

Intended for
Swedish Match

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REVIEW AND UPDATE OF THE LITERATURE ON USE BEHAVIOR AND RISK PERCEPTIONS RELATED TO SWEDISH SNUS

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EXECUTIVE SUMMARY

Ramboll (formerly ENVIRON) was asked and funded by Swedish Match to conduct an updated review of the literature relating to specific sections of the 2014 Modified Risk Tobacco Product Application (MRTPA) involving tobacco use behaviors, and perceptions of risk pertaining to the use of Swedish snus. The 2014 review included literature published through at least December 31, 2012, and this update includes articles published through July 28, 2017 (i.e., an additional four and a half years). In the first section of the report, Ramboll defines the study protocol and methods for identifying and updating the literature on these topics. In the following eight content sections of this report, Ramboll evaluated: the effect on tobacco behaviour among current tobacco users (section 2), the effect on tobacco use initiation among non-users (section 3), and consumer beliefs about the health risks of using Swedish snus (section 3). A summary of the results for each section are presented below.

Section 2 – Effect on Tobacco Use Behavior Among Current Tobacco Users

In the 2014 MRTPA, Swedish Match provided a summary of the available scientific evidence which addresses the following five areas of investigation:

1. the likelihood that current tobacco users will start using the proposed MRTP;
2. the likelihood that tobacco users who adopt the MRTP will switch to or back to other tobacco products that present higher risk;
3. the likelihood that consumers will use the MRTP in conjunction with other tobacco products;
4. the likelihood that users who may have otherwise quit using tobacco products will instead use the MRTP; and
5. the likelihood that consumers will use the MRTP as intended.

Most of the data relating to snus use and behavior patterns, including its effect on current tobacco users, were generated on populations in Sweden and other Scandinavian countries where snus use is common. This update is focused on Swedish snus, or use of smokeless tobacco in Scandinavia specifically, and not use behavior related to other smokeless tobacco products such as those commonly used in the United States. Nineteen new studies that investigated Swedish snus use behaviors were published since the 2014 MRTPA as of July 28, 2017.

Swedish usage rates

The 2014 MRTPA reported that 19% of Swedish men and 4% of women use snus daily, with an additional 6% of men and 4% of women using snus occasionally. Snus use is similarly common in Norway, and less common in Finland. Since the 1960s, snus use has gained popularity in Sweden and Norway, and remained steady since the 2000s. Similar to the findings in the 2014 MRTPA, studies published since the 2014 MRTPA on snus usage rates reported that about 25% of surveyed Scandinavians used snus at least occasionally, with a smaller proportion using snus daily. In Norway, 2016 survey data shows that daily snus use has nearly doubled from 6% in 2007 to 10% in 2016 mainly due to snus' increase in popularity among young adults. A Swedish survey showed that male daily snus users decreased from 22% in 2004 to 18% in 2016, with females remaining at around 3-

4%. Several studies reported slightly different statistics based on the size, population, and data stratification of each study. However, overall, tobacco use is declining, though snus use is declining at a slower rate than smoking. Snus use is still much more common among men than among women.

Among youth, overall tobacco use has declined compared to a decade ago, but snus use has surpassed cigarette smoking in popularity among at least some adolescent subgroups in Norway and Sweden. This trend in snus use is observed among both boys and girls.

Likelihood that current tobacco product users will start using snus

In regard to tobacco users taking up snus, the studies published since the 2014 MRTPA support the previous conclusions: that snus is commonly used as a smoking cessation aid and that the majority of users transition from cigarettes to snus as opposed to switching from snus use to cigarette use. No novel findings were published since the 2014 MRTPA regarding youth smokers taking up snus; as reported previously, transitioning between products is not common, and both smoking and snus use is more common among boys than girls. Prevalence of snus use and dual use are increasing among youth coupled with declining smoking prevalence rates.

Likelihood that tobacco users who adopt snus will switch to or switch back to other tobacco products that present higher levels of individual risk

Similar to the conclusions made in the 2014 MRTPA, two newly identified studies reported that only a small percentage of smokers made the transition to smoking from daily snus use. The 2014 MRTPA concluded that initiating tobacco use with both snus and cigarettes as an adolescent was a stronger predictor of being a current smoker later in life. The newly published studies reported that youth who started snus earlier in age were more likely to take up smoking later. However, the mean age at smoking initiation was lower than that of snus initiation, supporting that snus use is more commonly initiated after taking up smoking.

Likelihood that consumers will use snus in conjunction with other tobacco products (Dual use)

In the 2014 MRTPA, the frequency of daily dual use was reported as approximately 2% in men and less than 1% among women in Sweden. Dual use was cited as part of an attempt to reduce or quit smoking in a study reported in the 2014 MRTPA. Newly identified studies presented similar gender-specific prevalence rates and smoking cessation intentions associated with dual use in recent years. The studies published since the 2014 MRTPA examined adolescents' dual tobacco habits and presented similar findings to those reported in 2014 including a higher prevalence of risky and negative behaviors among dual users. Snus use in Finland comprised 2% of those surveyed in a large school-based study and in a smaller study of 15-year-olds in Norway, dual use comprised 8.2%. Dual use in adolescents was more common among daily smokers than among daily snus users.

Transition between snus and smoking among dual users

In the 2014 MRTPA, the studies evaluated did not identify a clear transition pattern among adult tobacco users. Snus users transition to smoking, and vice versa. However, one study showed that of snus users that became smokers during a 10-year follow-up, the majority were dual users at baseline. Another study reported that among dual users, almost a third transitioned to snus use, a quarter transitioned to cigarettes, and the remaining participants remained dual users or quit tobacco entirely.

One newly identified study examining dual users of tobacco showed that a large proportion of users who initiated with cigarettes reported exclusive snus use at the time of the survey (42.9%, 95% CI 35.9-49.9). Less than a quarter of dual users began their tobacco use with snus.

Experimentation with snus and smoking was common through adolescence with no overall inclination towards a tobacco type, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. The risk of current smoking or tobacco use was significantly higher for mixed starters compared with snus starters. The newly identified studies also showed that snus use was more prevalent among boys, and that dual use increased with age. Those who used snus either experimentally or habitually were more likely to smoke later in life.

Tobacco consumption among dual users

Similar to the findings from the 2014 MRTPA, three new studies reported that dual users tended to smoke fewer cigarettes than smokers not currently using snus. No new information related to youth behaviors was identified since the 2014 MRTPA. In the 2014 MRTPA, adolescent tobacco consumption did not differ significantly between snus, cigarette, and mixed starters, though mixed starters were over-represented in the highest category of tobacco consumption (85 or more cigarettes or snus portions per week).

Likelihood that users who may have otherwise quit using tobacco products will instead use snus

As summarized in 2014 MRTPA, the clinical trials in which snus use was specifically used for smoking cessation support resulted in a success rate roughly equivalent to that of other NRTs. The other studies examined in the 2014 MRTPA indicate that snus has been used more often than NRTs by Scandinavian males as an aid for smoking cessation, and that being a former smoker is common among snus users. Data consistently showed that male snus users are more likely to quit smoking than smokers who do not use snus, and that some successful quitters started using snus specifically to aid in smoking cessation. Consistent with findings presented in the 2014 MRTPA, newly identified studies provided evidence that use of snus is increasing in prevalence as an effective smoking cessation aid. Several newly identified studies presented evidence that snus use is more commonly linked with successful attempts in smoking cessation as opposed to other cessation tools, especially in men. Former or current smokers frequently use snus as a smoking cessation aid, and its use as a cessation aid is more common among male tobacco users than females. One large set of longitudinal data of Swedes reported that over three-quarters of smokers who picked up snus as a secondary daily tobacco product completely quit smoking. Among those who tried to quit smoking without the aid of snus, only half were successful. No new studies on snus and smoking cessation among youth were identified.

