U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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Subject: Summary of Health Effects of Smokeless Tobacco Products for Epidemiology Branch Product Application Review

Background

This memo is intended to provide the Division of Population Health Science (DPHS) and the Office of Science (OS) a high-level summary of the current observational literature describing health outcomes among smokeless tobacco (SLT) users, compared to nonusers, dual users of other tobacco products, and quitters using nicotine replacement therapy (NRT). SLT is defined by section 387 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as, "[...] any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity."(21 U.S.C. 387) OS has reviewed diverse SLT products including Swedish and US snus-style products, non-tobacco nicotine pouches, and traditional US SLT products including chewing tobacco and dry and moist snuff. OS has and will continue to review both Premarket Tobacco Product Applications (PMTAs) and Modified Risk Tobacco Product Applications (MRTPAs) for the diverse products in this class. It is also expected that applications for these products will increasingly seek to contrast different types of SLT products with each other as well as with cigarettes, requiring more detailed assessments of exposure. This memo seeks to standardize language for the comparative assessment of health outcomes, and biomarkers among users of these specific varieties of SLT, particularly for cases where applications may not provide detailed, product-specific estimates of health effects or biomarkers.

This memo will address SLT products collectively as a product class. This class includes: chewing tobacco, dry snuff, moist snuff including snus, 'tobacco-free' nicotine pouch products, and dissolvable products such as lozenges.

This document is primarily derived from previous DPHS literature reviews. These include a DPHS literature review of biomarkers conducted in August 2018, and the Epidemiology branches' reviews of the PMTAs for Swedish Match North America, Inc.'s General Snus (Submission Date: March 11, 2015, Signed by C. Chang October 6, 2015), R.J. Reynolds Tobacco Company's Camel Snus (Submission Date: June 19, 2017, Signed by H. Day March 30, 2020), and the MRTPAs for Swedish Match's General Snus (Submission Date: June 10, 2014, Signed by C. Chang November 2, 2016), and (b)(5) Deliberative Process Privilege The scope of biomarkers includes biomarkers of exposure identified by the OS Biomarkers Working Group, and biomarkers of potential harm identified by the April 2016 FDA/CTP Public Workshop.(Chang et al., 2019)

Executive Summary

Smokeless tobacco products fall into two primary categories: traditionally US products (e.g., chew, dry snuff, moist snuff, plug, etc.), and Swedish *snus* (lit. 'snuff,' a type of moist snuff often portioned in a pouch), which essentially refers to the entire Swedish SLT market. The US market is therefore relatively heterogenous, limiting generalizability of American studies to a type of SLT; studies of SLT use in Scandinavia are implicitly (and often explicitly) focused on Swedish snus. Newer products include 'tobacco-free' pouch products and dissolvables. Given their relative novelty, studies of these products tend to focus on biomarkers of exposure or potential harm in lieu of long-term outcome data.

Compared to non-use of tobacco, SLT product use is associated with some increased health risks, including oral cancer, heart disease, stroke. Findings differ somewhat between study settings. Studies in either setting have found no consistent association between SLT use and respiratory disease or lung cancer.

Analyses of outcome data on dual use of SLT and cigarettes suggest that long-term health outcomes in dual users are generally similar to those in smokers. These findings have been observed in US and Scandinavian settings. Few studies examining this contrast have used contemporary data. Overall, this literature suggests that health risks to dual users are similar to those of exclusive smokers. It can be inferred that smokers who become dual users after failing to switch completely to SLT do not decrease their long-term health risks significantly.

Complete switching to SLT as a harm reduction alternative to cigarette smoking continues to be an area of active research. Though SLT products are generally considered higher-risk than NRT, they are of considerably lower risk than continued smoking. The overall epidemiological literature supports that cigarette smokers who completely switch to SLT products are likely to substantially lower their risks of cardiovascular disease, lung cancer, and respiratory disease compared to smoking. Key gaps in the outcome literature can be augmented with biomarker data but must be appropriately caveated, as route of exposure also plays a key role in disease processes.

Summary of Health Effects

Health Outcomes – Smokeless tobacco users compared to never tobacco users (or never smokers)

All-cause Mortality

Analyses of US cohort studies have found elevated risks of all-cause mortality in exclusive current SLT users comparable to never tobacco users. Analysis of the CPS-I (1959-1972) cohort found elevated risks of all-cause mortality in never-smoking current SLT users compared to never-tobacco users (aHR: 1.17; 95% CI: 1.11, 1.23); this was also observed in CPS-II (1982-2000) (aHR: 1.18; 95% CI: 1.08, 1.29).(Henley et al., 2005) Other cohort studies, including some with shorter follow-up, have not found these associations. A study of NHANES-I/NHEFS

data (1971-1975) found no elevated risk of all-cause mortality and ever exclusive smokeless tobacco use for males (HR: 1.0; 95% CI: 0.8, 1.3) or females (HR: 1.3; 95% CI: 0.9, 1.7) (vs. non-use of tobacco) in adjusted analyses.(Accortt et al., 2002) Estimates were comparable in a study of never-smoker, exclusive current SLT users in the NLMS (1973-2011) cohort who participated in the TUS-CPS (between 1985 and 2011) (aHR: 1.01; 95% CI: 0.93, 1.10).(Timberlake et al., 2017)

