23*(1), 66-73.

Sterling, T. D., Rosenbaum, W. L., & Weinkam, J. J. (1992). Analysis of the relationship between smokeless tobacco and cancer based on data from the National Mortality Followback Survey. *Journal of Clinical Epidemiology, 45*(3), 223-231.

Strickland, P., & Kang, D. (1999). Urinary 1-hydroxypyrene and other PAH metabolites as biomarkers of exposure to environmental PAH in air particulate matter. *Toxicol Lett, 108*(2-3), 191-199.

Strickland, P., Kang, D., & Sithisarankul, P. (1996). Polycyclic aromatic hydrocarbon metabolites in urine as biomarkers of exposure and effect. *Environ Health Perspect, 104 Suppl 5*, 927-932.

Summerlin, D. J., Dunipace, A., & Potter, R. (1992). Histologic effects of smokeless tobacco and alcohol on the pouch mucosa and organs of the Syrian hamster. *Journal of Oral Pathology & Medicine, 21*(3), 105-108.

Surgeon General Report, & U.S. Department of Health and Human Services. (2004). The Health Consequences of Smoking: A Report of the Surgeon General. In. Washington, DC: U.S. Government Printing Office.

Surgeon General Report, & U.S. Department of Health and Human Services. (2014). The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Retrieved from https://www.surgeongeneral.gov/library/reports/50-years-of-progress/exec-summary.pdf

Tamakoshi, K., Toyoshima, H., Yatsuya, H., Matsushita, K., Okamura, T., Hayakawa, T., . . . Ueshima, H. (2007). White blood cell count and risk of all-cause and cardiovascular mortality in nationwide sample of Japanese--results from the NIPPON DATA90. *Circ J, 71*(4), 479-485.

Thorne, D., Larard, S., Baxter, A., Meredith, C., & Gaa, M. (2017). The comparative in vitro assessment of e-cigarette and cigarette smoke aerosols using the gammaH2AX assay and applied dose measurements. *Toxicol Lett, 265*, 170-178. doi:10.1016/j.toxlet.2016.12.006

Timberlake, D. S., Nikitin, D., Johnson, N. J., & Altekruse, S. F. (2017). A longitudinal study of smokeless tobacco use and mortality in the United States. *Int J Cancer, 141*(2), 264-270. doi:10.1002/ijc.30736

Tomar, S. L. (2002). Snuff use and smoking in U.S. men: implications for harm reduction. *American Journal of Preventive Medicine, 23*(3), 143-149.

U.S. Department of Health and Human Services. (1990). The health benefits of smoking cessation. A report of the Surgeon General, 1990. In. Rockville, Maryland: Public Health Service, Centers for Disease Control, Office on Smoking and Health,.

U.S. Department of Health and Human Services. (2010). The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. In. Washington, DC: U.S. Government Printing Office.

U.S. Dept. Health Human Services. (1986). *The Health Consequences of Using Smokeless Tobacco: A report of the Advisory Committee to the Surgeon General* (Vol. NIH Publication No.86-2874). Bethesda, Maryland: USDHHS, Public Health Service.

Watanabe, K. H., Djordjevic, M. V., Stellman, S. D., Toccalino, P. L., Austin, D. F., & Pankow, J. F. (2009). Incremental lifetime cancer risks computed for benzo[a]pyrene and two tobacco-specific N-nitrosamines in mainstream cigarette smoke compared with lung cancer risks derived from epidemiologic data. *Regul Toxicol Pharmacol, 55*(2), 123-133. doi:10.1016/j.yrtph.2009.06.007

Williams, R. R., & Horm, J. W. (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *Journal of the National Cancer Institute, 58*(3), 525-547.

Winn, D. M., Blot, W. J., Shy, C. M., Pickle, L. W., Toledo, A., & Fraumeni, J. F., Jr. (1981). Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med, 304*(13), 745-749.

Wolfe, M. D., & Carlos, J. P. (1987). Oral health effects of smokeless tobacco use in Navajo Indian adolescents. *Community Dentistry and Oral Epidemiology, 15*(4), 230-235.

Woo, S., Gao, H., Henderson, D., Zacharias, W., Liu, G., Tran, Q. T., & Prasad, G. L. (2017). AKR1C1 as a Biomarker for Differentiating the Biological Effects of Combustible from Non-Combustible Tobacco Products. *Genes (Basel), 8*(5). doi:10.3390/genes8050132

Wu, W., Ashley, D. L., & Watson, C. H. (2003). Simultaneous Determination of Five Tobacco-Specific Nitrosamines in Mainstream Cigarette Smoke by Isotope Dilution Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry. *Analytical Chemistry, 75*(18), 4827-4832. doi:10.1021/ac030135y

Wynder, E. L., & Stellman, S. D. (1977). Comparative epidemiology of tobacco-related cancers. *Cancer Research, 37*(12), 4608-4622.

Xu, J., Kochanek, K. D., Murphy, S. L., & Arias, E. (2014). Mortality in the United States, 2012. *NCHS Data Brief*(168), 1-8.

Yatsuya, H., & Folsom Aaron, R. A. G. A. (2010). Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. *American journal of epidemiology, 172*(5), 600-605.

Yuan, J. M., Koh, W. P., Murphy, S. E., Fan, Y., Wang, R., Carmella, S. G., . . . Hecht, S. S. (2009). Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. *Cancer Res, 69*(7), 2990-2995. doi:10.1158/0008-5472.can-08-4330

Zahm, S. H., Blair, A., Holmes, F. F., Boysen, C. D., Robel, R. J., & Fraumeni, J. F., Jr. (1989). A case-control study of soft-tissue sarcoma. *American journal of epidemiology, 130*(4), 665-674.

Zahm, S. H., Heineman, E. F., & Vaught, J. B. (1992). Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer causes & control, 3*(4), 371-376.

Zhang, L., Lee, J. J., Tang, H., Fan, Y. H., Xiao, L., Ren, H., . . . Mao, L. (2008). Impact of smoking cessation on global gene expression in the bronchial epithelium of chronic smokers. *Cancer Prev Res (Phila), 1*(2), 112-118. doi:10.1158/1940-6207.capr-07-0017

Zhang, X., Sebastiani, P., Liu, G., Schembri, F., Zhang, X., Dumas, Y. M., . . . Spira, A. (2010). Similarities and differences between smoking-related gene expression in nasal and bronchial epithelium. *Physiol Genomics, 41*(1), 1-8. doi:10.1152/physiolgenomics.00167.2009