No new studies were identified that investigate correct consumer use of snus or nicotine dependence in Swedish snus users since publication of the 2014 MRTPA.

Section 3 – Effect on Tobacco Use Initiation Among Non-users

A critical population health consideration under section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C Act is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users

(including never users and former users). Related studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

- The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco products;
- The likelihood that non-users who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk; and
- The likelihood that former users of tobacco products will re-initiate use with the tobacco product.

Six new studies that investigated Swedish snus use initiation among non-tobacco users were published since the 2014 MRTPA as of July 28, 2017

Likelihood that non-users, particularly youth and young adults, will initiate use of the tobacco product

In Sweden and Norway, uptake of snus occurred in a more evenly distributed pattern across all age categories compared to cigarette uptake which appeared to occur more frequently at a younger age. In addition, tobacco initiation was shown to be gender-dependent, as males were more likely to initiate snus while females were more likely to initiate cigarette smoking. As reported in the 2014 MRTPA, the newly identified studies concluded that snus uptake is more frequent among younger populations, and males are more likely to initiate tobacco use with snus. There is an increase in snus uptake in recent years regardless of age or gender, and there is an increasing proportion of snus users who have never smoked.

Likelihood that non-users who adopt snus will switch to products that present higher levels of individual health risk

The 2014 MRTPA concluded that there was little evidence to show that prior snus use leads to daily cigarette smoking among adults. Initiating tobacco use with snus is associated with a reduced risk of becoming or continuing to be a regular cigarette smoker, demonstrating an inverse relationship between snus starters and the initiation of cigarette smoking. Newly identified studies reported findings similar to those presented in the 2014 MRTPA. Among all tobacco users, the proportion of smokers who began their tobacco use with snus was small compared to the proportion of smokers who then added snus use as a habit. Furthermore, one study reported that those who started daily tobacco use with snus had a lower probability of acquiring a daily smoking habit compared to those who did not.

In the 2014 MRTPA, studies on tobacco initiation in adolescents showed that baseline snus users were not more likely to become cigarette smokers at follow-up compared to exclusive smokers and dual users were more likely to continue smoking. The impact of snus experimentation upon later smoking experimentation was smaller than vice versa which has been attributed to the greater prevalence of smoking experimentation than snus experimentation. However, among newly identified studies, the evidence is mixed, with one study showing that those who began snus earlier were more likely to be smokers later on in life.

Likelihood that former users of tobacco products will re-initiate tobacco use with snus

Data from Scandinavian cohorts have shown that being a former smoker is common among snus users. Furthermore, modified risk product claims did not encourage former tobacco users to re-initiate use of snus or motivate them to purchase snus in the Swedish Match Consumer Perception Study. Since the 2014 MRTPA, no observational studies nor clinical trials that directly investigated the likelihood that former tobacco users would re-initiate tobacco use with snus were published. However, a Norwegian study reported an increase in the proportion of snus users who had quit smoking in recent years, on a population level.

Section 4 – Consumers’ Beliefs About the Health Risks of Using Swedish Snus

This section of the report summarizes the available scientific literature describing studies that assessed current perceptions of risk about Swedish snus. We identified a total of five published product-specific studies which provided information on consumers’ beliefs about the health risks of using snus.

Ability of consumers to understand the modified risk claims and the significance of the information in the context of one’s health

In the 2014 MRTPA, one study addressed consumers’ ability to understand modified risk claims for Swedish snus by providing factual information on the relative harms of STPs and NRTs compared to smoking tobacco. The study included smokers in Sweden and other countries including the United States, and most smokers had little knowledge of harmfulness of nicotine products prior to the intervention. Increased knowledge levels on the relative harmfulness of STPs and NRTs compared to cigarettes increased participants’ interests in substituting or ceasing smoking with NRT or STPs.

Since the 2014 MRTPA, an independent analysis of a Swedish Match-sponsored U.S. consumer perception survey of current warning labels and proposed relative-risk labels on Swedish snus reported that the majority of smokers surveyed perceived snus to be harmful, regardless of which label was viewed. Significantly fewer ST users perceived snus as harmful regardless of the label viewed compared to smokers. More smokers and triers/never users of tobacco believed the current warning labels than those who believed the relative-risk labels. A greater proportion of ST users believed the relative-risk labels compared to smokers and triers/never users, though this ST portion was still smaller than those ST users who believed the current labels.

Similar to findings reported in the 2014 MRTPA, smokers who viewed the proposed modified-risk labels were more motivated to use snus than those who viewed current labels with no modified risk label. Regardless of which product label they viewed, smokeless tobacco users were more likely to be motivated to buy snus compared to smokers. The proposed modified-risk label prompted the greatest proportion of smokeless tobacco users to report motivation to use snus compared to the other labels.

One intervention study involving adolescents identified in the 2014 MRTPA reported that increased knowledge of tobacco and its harmful effects had no effect on tobacco use habits. No studies regarding risk perception among youth were identified since publication of the 2014 MRTPA.

Beliefs about health risks of using snus relative to other tobacco products, including those within the same class of products

Data summarized in the 2014 MRTPA showed that both adolescents and adults, especially adult smokers, had exaggerated perceptions of the health risks related to snus use. Those with beliefs more closely aligned with facts related to the relative risks of snus and cigarettes were more likely to be snus users or to have tried the product. A newly identified randomized control trial assessing perception of harm reduction warning labels on snus products reported that those who viewed the harm reduction label were significantly more likely than controls to perceive snus as less harmful than cigarettes.

Among youth, studies included in the 2014 MRTPA reported that smoking and snus use were considered unattractive, but that snus was trendier than smoking. Most adolescents expected their parents would attempt to make them stop using snus, indicating that they believed snus to be a habit of which their parents would disapprove. Almost half of adolescents surveyed rated snus as equally or more harmful than cigarettes. Among newly identified studies, a small focus group study reported a strong Swedish identity associated with snus, and that health risks of snus use were not common knowledge. Another study of adolescents reported that different types of packaging were associated with varying levels of perceived harmfulness.

Beliefs about the health risks of using snus relative to cessation aids and using snus relative to quitting altogether

In the 2014 MRTPA, the available studies indicated that knowledge of the relative harmfulness of cigarette alternatives (STPs or NRTs) increased participants' interests in using them as a cessation aid or cigarette substitute instead of smoking cigarettes. Furthermore, those who had used snus as a smoking cessation aid had more accurate perception of relative harmfulness. However, in the Norwegian medical community, snus was less likely to be recommended as a cessation tool compared to nicotine replacement therapy. One cross-sectional study identified after the 2014 MRTPA concluded that snus users regard snus as presenting fewer health risks than smoking cigarettes. No studies have been identified on youth consumer beliefs about health risks of snus relative to smoking cessation aids or quitting smoking altogether.

1. INTRODUCTION AND PROTOCOL

1.1 Introduction

Ramboll (formerly ENVIRON) was asked and funded by Swedish Match to conduct an updated review of the literature relating to specific sections of the 2014 Modified Risk Tobacco Product Application (MRTPA) involving tobacco use behaviors, and perceptions of risk pertaining to the use of Swedish snus.