A 2017 meta-analysis of never-smoker men in nine Swedish cohort studies (1978-2013, 1-26 years follow-up) found current snus use was weakly, though not significantly, associated with increases in all-cause mortality compared to never tobacco use (aHR: 1.16; 95% CI: 0.89, 1.50; n=9).(Araghi, Galanti, Lundberg, Liu, et al., 2017) However, restriction and adjustment for education and alcohol consumption resulted in a stronger association (aHR: 1.83; 95% CI: 1.16, 2.88). In the largest of these cohorts, the Swedish Construction Worker cohort (1978-1993, 11-26 years follow-up), current snus use was associated with elevated risk of all-cause mortality (RR: 1.4; 95% CI: 1.3, 1.8) (vs. never tobacco use).(Bolinder et al., 1994) A positive association was observed among never-smoking men in the Uppsala County cohort, where ever daily snus use was associated with an elevated risk of all-cause mortality (RR: 1.23; 95% CI: 1.03, 1.4) (vs. never daily use).(Roosaar et al., 2008)

Cardiovascular Disease, Stroke, and other circulatory diseases

A recent meta-analysis analyzed the associations between SLT use and multiple cardiovascular disease outcomes.(Rostron et al., 2018) Across three US studies of CPS-I, CPS-II, and the NLMS, the relative risk of ischemic heart disease (IHD) in never-smoking SLT users compared to never tobacco users was 1.17 (95% CI: 1.09, 1.27, n=3). For the outcome of stroke, the relative risk was 1.28 (95% CI: 1.01, 1.62; n=3). Based on CPS-I and CPS-II, the risk of other circulatory disease was not significantly elevated in never-smoking SLT users (RR: 1.06; 95% CI: 0.93, 1.20; n=2). Earlier studies using NHANES-I/NHEFS, CPS-I, and CPS-II reported a slightly elevated risk of fatal myocardial Infarction (MI) among ever exclusive US SLT users (RR: 1.11; 95% CI: 1.04, 1.19; n=3), with similar results for combined fatal and non-fatal MI.(Boffetta & Straif, 2009) Another analysis of the same 3 cohorts found a modest, non-significant association between US SLT use and IHD/acute MI (RR: 1.14; 95% CI: 0.96, 1.34; n=3).(Lee, 2007)

The association between SLT use and IHD (vs. no tobacco) was not observed in Swedish studies (RR: 1.04; 95% CI: 0.93, 1.06; n=3).(Rostron et al., 2018) This meta-analysis also reported an elevated but non-significant risk of heart failure among current Swedish snus users who may have also smoked (RR: 1.43, 95% CI: 0.91, 2.24; n=2) (vs. never tobacco users). It also reported an elevated risk of hypertension among current exclusive Swedish snus users (RR: 1.43, 95% CI: 1.12, 1.83) (vs. never users), although results were based on a single study.(Hergens et al., 2008) Rostron's meta-analysis also reported non-significant risk of all circulatory disease among ever exclusive Swedish snus users (RR: 1.15, 95% CI: 0.97, 1.37) (vs. never users) based on a single Swedish study.(Roosaar et al., 2008) A Swedish meta-analysis of 8 prospective cohort studies examined the association between SLT use and stroke, but did not find significant associations (overall aHR: 1.04; 95% CI: 0.92, 1.17; n=8).(Hansson et al., 2014) Earlier studies produced similar findings, including a 2009 meta-analysis that found a nonsignificant association between SLT use and fatal stroke (RR: 1.25; 95% CI: 0.91, 1.70; n=2), and no association with any stroke (RR: 1.02; 95% CI: 0.93, 1.13; n=3) in Swedish studies.(Boffetta & Straif, 2009) This meta-analysis did not identify a significant association between SLT use and any MI (RR: 0.87; 95% CI: 0.75, 1.02; n=6), but did identify a positive association between SLT use and fatal MI (RR: 1.27; 95% CI: 1.07, 1.52; n=5) in Swedish studies.(Boffetta & Straif, 2009) Similarly, Lee's meta-analysis of studies of never-smoking Swedish men found no overall association between SLT use and combined IHD/acute MI (RR/OR: 1.06; 95% CI: 0.91, 1.23; n=13), but did find a positive association between SLT use and fatal IHD/MI (overall RR/OR: 1.31; 95% CI: 1.09, 1.58; n=5) and a non-significant negative association between SLT use and non-fatal IHD/MI (overall RR/OR: 0.89; 95% CI: 0.79, 1.00; n=5).(Lee, 2013)

Cancer

US studies have not demonstrated a consistent association between SLT use and lung cancer.(Accortt et al., 2002) Meta-analyses have not found consistent associations between US SLT products and esophageal, pancreatic, stomach, or bladder cancers compared to non-users.(Boffetta et al., 2008; Lee & Hamling, 2009) Boffetta et al. found non-significant associations between US SLT use and lung cancer (RR: 1.8; 95% CI: 0.9, 3.5; n=3), pancreatic cancer (RR: 1.4; 95% CI: 0.7, 2.7; n=4), and esophageal cancer (RR: 1.2; 95% CI: 0.1, 13.00; n=1), but did find a significant association between US SLT use and oral cancer (RR: 2.6; 95% CI: 1.3, 5.2; n=9). This latter estimate of oral cancer relative risk was potentially biased by two estimates drawn from a study that did not adjust for cigarette smoking. An FDA re-analysis excluding this study yielded a lower point estimate (RR: 2.16; 95% CI: 1.08, 4.33; n=7).(Food and Drug Administration, 2017) Lee & Hamling found similar results for US SLT use and lung cancer (RR: 1.79; 95% CI: 0.91, 3.51; n=3) and oral cancer (RR: 3.33; 95% CI: 1.76, 6.32; n=5), as well as pancreatic cancer (RR:1.09; 95% CI: 0.44, 2.67; n=3), stomach cancer (RR: 1.96; 95% CI: 0.82, 4.70; n=2), bladder cancer (RR: 1.25; 95% CI: 0.69, 2.26; n=5) and non-Hodgkin's lymphoma (RR: 2.07; 95% CI: 0.70, 6.13; n=2) in analyses restricted to never smokers.(Lee & Hamling, 2009) The summary measure for oropharyngeal cancer using "overall data" (RR: 2.16; 95% CI: 1.55, 3.02; n=31) was comparable to the FDA re-analysis of Boffetta et al.'s summary measure, while the summary estimate in never-smokers was higher (RR: 3.33; 95% CI: 1.76, 6.32; n=5).(Lee & Hamling, 2009) Another more recent study not included in either meta-analysis evaluated associations for U.S. smokeless tobacco use and head and neck cancers from 11 U.S. case control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.(Wyss et al., 2016) The studies were conducted between 1981 and 2006 and included in total approximately 6,700 cases and 8,400 controls. In analyses stratified by tumor site, restricted to never cigarette smokers, and adjusted for duration of cigar and pipe use and demographics, Wyss et al. (2016) reported significant elevated associations for oral cavity cancer among ever snuff users (OR: 3.01; 95% CI: 1.63, 5.55) (vs. never users) and among ever chewing tobacco users (OR: 1.81; 95% CI: 1.04, 3.17) (vs. never users), although the numbers of exposed cases were small (n=20 and n=23, respectively).

With few exceptions, Scandinavian studies have not observed associations between SLT and a variety of cancers. A 2008 meta-analysis found no positive association between snus use and lung cancer (vs. tobacco nonusers) (RR: 0.8; 95% CI: 0.6, 1.0; n=2).(Boffetta et al., 2008) A 2009 meta-analysis, using a different approach, also drew similar conclusions for lung cancer (RR: 0.82; 95% CI: 0.52, 1.28; n=2).(Lee & Hamling, 2009) The "smoking-adjusted" estimates also found a negative association with lung cancer (RR: 0.71; 95% CI: 0.66, 0.76), though there is a potential for residual confounding in smoking-adjusted estimates. A 2020 pooled analysis of men in nine Swedish cohort studies found that snus ever-use vs. never-use was not associated with oral cancer (aHR: 0.90; 95% CI: 0.74, 1.09; n=9), including among never-smokers (HR: 0.87; 95% CI: 0.57, 1.32; n=9).(Araghi et al., 2020) These findings are comparable to earlier meta-analyses.(Boffetta et al., 2008; Lee & Hamling, 2009) A 2017 pooled analysis of the same nine cohort studies found that Swedish snus was not associated with increased risk of pancreatic cancer in men (aHR: 0.96; 95% CI: 0.83, 1.11; n=9) in analyses that adjusted for cigarette smoking.(Araghi, Galanti, Lundberg, Lager, et al., 2017) Another pooled analysis of the same nine cohorts found that current snus use in never-smokers was not associated with colorectal cancer overall in men (aHR: 1.16; 95% CI: 0.97, 1.37; n=9), but was associated with rectal cancer specifically (aHR: 1.38; 95% CI: 1.07, 1.77; n=9).(Araghi, Galanti, Lundberg, Liu, et al., 2017) A 2009 meta-analysis found no associations between SLT use and stomach cancer (RR: 0.90; 95% CI: 0.35, 2.30; n=2), bladder cancer (RR: 0.83; 95% CI: 0.62, 1.11; n=1), kidney cancer (RR: 0.72; 95% CI: 0.44, 1.18; n=1), laryngeal cancer (RR: 0.90; 95% CI; 0.50, 1.50; n=1), non-Hodgkin's lymphoma (RR: 0.77; 95% CI; 0.59, 1.01; n=1), or pancreatic cancer (RR: 1.61; 95% CI: 0.77, 3.34; n=2) in analyses restricted to never smokers or adjusted for smoking among studies of the whole population.(Lee, 2011; Lee & Hamling, 2009) However, Boffetta et al.'s 2008 meta-analysis did find a significant association for esophageal cancer (RR: 1.6; 95% CI: 1.1, 2.4; n=4) and pancreatic cancer (RR: 1.8; 95% CI: 1.3, 2.5; n=2).(Boffetta et al., 2008)

Respiratory Diseases

Analyses of NHANES-I/EFS (1971-1992) data found no association between ever exclusive SLT use and respiratory disease compared to non-tobacco users among men (aHR: 0.9; 95% CI: 0.3, 2.5) or women (aHR: 0.6; 95% CI: 0.1, 2.3).(Accortt et al., 2002) Analyses of CPS-I data (1959-1972) found modest associations between current exclusive SLT use and mortality (vs. never-users) from respiratory diseases (aHR: 1.28; 95% CI: 1.03, 1.59), COPD (aHR: 1.86, 1.12, 3.06), or influenza/pneumonia (aHR: 1.16; 95% CI: 0.88, 1.51).(Henley et al., 2005) Analyses of CPS-II data (1982-2000) demonstrated weak associations between current exclusive SLT use and mortality (vs. never tobacco users) from respiratory diseases (aHR: 1.11; 95% CI: 0.84, 1.45), COPD (aHR: 1.28; 95% CI: 0.71, 2.32), or influenza/pneumonia (aHR: 0.85, 95% CI: 0.56, 1.29).(Henley et al., 2005)

Analyses of the Swedish Uppsala County cohort (1973-2002) found no association between snus use and respiratory death among male never-smokers under 80 (aHR: 0.8; 95% CI: 0.2, 3.0), while a positive association was observed for male never-smokers 80 and older.(Roosaar et al., 2008) A cross-sectional study of the Swedish Construction Worker Cohort (1971-1974) found an association between daily snus use and increased odds of morning cough (OR: 2.1; 95% CI: 1.8, 2.4), more than 3 months' cough per year (OR: 1.4; 95% CI: 1.1, 1.7), and breathlessness on slight effort (OR: 1.4; 95% CI: 1.3, 1.6) compared to non-users.(Bolinder et al., 1992)

Oral Diseases

SLT products have been associated with a variety of non-cancer oral outcomes in selected studies. Current literature reviews produced by the Epidemiology branches have primarily drawn from Scandinavian studies.