The previous review included studies published through December 31, 2012, as well as some relevant articles published in early 2013. The objective of this review was to identify and evaluate all original primary scientific studies published since December 1, 2012 through July 28, 2017, and not included in the previous review, to comprehensively update previous conclusions contained within the following specific sub-sections of the June 6, 2014 Modified Risk Tobacco Product Application for Swedish Match North America Snus Products:

- Section 6.2: Effect on Tobacco Use Behavior among Current Users
- Section 6.3: Effect on Tobacco Use Initiation among Non-Users
- Sections 6.4.1.1-6.4.1.2: Consumers' beliefs about the health risks of using the product

This updated report includes a summary of the conclusions from the sections of the 2014 MRTPA listed above (which are comprehensive through at least December 2012), a presentation of new information (if available) for each topic, and an updated evaluation of the total available evidence and conclusion.

The updated review included the following steps:

- Development of a comprehensive literature search strategy;
- Systematic literature searches;
- Screening of potentially relevant literature identified in the comprehensive searches, including the application of inclusion and exclusion criteria;
- Detailed evaluation of literature deemed potentially relevant from the initial screening;
- Summaries of total available evidence and preparation of written report

1.2 Methods & Search Results

1.2.1 Overview

As described in Section 1, the purpose of this update is to identify and evaluate all new literature that falls within the following research topics:

1. The tobacco use behaviors of current Swedish snus users;
2. The tobacco use behaviors of non-users of Swedish snus;
3. The health risk perceptions related to Swedish snus use;

This section describes in detail the steps taken to identify all relevant literature, and evaluate and report upon the reviewed literature.

1.2.2 Literature Identification and Screening

1.2.2.1 Relevant Literature Definitions

Relevant literature for this update included publications pertaining to research topics 1 through 3, described in the previous Section (1.2.1), that have been published and/or made publicly available after December 1st, 2012, and were not included in the 2014 Swedish Match MRTPA.

Attention was paid to the snus product evaluated within publications, as publications considered relevant will have evaluated the exposures, use, and/or perceptions of Swedish snus in particular. Studies of other or unknown brands of snus were not included or evaluated in this review, with the exception of Swedish or Norwegian studies that do not disclose the brand of snus or type of smokeless tobacco evaluated. Due to Swedish Match's dominant market share in these countries, Ramboll assumed that the vast majority of snus and/or smokeless tobacco used in these countries was likely Swedish Match snus products.

The publication types considered for this update included:

- Peer-reviewed primary studies;
- Publicly available primary data sources, including scientific abstracts, clinical trial data, and academic theses providing relevant results

The peer-reviewed literature considered for this report includes epidemiological studies, human clinical studies, survey reports, and focus group studies. Due to the extensive use of Swedish snus in countries such as Sweden and Norway, relevant studies also included those published in languages other than English. Potentially relevant non-English studies were considered for inclusion in the final evaluation if the studies could be translated into English.

1.2.2.2 Literature Databases and Search Terms

Structured searches in PubMed/Medline (<http://www.pubmed.com>), Scopus (<http://www.scopus.com/>), and ClinicalTrials.gov (<http://clinicaltrials.gov/>) were used to identify the relevant literature spanning across the disciplines and publication types of interest. Additionally, searches of select, pre-determined government and non-government organization websites were also conducted to identify reports of primary data not traditionally captured in literature databases. The searches were completed on July 28, 2017.

Our objective was to capture all Swedish snus-related literature in one step to allow us to be as systematic and comprehensive as possible in updating the literature for Research Topics 1-3. Thus, following exploratory searches of the National Library of Medicine's PubMed database, we developed search terms for these topics that were general and broad, and designed to capture all relevant literature on Swedish snus. Each batch of search results were saved and imported into Mendeley¹ reference manager software for additional review, screening, and tagging (categorizing). Details of

¹ For more information, visit <http://www.mendeley.com>.

these literature searches are provided in Appendix A. The numbers of articles saved from each search and database were documented. Mendeley includes an automated feature by which duplicates are eliminated; the table in Appendix A also includes the total number of unique articles that required screening.

1.2.2.3 Inclusion and Exclusion Criteria

Articles imported into Mendeley were initially screened according to their title, abstract, and key words. Following the initial review of this information, the article was labeled with pre-determined “inclusion” or “exclusion” tags to reflect the reviewers’ initial judgment regarding potential relevance. Full-text copies of articles marked for inclusion were ordered, and reviewed in detail, while articles marked for exclusion were not reviewed further. If a reviewer was unsure of an article’s overall relevance, the article was initially included as “check” so that it could be reviewed further. The intention of this approach was to help minimize the number of missed relevant articles prior to the full-text review.

Table 1 describes the inclusion and exclusion criteria used in this review, and lists the “tags” used in Mendeley to label publications determined potentially relevant to Research Topics 1-3. In general, only one tag was applied per article, with the exception of one study (Lund et al. 2014).

Table 1: Inclusion and Exclusion Criteria for Research Topics 1-3	
Topic / Mendeley Tag	Criteria
Included Studies (Potentially Relevant)	
Use	Publications involving primary data that evaluate the use patterns related to Swedish snus in human populations
Risk Perception	Publications evaluating the risk perceptions of Swedish snus
Check	Publications requiring additional discussion or consideration by the reviewing team; these articles were converted into another inclusion or exclusion tag following discussion
Excluded / Non-Relevant Studies	
Health	Publications evaluating the human health effects of Swedish snus <ul style="list-style-type: none"> • Primary epidemiology studies of any health effect • Involves use of Swedish snus, or smokeless tobacco use in a Scandinavian country
Not a study	Publications that are not primary studies and do not provide primary evidence related to research topics 1-3. <ul style="list-style-type: none"> • May include commentaries, editorials, policy-related articles, etc. that otherwise do not provide reliable primary scientific evidence.
Meta/Review	Reviews, and/or meta-analyses related to the health effects of snus
Not snus	Health and/or tobacco use-related publications that do not consider exposure to Swedish snus. <ul style="list-style-type: none"> • May include studies of non-Swedish snus (e.g., snus from brands other than

	Swedish Match), smokeless tobacco as a group, cigarettes, or other unrelated or grouped exposures
Other KAB	Studies on knowledge, attitudes, or beliefs related to Swedish snus that do not include an evaluation of health risk perceptions of Swedish snus
Tox	Toxicology or <i>in vitro</i> studies involving Swedish snus
Animal/cell	Toxicology or <i>in vitro</i> studies involving tobacco/tobacco component exposures other than Swedish snus
Chemistry	Studies of the chemical composition of Swedish snus
Misc	Any other non-relevant publications

1.2.3 Preliminary Literature Screening Results

Detailed screening results of the literature searches for Research Topics 1-3 through December 1, 2012 are provided in a PRISMA diagram in Appendix B. After conducting the literature searches described in Appendix A, and after removing duplicates, we identified 1,434 articles that potentially relate to Research Topics 1-3. Following the preliminary screening of these articles, 1,277 were excluded, with 157 identified as potentially relevant requiring further review.

1.2.3.1 Quality Assurance/Quality Control (QA/QC) of Screened Literature

An independent reviewer conducted an initial QA/QC review following the review of the first 100 publications by each reviewer. The reviewer blindly selected 10 (10%) of the screened publications, and documented their own determination regarding inclusion or exclusion. Following this initial QA/QC check, an error rate of 0% was identified for the updated Topics 1-3 search. Since no error patterns were identified, the preliminary screening progressed.

Following the screening of all publications in the databases, an independent reviewer randomly screened 10% of excluded references and 20% of the included. Following the QA/QC review of the Topic 1-3 results, none of the excluded articles were determined to be potentially relevant, and no serious patterns of disagreement were observed.