SLT increases the risk for oral mucosal lesions such as leukoplakia and erythroplakia.(Kallischnigg et al., 2008) These lesions have been considered by some to be precancerous although there has been debate on this.(IARC, 2012; Kallischnigg et al., 2008) US studies have found strong dose–response relationships between intensity and duration of use of SLT and leukoplakia. Leukoplakia occurs more commonly among smokeless tobacco users and The location of the lesion in the mouth has been shown to correspond to where the smokeless tobacco is typically placed (IARC, 2012) although this has not been seen for every study.(Kallischnigg et al., 2008)

One cross-sectional study of Swedish snus and dental caries found an association in an unadjusted analysis of adolescents.(Hirsch et al., 1991) More recent adjusted analyses failed to find such an association in Swedish adults.(Hugoson et al., 2012) Additionally, no Scandinavian studies have found associations between SLT use and plaque.(Bergström et al., 2006; Hugoson & Rolandsson, 2011; Montén et al., 2006; Rolandsson et al., 2005; Wickholm et al., 2004) Only one study found Swedish snus use significantly associated (OR: 3.98; $p < 0.020$) for a single indicator of periodontal disease (probing pocket depth) in 1983, but not in in 1993 or 2003.(Hugoson & Rolandsson, 2011) Overall, studies on Swedish snus and gingivitis are mixed. One study with specific aims to evaluate Swedish snus and oral health found gingival index was significantly higher in 12-13-year-old Swedish snus users than non-users after adjusting for plaque index and brushing frequency (Modeer et al. 1980). Several unadjusted studies found no association between Swedish snus and gingivitis. A small cross-sectional study of male adolescents in Göteborg found a significant association between Swedish snus and gingival recession in 19-year-olds after adjusting for plaque, gingivitis and tooth brushing.(Montén et al., 2006) Other studies did not find an association.

Developmental and Reproductive Effects

A 2015 review assessed the risks of adverse health outcomes in newborns among pregnant smokeless tobacco users in nine observational studies from multiple geographic regions which overall indicated evidence for increased risk of low birth weight, preterm, and stillbirth with maternal SLT use.(Inamdar et al., 2015) In this review, a single US case-control study was identified that examined risk of preterm birth among Alaska Native women who were users of iqmik or US SLT products, finding an elevated but non-significant association between smokeless tobacco use and preterm delivery (OR: 1.23; 95% CI: 0.78, 1.93).(England et al., 2013)

Several studies based on the Swedish Medical Birth Register have assessed reproductive effects of use of Snus. Three cohort studies of Swedish snus use and preterm birth observed significant associations compared to nontobacco use with point estimates ranging between 1.29 and 1.98.(Baba et al., 2012; England et al., 2003; Wikström, Cnattingius, Galanti, et al., 2010) Swedish snus use is associated with stillbirth compared to nontobacco use, in studies over 1999-2010 (aOR: 1.43; 95% CI: 1.02, 1.99), and 1999-2006 (aOR: 1.60; 95% CI: 1.13, 2.29).(Baba et al., 2014; Wikström, Stephansson, et al., 2010) A significant association was found for preeclampsia in 1999-2000 (aOR: 1.58; 95% CI: 1.09, 1.27), but not a study of 1999-2006 (aOR: 1.11; 95% CI: 0.97, 1.28).(England et al., 2003; Wikström, Stephansson, et al., 2010) Snus was associated with small-for-gestational-age birth over 1999-2010 (aOR: 1.26; 95% CI: 1.09, 1.46).(Baba et al., 2013) Snus was also associated with infant apnea over 1999-2006 (aOR: 1.96; 95% CI: 1.30, 2.96).(Gunnerbeck et al., 2011) Finally, a study of 1999-2009 found a crude association between snus and oral cleft that did not persist in adjusted models (aOR: 1.48; 95% CI: 1.00, 2.21).(Gunnerbeck et al., 2014)

Biomarkers

Studies of SLT users and nonsmokers have demonstrated increased levels of both biomarkers of exposure and potential harm compared to nonsmokers. A study of 1999-2012 NHANES data demonstrated increased levels of serum cotinine, urinary NNAL, and blood lead among exclusive SLT users (vs. nontobacco users).(Rostron et al., 2015) However, levels of blood cadmium, blood mercury, urinary arsenic, and CYMA were not significantly elevated. Analysis of PATH data (Wave 1, 2013-2014) found that biomarkers of nicotine (TNE2), TSNAs (NNAL, NNN), PAHs (1-PYR, 2-FLU), VOCs (CYMA), and heavy metal (cadmium, lead) exposures were elevated in daily SLT users compared to never tobacco users.(Cheng et al., 2020) Nondaily SLT users also had elevated TNE2, NNAL, NNN, and 2-FLU relative to never tobacco users. A review of 1999-2008 NHANES biomarker data found biomarkers in SLT users not significantly different from those in nontobacco users with the exception of NNK and some PAHs.(Naufal et al., 2011)

A US study of adult male cigarette smokers, SLT users, and tobacco non-users found the levels of leukotriene E4, 11-dehydrothromboxane B2, and the F2-isoprostanes iPF2a-III and 8,12-iPF2a-VI in SLT users comparable to those in tobacco non-users, though iPF2a-VI levels in SLT users were significantly higher than in non-users.(Prasad et al., 2016) A study of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (enrollment 2000-2002, mean follow-up 10 years) found significantly higher baseline levels of biomarkers of insulin resistance (IR) including glucose, insulin and HOMA-IR in SLT users compared to tobacco non-users.(Keith et al., 2016) These elevated biomarkers also persisted after adjustment for multiple diabetes risk factors. A 2008-2009 cross-sectional US study of cardiovascular biomarkers comparing moist snuff users to nontobacco users found significant elevations in IL-8, MCP-1, VEGF, and PDGF across all ages.(Nordskog et al., 2015) However, many other biomarkers assessed were not significantly different between these groups, including WBC counts, cholesterols, fibrinogen, IL-12(p40) and (p70), and sICAM-1.

Conclusion

Compared to non-use of tobacco, SLT product use is associated with some increased health risks. Findings differ somewhat between study settings. In US studies in particular, these include heart disease, stroke, oral cancer, and increased biomarkers of exposure and insulin resistance. Comparatively, Swedish studies have demonstrated fewer overall risks. Swedish studies have demonstrated no association between SLT use and oral cancer, though associations with several cardiovascular outcomes persist, and other studies have identified associations with a variety of reproductive outcomes, and oral lesions. Studies in either setting have found no consistent association between SLT use and respiratory disease or lung cancer.

Health Outcomes – Dual users of cigarettes and smokeless tobacco

Typically, studies of dual use of SLT and cigarettes have not reliably captured true concurrent dual use, with many studies relying on populations of current smokers who have ever used SLT to approximate dual use. Additionally, estimates are typically reported with non-tobacco user referents, requiring re-analysis or comparison of multiple estimates to contrast dual use with smoking or SLT use alone.

All-cause Mortality

Analysis of a 1971-1992 natural cohort of Swedish construction workers found no association between dual use and any cause mortality compared to exclusive smoking (HR: 0.97; 95% CI: 0.93, 1.00).(Lee, 2014; Nordenvall et al., 2013) A study of a 1973-2002 cohort from Uppsala County found no association between dual use and mortality relative to smoking only (RR: 0.97; 95% CI: 0.85, 1.11).(Lee, 2014; Roosaar et al., 2008)

Cardiovascular Disease, Stroke, and other circulatory diseases

A study of male participants in the NHANES-I/EFS cohort (1971-1992) contrasted the hazard ratio of IHD in dual users (aHR: 0.8; 95% CI: 0.5, 1.5) with that in exclusive smokers (aHR: 2.0; 95% CI: 1.4, 2.8) (both vs. nontobacco use).(Accortt et al., 2002)

In a systematic review of Scandinavian studies examining a broad range of outcomes, Lee found a nonsignificant negative association between dual use and IHD, coronary heart disease, or acute MI compared to exclusive smokers (aOR: 0.82; 95% CI: 0.67, 1.01; n = 7).(Lee, 2014) By reanalyzing estimates from a study by Hansson et al., Lee also found similar associations for incident stroke (aOR: 0.90; 95% CI: 0.36, 2.27) and all incident CVD among current users (aOR: 0.81; 95% CI: 0.46, 1.43).(Hansson et al., 2009)

Cancer

A study of male participants in the NHANES-I/EFS cohort (1971-1992) found the hazard ratio of lung cancer mortality among currently-smoking, ever-SLT users compared to non-tobacco users (aHR: 33.9; 95% CI: 8.0, 143.7) was elevated to that of current exclusive smokers (aHR: 24.7; 95% CI: 8.3, 73.5).(Accortt et al., 2002) Using a broader outcome of all cancer mortality, hazard ratios were also elevated in currently-smoking, ever-SLT users (aHR: 2.2; 95% CI: 1.2, 3.7) compared to current exclusive smokers (aHR: 1.8; 95% CI: 1.1, 3.1) (both vs. never-tobacco users). A 1981 case-control study of North Carolina women with oral and pharyngeal cancer reported odds ratios of white women who exclusively smoked (OR: 2.9; 95% CI: 1.8, 4.7) comparable to those of dual user white women (OR: 3.3; 95% CI: 1.4, 7.8) (both relative to no tobacco use).(Winn et al., 1981) Re-analysis of the crude data comparing dual use to smoking only among white and black women combined also shows similar risks of oropharyngeal cancer with dual use (OR: 1.17; 95% CI: 0.57, 2.41). A study of Agricultural Health Study data (1993-2010, North Carolina and Iowa) found a lower incidence of lung cancer in dual users relative to exclusive smokers (aHR: 0.50; 95% CI: 0.27, 0.92), but a nonsignificant negative association for all smoking cancers[1] (aHR: 0.82; 95% CI: 0.59, 1.14).(Andreotti et al., 2017)

Lee's 2014 review of dual use in Scandinavian studied the risks of dual use relative to smoking only. Dual use (compared to exclusive smoking) was not significantly associated with smoking-related cancers (RR: 0.79; 95% CI: 0.54, 1.16), including esophageal adenocarcinoma (RR: 1.00; 95% CI: 0.60, 1.50), gastric cancer (RR: 0.80; 95% CI: 0.57, 1.13), cardia and non-cardia stomach cancer, colon cancer, rectal cancer, anal cancer (RR: 1.44; 95% CI: 0.74, 2.81), and smoking-related cancer incidence overall (RR: 0.79; 95% CI: 0.54, 1.16).(Lee, 2014; Nordenvall et al., 2011; Roosaar et al., 2008; Ye et al., 1999; Zendehdel et al., 2008) Dual use was not significantly associated with incidence of any cancer (RR: 0.94; 95% CI: 0.78, 1.12) or cancer mortality (RR: 0.80; 95% CI: 0.62, 1.04), and

[1] "All smoking cancers" defined as: bladder, colon, cervix, esophagus, kidney, larynx, lip, liver, lung, myeloid leukemia, nasal and sinus, oral cavity, pancreas, pharynx, rectum, stomach, tongue, ureter, and uterine.