1.2.4 Full-Text Literature Review

Detailed screening results of articles identified as potentially relevant following the preliminary screening of articles related to Research Topics 1-3 are provided in the PRISMA diagram in Appendix B.

Following the retrieval and/or purchase of publications initially identified as potentially relevant, each full-text publication was reviewed in detail. 23 studies were ultimately included in the qualitative synthesis. These included 19 "Use" studies (one of which was also categorized as a "Risk Perception" study) and 5 "Risk Perception" studies.

157 "Use" and "Risk Perception" studies were reviewed in detail, and 134 were excluded for various reasons including the following:

- Previously included in the 2014 MRTPA

- Did not include an evaluation of Swedish snus (e.g., cigarettes, combined tobacco, non-relevant brands or tobacco types, etc.)
- Non-relevant study (e.g., case report, use-behavior, commentary, animal study)

23 relevant primary studies on use behavior and risk perceptions related to Swedish snus were identified and included in the qualitative syntheses.

2. EFFECT ON TOBACCO USE BEHAVIOR AMONG CURRENT TOBACCO USERS

To permit FDA to evaluate the full effect that a Modified Risk Tobacco Product (MRTP) and its marketing may have on population health under Section 911(g)(1)(B) of the Act, an MRTP application must contain scientific evidence about the effect the product may have on tobacco use behavior among current tobacco users. According to FDA's MRTP Guidance, the submission must include information about all the following:

1. the likelihood that current tobacco users will start using the proposed MRTP;
2. the likelihood that tobacco users who adopt the MRTP will switch to or back to other tobacco products that present higher risk;
3. the likelihood that consumers will use the MRTP in conjunction with other tobacco products;
4. the likelihood that users who may have otherwise quit using tobacco products will instead use the MRTP; and
5. the likelihood that consumers will use the MRTP as intended.

In the 2014 MRTPA, Swedish Match provided a summary of the available scientific evidence which addresses these areas of investigation. Most of the data relating to snus use and behavior patterns, including its effect on current tobacco users, were generated on populations in Sweden and other Scandinavian countries where snus use is common. This update is focused on Swedish snus, or use of smokeless tobacco in Scandinavia specifically, and not use behavior related to other smokeless tobacco products such as those commonly used in the United States.

Nineteen new studies that investigated Swedish snus use behaviors were published since the 2014 MRTPA as of July 28, 2017 (8 with a Swedish population: Hedman et al. 2015; Sohlberg 2015; Joffer et al. 2014; Lindroth et al. 2014; Rodu et al. 2013; Rutqvist 2012; Leon et al. 2016; Ramstrom et al. 2016; 10 with a Norwegian population: Lund and McNeill 2013; Lund and Scheffels 2014b; Lund et al. 2014; Skogen et al. 2016; Kvaavik et al. 2014; Lund et al. 2017; Lund and Scheffels 2016; Pedersen and von Soest 2014; Lund and Lund 2014; Kvaavik et al. 2016; one with a Finnish population: Tseveenjav et al. 2015).

2.1 Overview of Swedish Use Data

2.1.1 Swedish Usage Rates

Summary from 2014 MRTPA

In Sweden, daily snus use is reported by 19% of adult males and 4% of adult females. Occasional use is reported by an additional 6% of males and 4% of females. Snus use is also common in Norway (i.e., use by 15 to 20% of adult males), and to a lesser extent in Finland. Although there have been substantial increases in snus use in Sweden and Norway since the 1960s, use rates have remained relatively stable since about 2000 (Hvitfeldt and Gripe 2009; Nordgren and Ramström 1990).

Newly Identified Studies

Six new studies reported on snus usage rates in Scandinavia (Lund and McNeil 2013; Lund and Lund 2014; Lund et al. 2017; Rodu et al. 2013; Rutqvist 2012; Lindroth et al. 2014).

In a Norwegian study of six pooled cross-sectional studies from 2005-2010, 6.8% of men were currently using snus and cigarettes, with 1% using both products daily. The most common habit was to use one product daily and the other occasionally. Among daily snus users, 21.6% smoked occasionally and 9.8% smoked daily. The proportion of snus users among daily smokers was not reported, but daily smokers comprised a larger proportion of occasional snus users: 40.9% smoked daily and 15.6% smoked occasionally (Lund and McNeil 2013).

Based on data from population-based cross-sectional surveys and domestic annual tobacco sales, the prevalence of daily or occasional smoking in Norwegian men aged 16-30 years old was lower in 2013 than in 1985 (21% and 50%, respectively). On the other hand, the prevalence of snus use in this sample population increased from 9% in 1985 to 33% in 2013, and snus surpassed cigarettes as the most popular nicotine product around 2008 (Lund and Lund 2014).

Lund and colleagues (2017) conducted repeated nationally representative cross-sectional surveys from 2003-15 in Norway, with male respondents totaling 8157 tobacco users. The mean age was 44.4 years. Ever-snus users consisted of 23% (n=2067) of tobacco users over the entire duration of the study.

In Sweden, use of smokeless tobacco (primarily snus) was about 10-fold higher than the rest of Europe and more prevalent in men than in women in a cross-sectional study with representative samples of 1000 individuals from 18 countries (Leon et al. 2016). In recent years in Sweden, the prevalence of tobacco use from 2004 to 2009 in men dropped from 38% to 35% ($p=0.23$) and dropped significantly in women from 27% to 20% ($p=0.001$) based on data from the Northern Sweden MONICA study (Rodu et al. 2013). In men, snus use dropped from 27% to 24% ($p=0.27$), and smoking (8.8%) and dual use (2%) remained similar to the prevalence in 2004. In the women surveyed, snus use prevalence dropped from 9% to 8% ($p=0.65$) but smoking and dual use prevalence decreased significantly to 11% ($p=0.005$) and 1% ($p=0.04$), respectively. Overall, snus use was found to have lowered by 11% in men and 9% in women from 2004 to 2009. The overall prevalence of tobacco use was similar for younger (25-44 years old) and older (45 years or older) participants when stratified by gender, but snus and smoking rates differed between the age groups. A greater proportion of younger men used snus exclusively (18.6%) compared to older men (8.8%), and a greater proportion of older men were former smokers currently using snus (11.7%) compared to younger men (6.8%). Exclusive smoking was more common in older men (8.4%) than younger men (1.7%). The prevalence of snus use remained low in women no matter the age, but was higher in younger women (3.7%) than older women (0.9%). Similar to the trend in men, more older women were exclusive smokers (12.5%) compared to younger women (6.2%) (Rodu et al. 2013).

A cross-sectional, population-based sample of Swedes aged 18 years or older (2,599 men and 3,409 women) reported the overall prevalence of tobacco use to be 31.3% in men and 17.5% in women. Consistent with previously reported gender trends, more men than women used snus: 21.1% of men and 3.8% of women. 1.5% of men reported regular use of snus and cigarettes, and 0.2% of females reported dual use (Rutqvist 2012).

Also using data from the Northern Sweden MONICA study, Lindroth and colleagues (2014) reported that the prevalence of regular smokers or snus users did not differ between communities of different sizes. With city dwellers as the reference group, the odds ratio of regular snus use in an adult individual living in town was 0.98 (95% CI 0.67-1.32) and that of someone living in a rural area was 1.01 (95% CI 0.70-1.46).

Various surveys have been conducted by Scandinavian public health agencies investigating snus use among people living in their countries (e.g., Statistics Norway, Helsedirektoratet, National Public Health Survey "Equal health" in Sweden, and Statistics Sweden).