was weakly negatively associated with same-site cancer mortality among primary cancer survivors (HR: 0.94; 95% CI: 0.89, 0.99).(Nordenvall et al., 2013; Roosaar et al., 2008)

Respiratory Diseases
Lee's review of Scandinavian studies found nonsignificant associations between dual use and respiratory mortality in adults under 80 years (RR: 0.80; 95% CI: 0.36, 1.79) and over 80 years (RR: 1.53; 95% CI: 0.86, 2.92) compared to smoking only.(Lee, 2014; Roosaar et al., 2008)

Developmental and Reproductive Effects
Lee's 2014 systematic review of Scandinavian studies examined four studies of dual use conducted using the Swedish Medical Birth Register, to determine if there were any conditions for which there was evidence of multiplicative interaction between snus and cigarette dual use.(Gunnerbeck et al., 2011; Lee, 2014; Wikström, Cnattingius, Galanti, et al., 2010; Wikström, Cnattingius, & Stephansson, 2010; Wikström, Stephansson, et al., 2010) Of the nine conditions, only gestational hypertension had indication of a significant positive interaction for dual users (RR for dual use vs. smoking: 2.72; 95% CI: 1.30, 5.69).(Wikström, Stephansson, et al., 2010) Among other conditions, contrasts between dual use and smoking only were non-significant with the exception of diabetes (RR: 0.88; 95% CI: 0.42, 0.84).(Lee, 2014; Wikström, Cnattingius, & Stephansson, 2010) Neonatal apnea could not be assessed due to a lack of cases among dual users.(Gunnerbeck et al., 2011) Lee's review did not include any studies of dual snus and cigarette use and adverse developmental outcomes.

Biomarkers
In Rostron et al.'s study of 1999-2012 NHANES data, dual users of SLT and cigarettes were found to have significantly elevated urinary NNAL relative to exclusive smokers, while serum cotinine, blood cadmium, blood lead, blood mercury, urinary arsenic, and urinary CYMA were comparable.(Rostron et al., 2015) Analysis of PATH data (Wave 1, 2013-2014) found that biomarkers of exposure varied between dual users, SLT users, and cigarette smokers. NNAL and NNN concentrations were higher in dual users than in exclusive smokers, while VOC biomarkers HPMA, CYMA, and MHB3 were significantly lower in daily users compared to daily exclusive smokers.(Cheng et al., 2020)

In a 5-day US study of smokers randomized to conditions including continued smoking and dual use with a dissolvable product, biomarkers of TSNAs did not change significantly in dual users, while some biomarkers of PAHs and VOCs did decrease modestly over the study period. However, similar decreases over time were also observed in the continued smoking arm, suggesting limited benefit of dual use compared to exclusive smoking.(Krautter & Borgerding, 2014)

Conclusion
Analyses of outcome data on dual use of SLT and cigarettes with a smoking-only referent suggest that long-term health outcomes in dual users are generally similar to those in smokers, with some notable exceptions, such as further increased risk of gestational hypertension. These findings have been observed in US and Scandinavian settings. Few studies examining this contrast have used contemporary data. Overall, this literature suggests that health risks to dual users are similar to those of exclusive smokers. It can be inferred that smokers who become dual users after failing to switch completely to SLT do not decrease their long-term health risks significantly.

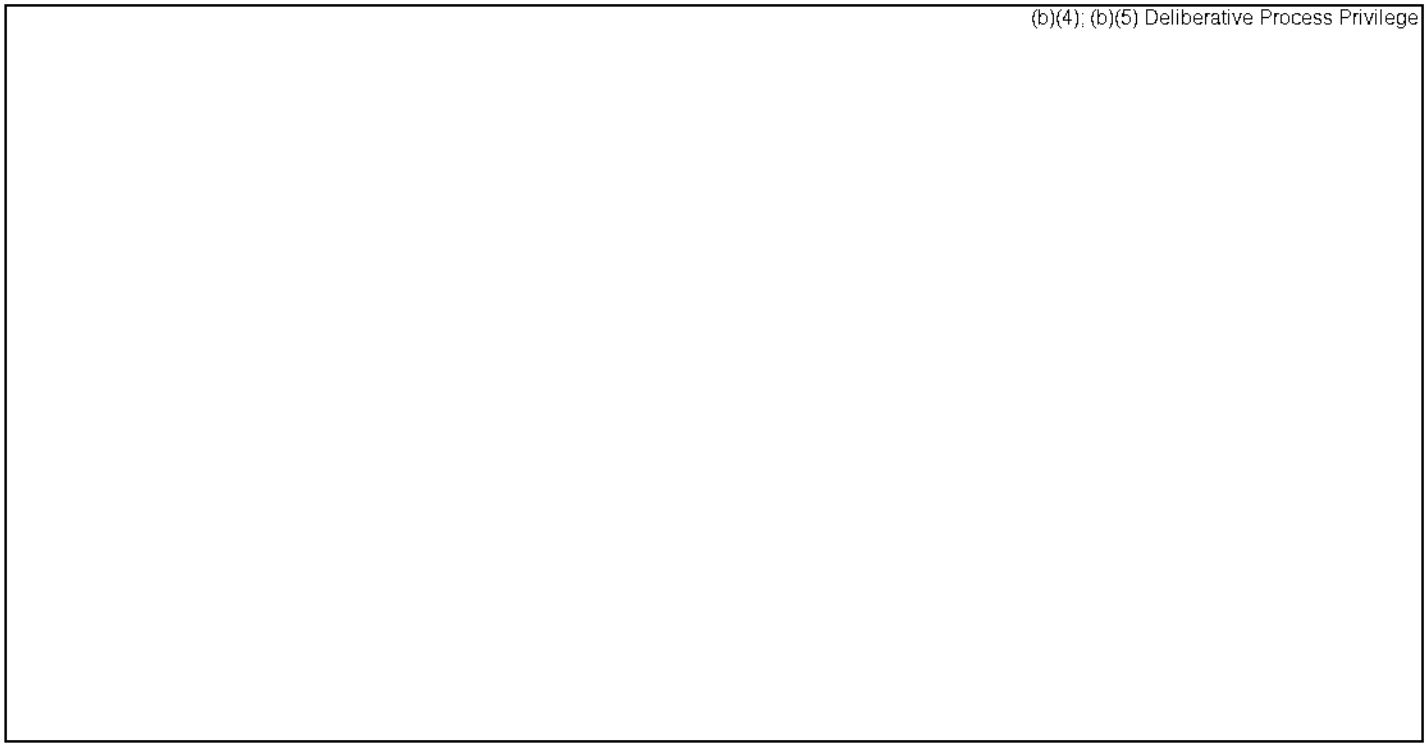
Health Outcomes – Switching to smokeless products compared to nicotine replacement therapy (NRT) and cessation
Cigarette smokers intending to reduce their long-term health risks may pursue complete cessation with the aid of NRT or may pursue a harm reduction approach by switching completely to SLT. As with dual use, few direct estimates of the effects of quitting or switching exist. Indirect comparisons are possible by comparing effect estimates in smokers (vs. nonusers) to estimates in SLT users (vs. nonusers).