In a survey conducted by Statistics Sweden (2016) in 2014/15, the proportion of those who smoked and/or used snus daily was highest among 25-44 year-old men (37.8%) and 45-64 year-old women (18.6%) when separated by sex. The age group with the smaller proportion of tobacco use were people aged 75-84 years. 16-24 year-olds and 25-44 year-olds used snus slightly less: 21.1% of 16-24 year-old men and 37.8% of 25-44 year-old men, and 14.5% of women in both age groups. According to National Public Health Survey "Equal Health," which surveyed approximately 20,000 people aged 16-84 years, the proportion of daily smokers decreased from 16% in 2004 to 9% in 2016 (Folkhalsomyndigheten 2014a). The proportion of male daily snus users decreased from 22% in 2004 to 18% in 2016, and the proportion of female daily snus users remained stable through the years at around 3-4%. Daily snus use was more common among those under age 44, with the greatest proportion among 30-44 year-olds (15%), closely followed by 15-29 year-olds (10%) in 2016. There was no obvious trend among different socioeconomic classes; however, the group with the greatest proportion (15%) of daily snus users through the years were those in "economic crisis" (however, this is also the group with the smallest number of people surveyed n=999 in 2016; compared to 11% of 8,290 people "not in economic crisis"). Daily snus use was least common among those with post-secondary education (9%) compared to 10% among those with primary education and 14% of those with secondary education. In terms of ethnic identity, about 13% of Swedes surveyed reported using snus daily compared to 6% of people from other Nordic countries, 6% of people from other European countries, and 3% of people from other countries in the world.

Based on data from the "Equal Health" survey in 2016, those who responded as "sometimes snus" users were 2% of Swedes, 1% of women and 3% of men (Folkhalsomyndigheten 2014a). This is a smaller proportion compared to 2015 and years prior: in 2015, 5% of Swedes, 3% of women and 6% of men responded as "sometimes snus" users.

Numerous relevant statistics from Statistics Norway have been reported by public health agencies Norway. In Norway in 2017, 29% of 16-74 year-olds reported smoking or using snus (FHI 2017). 10% of the adult population used snus daily (approximately 430,000 people) in 2016, 13% of Norwegian men and 7% of Norwegian women (Helsedirektoratet 2017). About 5% of Norwegians use snus occasionally (Helsedirektoratet 2017). The proportion of people who use snus daily has doubled in the past decade (from 6% in 2006 to 10% in 2016) mainly due to snus' increase in popularity among young people (Helsedirektoratet 2017). Many more young men and women aged 16-24 use snus daily rather than smoke: 21% of young men use snus compared to 5% who smoke; 17% of young women use snus compared to 2% who smoke (Helsedirektoratet 2017). Snus was the more common tobacco product among 16-24 year-olds: 26% of men and 14% of women reported daily snus use compared to 25% of 25-44 year-old men (FHI 2017). Daily snus use has gained popularity since 2013-2015

among 16-24 year-olds, with 21% of men and 5% of women reporting snus use (FHI 2017). 11% of 45-64 year-old men and 9% of 25-44 year-old women reported daily snus use in 2017, and no snus data was reported for women 45 years and older (FHI 2017).

The studies published since the 2014 MRTPA came to similar conclusions, that snus use comprises about 25% of those surveyed in Scandinavia, with daily snus users making up a smaller proportion. Tobacco use overall is declining, with snus use trending similarly, though at a slower rate. Men are more likely to be snus users, though snus is gaining popularity over smoking among young women. There is evidence showing that young adults prefer snus over smoking.

2.1.2 Youth Behaviors

Summary from 2014 MRTPA

Among adolescents, daily snus use was higher among those in higher grades compared to the lower grades (Lund and Lindbak 2007). Galanti and colleagues (2001) conducted six follow-up assessments on tobacco use behaviors among adolescents in the BROMS cohort, which followed students from fifth grade (approximately age 11 years old) to three years after compulsory school (approximately age 19 years old) (Galanti et al. 2001; Galanti et al. 2008; Lager et al. 2012). Among girls, daily snus use was low in compulsory school (1-2%) and was still low two to three years after compulsory school (2-3%). Cigarette use among school-age girls increased from 7th through 9th grades from approximately 3% to 12%; with the increasing trend continuing two to three years following completion of compulsory school, 15% to 17%. Among school-aged boys, daily snus use increased from 7th to 9th grades from about 3% to 13%. Two to three years after compulsory school, daily snus use had increased, and was reported by 18 to 20% of these boys. Cigarette use among boys, typically followed a similar trend, with an increase from 2% to 6%, from 7th through 9th grade.

Newly Identified Studies

Five studies published since the 2014 MRTPA reported on snus use among youth: Tseveenjav et al. 2015, Hedman et al. 2015, Skogen et al. 2016, Lund and Scheffels 2016, Lund and Lund 2014. Swedish authorities also collected data on snus use among schoolchildren (Folkhalsomyndigheten 2014b; Statistics Sweden 2016).

Since the 2000s, snus use has decreased among boys, from 21% of 15-year-olds and 8% of 13-year-olds in 2001/02 to 5% of 15-year-olds and 1% of 13-year-olds reported daily or at least once a week snus use in 2013/14 (Folkhalsomyndigheten 2014b). Among girls throughout the survey years, only 1-2% of 15-years-old use snus, and less than 1% of 13-year-olds. In a different study of Swedish 9th graders in 1985, 2000, and 2015, tobacco use (cigarettes or snus) peaked in 2000 with 36% of girls and 38% of boys using tobacco. Overall, in recent years tobacco use has dropped; in 2015, only 15% of girls and 14% of boys reported tobacco use. Boys tended to use snus more than smoke than girls, and vice versa. Less than 1% of girls and 5% of boys reported using snus in 2015, compared to 13% of girls and 5% of boys reporting smoking (Statistics Sweden 2016).

According to a 2010-2011 nationally representative cross-sectional school-based study of almost 190,000 Finnish adolescents between 13 and 19 years of age, 18% of adolescents had used snus (2% daily use, 16% had experimented with the product) (Tseveenjav et al. 2015). Snus use was significantly more common among boys than girls ($p < 0.05$). 19% were daily smokers and 15% were

occasional smokers with two-thirds smoking less than weekly. Furthermore, the likelihood of snus use among smokers was high, ranging from 65-79% of smoking boys and 75-89% of smoking girls. The authors concluded that current use of snus is connected to other risky behaviors including smoking and alcohol use and the propensity to have positive attitudes towards such.

Among a population-based cohort of over 2000 14-15-year-old Swedes, the prevalence of daily smoking was 3.5% and daily snus use was 3.3% (Hedman et al. 2015). Tobacco use decreased compared to a similar cohort from 10 years ago, wherein the prevalence of daily smoking was 5.8% and daily snus use was 9.9%. In this 2010 cohort (Hedman et al. 2015) being male was a risk factor for daily snus use, and being female was a risk factor for daily smoking. The prevalence of daily smoking and daily snus use were both significantly higher among those with smoking or snus-using parents, living in an apartment, living in a single parent household, not participating in sports and among those with lower parental SES. The prevalence of smoking and use of snus was significantly lower among the participants in a prevention program compared with the non-participants and similar controls from another cohort (Hedman et al. 2015).

In a cross-sectional study of adolescents aged 16-19 years in Hordaland county, 10,220 respondents out of 19,430 contacted (53% participation rate) responded to a survey on snus use and other risky behaviors including alcohol and smoking (Skogen et al. 2016). Compared with ethnic Norwegian adolescents, EU/EEA adolescents were less likely to have tried snus (adjusted OR=0.64; 95% CI 0.43-0.97, $p<0.05$) and less likely to report daily snus use (adjusted OR=0.31; 95% CI 0.15-0.67 $P<0.01$). Similarly, non-EU/EEA adolescents were less likely than ethnic Norwegians to have ever tried snus (adjusted OR=0.47 95% CI 0.34-0.65, $p<0.001$) and less likely to report daily snus use (adjusted OR=0.36; 95% CI 0.21-0.62, $p<0.001$). Odds ratios were adjusted for gender, age, and family socioeconomic status.

Among 736 tobacco-using 15-year-olds surveyed in a school-based cross-sectional survey in Norway, 19% exclusively smoked, 39.5% exclusively used snus, and 41.5% were dual users, with 8.2% reporting daily dual use (Lund and Scheffels 2016). Out of the total study sample, tobacco users consisted of 23%.

Using national tobacco sales data recorded by the Norwegian Directorate of Customs and Excise, the overall per capita consumption of tobacco among those 15 years or older was 2,065 grams in 1984-1986. 96% of the tobacco consumed was cigarettes and 4% was snus. In the more recent period 2010-2012, the annual overall per capita consumption was 1,646 grams of tobacco. Cigarettes comprised 72% of the market whereas snus had increased to 28% (Lund and Lund 2014). Lund and Scheffels (2016) concluded in their school-based cross-sectional survey of 15-year-olds that though boys had a stronger tendency to use snus daily and girls had a stronger tendency to smoke daily, there were more boys among the subset of those who smoked more than 10 cigarettes per day.

Among youth, overall tobacco use has declined compared to a decade ago, but snus use has surpassed cigarette smoking in popularity among at least some adolescent subgroups in Norway and Sweden. This trend in snus use is observed among both boys and girls.

2.2 Likelihood that current tobacco product users will start using snus

Summary from 2014 MRTPA

Data from the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases project in northern Sweden, an area with a high prevalence of snus use, and the Vasterbotten Intervention Programme (“VIP”) provide evidence of population-level transitioning (Lindahl et al. 2003; Rodu et al. 2002; Rodu et al. 2003; Stegmayr et al. 2005). From approximately the mid-1980s to 2007, these studies monitored trends in cigarette smoking and snus use and found a decreasing trend of daily smokers with a corresponding increase in snus users. Some women transitioned from cigarettes to snus, but the population shift was far more pronounced in men, with a 56% increase in the proportion of those who smoked transitioning to snus use.

Several Swedish studies (Furberg et al. 2005; Furberg et al. 2006; Galanti et al. 2008; Gilljam and Galanti 2003; Lindstrom and Isacson 2002a; Lindstrom and Isacson 2002b; Ramström and Foulds 2006; Rodu et al. 2002; Rodu et al. 2003; Stegmayr et al. 2005) and Norwegian studies (Grotvedt et al. 2013; Lund et al. 2010; Lund et al. 2011; Scheffels et al. 2012) of various epidemiological study designs have shown a gradual trend toward uptake of snus with decreasing cigarette smoking. In addition, several Scandinavian cohort studies have assessed snus uptake as a cessation aid among current smokers and observed trends in tobacco use patterns among adults (Lindstrom and Isacson 2002b; Lundqvist et al. 2009), and among youths (Galanti et al. 2001; Grotvedt et al. 2013).

In Sweden and Norway, uptake of snus occurred across all age categories as compared to cigarette uptake which appeared to occur more frequently at a younger age. Further, tobacco initiation was shown to be gender-dependent, as males were more likely to initiate snus while females more likely to initiate cigarette smoking. Studies in Sweden and Norway have shown that snus initiation is more prevalent among former cigarette smokers than among non-tobacco users (Furberg et al. 2005; Furberg et al. 2006; Lund et al. 2010; Lund et al. 2011).

Newly Identified Studies

One cross-sectional study informed on the likelihood that current tobacco users would take up snus use (Lund and McNeill 2013). Using data from six Norwegian population-based cross-sectional studies with 3,524 men aged 16-74, almost 75% of dual users started their tobacco use as cigarette smokers (Lund and McNeil 2013).

Overall, the epidemiological data published since the 2014 MRTPA is congruent with the previous finding that snus is used as a smoking cessation aid, and the majority transition from cigarettes to snus as opposed to switching from snus use to cigarette use.

2.2.1 Youth Behaviors

Summary from 2014 MRTPA

The gradual transitioning from smoking to snus observed in adults was not as apparent among adolescents. Experimentation with snus and smoking—without an inclination towards a tobacco type—was common through the teenage years, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. The Children’s Smoking and Environment in Stockholm County, or BROMS cohort, is one of the larger studies that have collected information on

tobacco use behaviors among Swedish adolescents. Galanti and colleagues (2001) reported that prevalence of cigarette smoking and snus use increased among students age 11 to 12 years followed from 5th to 6th grade by gender. Experimentation with both tobacco products was far more frequent among boys than among girls, and cigarette smoking often marked the onset of tobacco use. The authors reported that, at 1-year follow-up, 4 in 10 boys with initial experience of snus had experimented with cigarette smoking, while only 2 in 10 smokers had experimented with snus. Overall, for both cigarette only users or snus only users at baseline, each were more likely to remain in their baseline category or become a mixed user (Galanti et al. 2001). In another study, Grotvedt et al (2013) examined patterns of tobacco use among 16-year old Norwegian students (n=1,440) followed for three years. Baseline smokers were more likely to remain smokers or dual users at follow-up, while the odds for switching from smoking only to snus only were not significant (OR=1.53; 95% CI: 0.71 - 3.31).

Newly Identified Studies

Two observational studies of Swedish adolescents and Norwegian adolescents investigated the likelihood of snus use among current tobacco users (Joffer et al. 2014, Pedersen and von Soest 2014). Joffer and colleagues (2014) conducted a school-based longitudinal cohort study wherein the tobacco habits were surveyed among 12-14-year-olds in 2003 and again in 2008 at age 17-18. This study reported that both snus use and smoking were more common among boys than girls, regardless of age. In a population-based Norwegian survey of adolescents conducted in 2002 and 2010, the prevalence of daily smoking decreased from 12.2 to 8.1% ($p < 0.001$) but the proportion of non-daily smokers increased (Pedersen and von Soest 2014). The relative proportion of non-daily smokers who used snus on a non-daily or daily basis tripled, from 17.5% in 2002 to 56.8% in 2010. Though smoking decreased, the available evidence shows that occasional use is still common and paired with non-daily or daily snus use. The proportion of dual daily users among tobacco users remained similar (17.8% in 2002 and 15.2% in 2010) but the proportion of daily smokers who used snus daily or non-daily increased (31.8% in 2002 and 42.4% in 2010) (Pedersen and von Soest 2014).

Adding to the findings in the 2014 MRTPA, tobacco use of either form (snus or cigarettes) was more common among boys than girls (Joffer et al. 2014). Smoking prevalence rates are declining, but snus use and dual use (with occasional use of one product) are increasing in prevalence (Pedersen and von Soest 2014).

2.3 Likelihood that tobacco users who adopt snus will switch to or switch back to other tobacco products that present higher levels of individual risk

Summary from 2014 MRTPA

Based upon longitudinal and cross-sectional studies that examined snus use and the risk of future smoking in several populations in Sweden and other Scandinavian countries, there is little evidence that prior snus use leads to daily cigarette smoking among adults. In fact, these studies show that there is an inverse association between snus use and cigarette smoking initiation and that snus use is associated with a reduced risk of becoming or continuing to be a regular cigarette smoker, as compared to those who start using tobacco as smokers or non-tobacco users.