All-cause Mortality

A study of men who switched from cigarettes to US SLT using CPS-II data (1982-2002) found an association between switching to SLT switching and all-cause mortality versus complete quitting (aHR: 1.08; 95% CI: 1.01, 1.15).(Henley et al., 2007)

Figure 1 describes the hazards of complete switching from cigarettes to SLT compared to complete tobacco cessation, using US estimates of disease-specific risks in continuing smokers versus former smokers (i.e., quitters), which can be compared with similar estimates for complete switchers versus former smokers.(Henley et al., 2007; Thun et al., 2013) These estimates demonstrate that much of the benefit of complete cessation can be accomplished by complete switching to SLT products, for several outcomes.

Figure 1. Disease-Specific Relative Risks for Mortality for Exclusive Smokers and Switchers from Cigarettes to Smokeless Tobacco (each vs. former smokers), U.S. males (Source: FDA analyses and Section 6.1.1.5 of the Camel Snus MRTPAs)



Cardiovascular Disease, Stroke, and other circulatory diseases

A study of men enrolled in CPS-II (1982-2002) who switched from cigarettes to SLT found modest associations between switching to SLT and coronary heart disease mortality (aHR: 1.13, 95% CI: 1.00, 1.29) and stroke mortality (aHR: 1.24; 95% CI: 1.01, 1.5) compared to quitting entirely (Figure 1).(Henley et al., 2007)

According to the 2014 U.S. Surgeon General's Report, among participants of the CPS-II, the mortality risk of ischemic heart disease/coronary heart disease (ICD-10: I20-I25) among U.S. current smokers (vs. never smokers) was RR=2.80 for males aged 35-64 years and RR=1.51 for those aged >65 years, while for females it was RR=3.08 for those aged 35- 64 years and RR=1.60 for those aged >65 years.(US DHHS, 2014) Among participants of the CPS-II, the mortality risk of stroke (ICD-10: I60-I69) among U.S. current smokers (vs. never smokers) was RR=3.27 for males aged 35-64 years and RR=1.63 for those aged >65 years, while for females it was RR=4.00 for those aged 35-64 years and RR=1.49 for those aged >65 years.

Several Scandinavian studies examined Swedish snus use in association with cardiovascular outcomes including heart disease, stroke, fatal and non-fatal MI, sudden cardiac death and overall cardiovascular disease.(Hansson et al., 2009; Hergens et al., 2005; Johansson et al., 2005; Wennberg et al., 2007) No consistent associations with cardiovascular events were reported among current Swedish snus users who had previously smoked cigarettes (vs. never tobacco users). In all four studies, current smoking was associated with elevated risks of cardiovascular events (vs. never tobacco users).

Cancer

In a study of male participants in the NHANES-I/EFS cohort (1971-1992), hazard ratios for all cancer mortality were comparable between formerly-smoking current-SLT users (aHR: 0.9; 95% CI: 0.4, 1.8) and former exclusive smokers (aHR: 1.0; 95% CI: 0.5, 1.8) (both vs. non-tobacco users).(Accortt et al., 2002) A study of men enrolled in CPS-II (1982-2002) who switched from cigarettes to SLT found modest associations between switching to SLT and lung cancer mortality (aHR: 1.46, 95% CI: 1.24, 1.73) compared to quitting entirely (Figure 1).(Henley et al., 2007) This study did not address risks of oral cancer among switchers. As a reference, the association between smoking (vs. never smoking) and lip, oral cavity, and pharynx cancers is 10.89 among males and 5.08 among females, based on CPS-II data.(US DHHS, 2014)

A Swedish case-control study examined oral cancer risks among snus users who had previously smoked cigarettes. The study reported that current snus users who were former smokers had oral cancer risks (OR: 0.6; 95% CI: 0.3, 1.3) that were similar to former smokers (OR: 0.9; 95% CI: 0.6, 1.4) (each vs. never users).(Schildt et al., 1998)

Respiratory Diseases

A study of men enrolled in CPS-II (1982-2002) who switched from cigarettes to SLT found non-significant modest associations between switching to SLT and COPD mortality (aHR: 1.31, 95% CI: 0.96, 1.78) compared to quitting entirely (Figure 1).(Henley et al., 2007) Reviews have not identified Scandinavian studies examining COPD risk among switchers from cigarettes to SLT.