Longitudinal studies provide evidence of transitioning from cigarettes to snus as compared to switching from snus use to cigarette smoking. A review of studies among adolescents in Sweden,

Norway, and Finland showed that baseline snus use was not a precursor to exclusive cigarette smoking. In other words, neither tobacco initiation with snus nor current snus use is a predictor of future cigarette smoking. According to the 2007 SCENIHR report, “the Swedish data, with its prospective and long-term follow-up do not lend much support to the theory that smokeless tobacco (i.e. Swedish snus) is a gateway to future smoking” (SCENIHR 2007). Four additional studies published since the SCENIHR report support the same conclusion (Grotvedt et al. 2013; Lundqvist et al. 2009; Norberg et al. 2011; Stenbeck et al. 2009).

Some evidence from these studies showed that dual use of both cigarette and snus may be a stronger predictor of future smoking. Finally, most of the studies focused on tobacco use behaviors among males, due to the low prevalence of snus use among females. The variations in study design, population studied, methods of estimating the risk of starting to smoke cigarettes and methods of modeling smoking predictor variables have contributed to the difficulty in understanding the gateway hypothesis as it relates to cigarette use (Colilla 2010).

Newly Identified Studies

One Swedish longitudinal study and one Norwegian cross-sectional study reported on the likelihood that tobacco users would switch to, or back to smoking (Ramstrom et al. 2016; Lund and McNeill 2013). A nationally representative longitudinal study in Sweden that followed daily tobacco users reported that only a small proportion of men who initiated daily smoking began smoking following daily snus use: 7.6% (95% CI 7.1-9.10), n=877/11,557. An even smaller percentage of female daily smokers (<0.1%, n=43/12,798) made the transition from daily snus use (Ramstrom et al. 2016). In a sample of 3,524 men from pooled cross-sectional studies over the period of 2005-2010, 3.3% had quit snus and were exclusively smokers, whereas 5.3% of men who were former smokers were current snus users (Lund and McNeill 2013). No subset sample sizes nor analyses for significance were reported.

Supporting the conclusion made in the 2014 MRTPA, only a small percentage of smokers made the transition to smoking from daily snus use.

2.3.1 Youth Behaviors

Summary from 2014 MRTPA

Most of the literature addressing the transition from snus to cigarette use in Sweden has focused on males and adolescents/young adults, as most tobacco habits are formed before age 25 years (Colilla 2010; Stenbeck et al. 2009; USDHHS 2012). The literature on adolescents surveyed as part of several Swedish and Norwegian cohorts found that tobacco initiation with snus or current snus use was not a predictor of future cigarette smoking (Galanti et al. 2001; Galanti et al. 2008; Grotvedt et al. 2013; Haukkala et al. 2006).

Using data from the BROMS cohort where schoolchildren were followed from age 11 to 18, Galanti and colleagues concluded that initiating tobacco use with both snus and cigarettes was a stronger predictor of being a current smoker by the end of follow-up. Snus starters had a lower risk of ending up as a current smoker when compared to those who had experimented with both products earlier (Galanti et al. 2008). The authors found that, compared to non-tobacco users, baseline snus users were not more likely to become cigarette smokers at follow-up (OR= 1.95; 95% CI: 0.96 – 3.8) while exclusive

cigarette users (OR= 2.89; 95% CI: 2.25 – 3.71) and mixed starters (OR= 4.81; 95% CI: 3.09 – 7.5) were more likely to smoke cigarettes at the end of follow-up. Additionally, the likelihood of being a current smoker at end of follow up was higher, but not significantly increased for cigarette starters compared with snus starters (OR=1.42; 95% CI: 0.98 - 2.1); those who were mixed starters (cigarette and snus) were more likely to smoke at follow-up (OR=2.54; 95% CI: 1.68 – 3.91) (Galanti et al. 2008). Grotwedt and colleagues (2013) reported that baseline snus use was not associated with increased risk of only smoking at follow-up (OR=0.86; 95% CI 0.40-1.81) after adjusting for “previous smoking” experience. However, baseline snus users were more likely to be daily snus users who occasionally smoked (OR=1.88; 95% CI 1.06-3.33). Adolescents using snus only at baseline were more likely to be tobacco free (24%) at follow-up than smokers and dual users (14% and 15%, respectively). Furthermore, smokers at baseline were most likely to remain smokers (OR=13.31; 95% CI 8.2 - 21.6) or become dual users (OR=10.74; 95% CI: 6.56 - 17.57).

Newly Identified Studies

Two observational studies addressed the likelihood of snus users switching back to smoking among youth (Lund and Scheffels 2014b, Joffer et al. 2014). A study of representative repeated cross-sectional surveys in Norway reported that among dual users who initiated snus earlier in life (i.e. before age 16), there was a greater proportion of current smokers (22.9%) compared to later snus initiators (5.9%) (Lund and Scheffels 2014b). Furthermore, the evidence suggests that snus use is likely more commonly initiated after smoking: among lifetime snus users (n=409), the mean age of snus initiation was 17.7 years (range 10-50) whereas the mean age of smoking initiation among lifetime snus users (n=65) was 16.2 years (range 12-22). However, the number of responses for the question regarding the age of smoking initiation among lifetime snus users was low, and no p-value was reported (Lund and Scheffels 2014b). In a longitudinal cohort study where Swedish adolescents (n=649) were surveyed at age 12-13 in 2003 and again at age 17-18 in 2008, ever use of snus at age 12-13 was a significant predicting factor for reporting smoking at follow-up at 17-18 years old: odds ratio 3.43; 95% CI 1.78-6.62 compared to those who did not use snus at age 12-13 (Joffer et al. 2014).

Adding to the evidence reported in the 2014 MRTPA, those who started snus earlier in age were more likely to take up smoking later. However, the available evidence shows that the mean age of smoking initiation was lower than that of snus initiation supporting that snus use is more commonly initiated after taking up smoking.

2.4 Likelihood that consumers will use snus in conjunction with other tobacco products (Dual use)

Summary from 2014 MRTPA

Several studies have reported the frequency of daily dual use as approximately 2% in men and less than 1% in women, although the frequency appears to vary slightly depending on whether the criterion is daily dual use, or occasional use of one of the tobacco types. Other studies have reported a slightly higher prevalence of dual use in Sweden. For example, in the VIP cohort, 3.2% of male and 4.4% of female snus users in northern Sweden were found to smoke regularly (Lundqvist et al. 2009), and Digard et al. (2009) reported a prevalence of about 9.8% (daily and/or occasional). Taken together, among adults and adolescents, the range of dual use appears to be less than 10% in the Swedish population of snus users. Dual use appears to mark a transitional period in tobacco use.

Among adult tobacco users, baseline dual users were most likely to transition to snus use or remain dual users; whereas among adolescents, approximately 38% of dual users transitioned to smoking (Galanti et al. 2008). Some evidence suggests slightly lower overall tobacco use among the dual tobacco users.

Recent cross-sectional studies in Sweden and Norway have reported the prevalence of dual use of cigarettes and snus from 2% to approximately 10%, depending on whether the criterion is daily dual use, or occasional dual use of one of the tobacco types. Dual use was more prevalent among males and those with low education. (Norberg et al. 2011).