Developmental and Reproductive Effects

In a nationwide study using the Swedish Medical Birth Register (1999-2009), odds ratios of spontaneous preterm birth were comparable between current snuff users (aOR: 1.3; 95% CI: 1.15, 1.45) and current smokers (aOR: 1.32; 95% CI: 1.26, 1.38) compared to nonusers.(Baba et al., 2012) Though this study did not address switching, it does suggest that risks of preterm birth among switchers may be comparable to those in smokers.

The 2014 U.S. Surgeon General's Report reviewed evidence on reproductive health effects of prenatal smokeless tobacco use and of prenatal smoking to provide insights on the effects of nicotine on the fetus. While the risk of small for gestational age was elevated for smokeless tobacco users (vs. non-users) and cigarette smokers (vs. non-users), risks tended be somewhat greater in smokers.(US DHHS, 2014) However, for risk of preterm delivery and risk of stillbirth, the magnitudes of the associations among smokeless tobacco users (vs. non-users) and for smokers (vs. non-users) were similar.(US DHHS, 2014)

Biomarkers

Product studies of US SLT and Swedish snus have demonstrated that tobacco-specific nitrosamines (TSNAs), including carcinogens NNN and NNK, are higher in SLT products than in NRT products.(Stepanov et al., 2006) Product studies have also demonstrated decreased levels of these TSNAs in more recently introduced US SLT products.(Stepanov et al., 2008) In a clinical study of US SLT users randomized to either Swedish snus or NRT, subjects' NNAL levels decreased significantly for both arms, but decreased further for those using NRT.(Hatsukami et al., 2004) A trial of cigarette smokers randomized to US snus or NRT found similar overall efficacy in cigarette avoidance at 12 weeks (21.9% vs 24.6%), though participants randomized to snus had no

decrease in urine NNAL over the study period.(Hatsukami et al., 2016) In a 4-week US study of smokers randomized to US snus products or NRT, significant decreases were observed in CO, total cotinine, total NNAL, and total NNN in all groups with the exception of total NNN in 1 of the 2 SLT products assessed.(Kotlyar et al., 2011) In a 5-day US study of smokers randomized to smoking, dual use with a dissolvable product, dissolvable product only, and complete abstinence, multiple biomarkers of TSNAs, PAHs, and VOCs decreased significantly in both dissolvable product and abstinent arms, with decreases in the dissolvable product arms generally 60%-100% of the decrease observed in abstinent patients.(Krautter & Borgerding, 2014) A review of 1999-2008 NHANES biomarker data found biomarkers in SLT users significantly lower than in smokers with the exception of NNK and some halogenated aromatic hydrocarbons.(Naufal et al., 2011)

A US study of biomarkers of potential harm in adult male cigarette smokers, SLT users, and tobacco non-users found only one of ~40 biomarkers of oxidative stress, iPF2a-VI, to be comparable between smokers and SLT users.(Prasad et al., 2016) Other biomarkers assessed, including other F2-isoprostanes, were lower in SLT users compared to smokers. In a US study of switching from cigarette smoking to either heated tobacco products, US snus, or low-tar cigarettes, participants randomized to snus had significant decreases in iPF2a-III (24%) and 8,12-iPF2a-VI (17%) at 24 weeks, while decreases in 2,3-dinor-iPF2a-III (15%) and (±)5-iPF2a-VI (10%) were not significant.(Ogden et al., 2015)

Indirect comparisons of exclusive SLT users and exclusive cigarette smokers may also provide insight into the relative benefits to smokers who switch to SLT products. In Rostron et al.'s study of 1999-2012 NHANES data, geometric mean serum cotinine and urine NNAL were significantly higher in SLT users compared to cigarette smokers, while blood cadmium and urine CYMA were reduced.(Rostron et al., 2015) However, it must also be noted that urinary NNAL levels among SLT users fell by more than two thirds between 2007 and 2012, with additional product research implicating declining TSNA concentrations and market shifts to lower-TSNA products. More recently, analysis of PATH data (Wave 1, 2013-2014) demonstrated increased levels of TNE-2, NNAL and NNN among daily SLT users compared to daily cigarette smokers, while PAHs, VOCs, cadmium and lead were significantly lower.(Cheng et al., 2020) Though inexact, these comparisons do suggest that smokers who switch to SLT rather than pursue tobacco cessation may still reduce their PAH and VOC exposures relative to smoking. A 2008-2009 cross-sectional US study comparing smokers, moist snuff users, and tobacco non-users identified cardiovascular biomarkers of effect that differed significantly between SLT users and cigarette smokers, including decreased alpha-1-antitrypsin (AAT), decreased IL-12(p70), and decreased sICAM-1, while other biomarkers were elevated or not changed compared to smokers.(Nordskog et al., 2015)

A 1991 cross-sectional study in Sweden also found that SLT users had significantly lower hemoglobin, white cell count, serum cholesterol, and serum triglycerides compared to cigarette smokers.(Eliasson et al., 1991) A study of participants in the Northern Sweden MONICA Project (enrolled 1990) drew similar conclusions, noting increased fibrinogen in smokers compared to SLT users.(Eliasson et al., 1995)

Conclusion

Complete switching to SLT as a harm reduction alternative to cigarette smoking continues to be an area of active research. Though SLT products are generally considered higher-risk than NRT, they are of considerably lower risk than continued smoking. Cigarette smokers who completely switch to SLT products will substantially lower their risks of cardiovascular disease, lung cancer, and respiratory disease compared to smoking. However, smoking cessation using NRT further reduces mortality due to lung cancer, coronary heart disease, and stroke. Key gaps in the outcome literature can be augmented with biomarker data but must be appropriately caveated, as route of exposure also plays a key role a in disease processes.

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