Newly Identified Studies

Four cross-sectional studies reported the prevalence of dual use of cigarettes and snus among Norwegian and Swedish cohorts (Rodu et al. 2013, Rutqvist 2012, Kvaavik et al. 2014, Kvaavik et al. 2016). Three sources published by Norwegian and Swedish public authorities were identified that included information on the prevalence of dual use among their citizens (FHI 2013; FHI 2017; Folkhalsomyndigheten 2014a). According to Statistics Norway, in 2013-2015, the proportion of dual users among those aged 16-74 years old was 6% among men and 2% among women. Among younger adults aged 16-24 years old, 13% of men and 7% of women were dual users (FHI 2017). In a population-based study of 16-79 year-olds conducted in 2012 by SIRUS, the Norwegian Institute for Alcohol and Drug Research, 5% of the population were dual users (FHI 2013). The National Public Health Survey "Equal Health" in Sweden surveyed approximately 20,000 people aged 16-84. As expected, the proportion of women who reported daily dual use of cigarettes and snus was lower than reported by men (0.3% compared to 1.2% in 2016). Furthermore, the proportion of daily dual users appears to be dropping; in 2015, 1.2% of those surveyed by the "Equal Health" National Public Health Survey reported dual use, compared to 0.7% in 2016 (Folkhalsomyndigheten 2014a).

Based on data from the Northern Sweden MONICA study (Rodu et al. 2013), among men surveyed in 2004 and 2009, snus use dropped from 27% to 24% ($p=0.27$), and smoking (8.8%) and dual use (2%) in 2009 remained similar to the prevalence in 2004. Among the women surveyed, snus use prevalence dropped from 9% to 8% ($p=0.65$), but smoking and dual use prevalence decreased significantly to 11% ($p=0.005$) and 1% ($p=0.04$), respectively.

Another study in Sweden reported that 1.5% of males have regular dual use of cigarettes and snus and 0.2% of women have regular dual use weighed by age to correctly represent the national population, based on a nationally representative survey of 2,599 men and 3,409 women 18 years and older (Rutqvist 2012). Snus was the most frequent reported cessation aid among ever smoking males, who had made an assisted quit attempt at 22%. Of those who reported using snus at their latest quit attempt, 81% of males and 72% of females were successful quitters compared to about 50-60% for pharmaceutical nicotine and counseling.

In Norway, Lund and McNeill (2013) reported on the use behavior of 3,524 men between the ages of 16-74 collected between 2005-2010 during cross-sectional surveys. 6.8% of men currently used snus and cigarettes concurrently, and 1% reported daily consumption of both. More common dual use habits consist of daily use of one product and occasional use of the other. Among daily snus users, 21.6% were occasional smokers and 9.8% were daily smokers (Lund and McNeill 2013). Among dual users, 43.3% reported that the purpose of their snus use was to quit smoking. A significantly higher

proportion of daily snus users (53.6%) as compared with occasional snus users (34.1%) reported that the purpose of their snus use was to quit smoking. Among smokers with occasional snus use, smoking reduction (53.2%) and smoking substitution (55.6%) were significantly more prevalent reasons to use snus than smoking cessation, mirroring the pattern with all dual users.

Another study involving a nationally representative survey of 2010 and 2011 data on 8,700 participants, age 16-74 years from Statistics Norway reported that a higher proportion of occasional smokers used snus daily compared to daily smokers (17% vs. 3%, respectively) (Kvaavik et al. 2014). For studies that evaluated tobacco consumption among dual users, see section 6.4.3.

A repeated nationally representative cross-sectional survey in Norway reported that dual use among ever-snus users decreased from 2003-05 to 2012-15: 33% and 18.9%, respectively (Lund et al. 2017). A population-based cross-sectional study of over 13,000 women in Norway reported that ever-dual use was negatively associated with educational level and physical activity, which contrasted with the findings for those who used snus exclusively. Similar to exclusive snus use, ever-dual use was positively associated with alcohol consumption and number of lifetime sexual partners (Kvaavik et al. 2016).

Studies published since the 2014 MRTPA present similar statistics regarding dual use of snus and cigarettes. Women were less likely than men to use snus, and dual use was commonly cited as part of an attempt to reduce or quit smoking.

2.4.1 Youth behaviors

Summary from 2014 MRTPA

In Norway, Grotvedt et al. (2013) examined patterns of tobacco use among tenth graders living in Oslo County surveyed as part of the Oslo Health study (n=1395), with a three-year follow-up. The prevalence of dual use was 10%, 6% were snus users, and 13% smoked. Hamari et al. (2013) conducted a study among young male military recruits (n=1174) living in Northern Finland. The prevalence of daily snus use in this study was 15.6% (Hamari et al. 2013), which was higher than the rate (2.1%) observed in the general male population (Statistics Finland 2008). The authors found the prevalence of dual daily use of both snus and cigarettes to be 6.9%. Occasional smokers were twice as likely to be daily snus users than daily smokers, 30.1% vs. 15.1%. The authors concluded that concomitant snus use appeared to increase dependence on cigarettes in dual users, although the difference was not statistically significant. They also suggested that snus did not seem to serve as a substitute for cigarettes in adult daily smokers, but instead it served as an additional habit. This study has no information on duration of use and daily tobacco consumption.

In the BROMS cohort which followed students from approximately age 11 to age 19, cigarette use remained steady, at approximately 5-6%, two to three years post compulsory school (Galanti et al. 2001, Galanti et al. 2008, Lager et al. 2012). One-year follow-up revealed that among male baseline non-tobacco users (n=1,114), 1.7% became oral snuff users, 12.3% became cigarette smokers, and 5.7% became dual users by follow-up in the 6th grade. Among female non-tobacco users (n=1,185) by one-year follow-up, 1% became oral snuff users, 15.5% initiated cigarette smoking and 1.8% became dual tobacco users (Galanti et al. 2001). For both male and female non-tobacco users, snus-only initiation was lower than for smoking. Overall, compared with never users, ever users of tobacco

at baseline had a higher risk of continuing to smoke or to be smokeless tobacco users at the end of follow-up.

Newly Identified Studies

Three school-based cross-sectional studies and one cohort study in Sweden investigated the prevalence of and the lifestyle factors associated with dual use among adolescents (Tseveenjav et al. 2015, Pedersen and von Soest 2014, Lund and Scheffels 2014b, Lund and Scheffels 2016, Hedman et al. 2015). In Finland, a large (n=183,226) nationally representative school-based cross-sectional study reported that the proportion of current smoking among current snus users ranged between 65-79% for boys and 75-89% for girls (Tseveenjav et al. 2015). Overall, snus use was reported in 2% of the population surveyed, including all genders, schools, and ages.

In a population of 736 15-year-olds in Norway who were tobacco users identified during a school-based survey from 2005-2010 (response rate 73%), 41.5% of tobacco users were dual users. Dual use was more common among daily smokers (78%) than among daily snus users (59%). Daily dual use was reported by 8.2% of respondents and occasional dual use was reported by 14.4% (Lund and Scheffels 2016).

Early snus initiation was a risk factor for being a lifetime smoker according to data from repeated nationally representative cross-sectional studies in Norway; the adjusted odds ratio for being a lifetime smoker among those who initiated before 16 years of age was 2.8 ($p < 0.001$) (adjusted for age and gender) (Lund and Scheffels 2014b).

In a population of 16-17 year-old Norwegian adolescents surveyed in 2002 and 2010, those who used tobacco had more adverse socioeconomic backgrounds, less favorable school adjustment, and higher levels of other alcohol and cannabis use (Pedersen and von Soest 2014). Compared to daily snus users, daily smokers had lower school adjustment scores and used cannabis more. Comparing daily dual users with all other tobacco users among 736 15-year-old tobacco users in Norway, the odds of having gambling behaviors (OR=1.78 (95% CI 1.25-2.53)) and legal risk (OR=1.93 (95% CI 1.38-2.70)) were significantly greater ($p < 0.001$) for daily dual users (Lund and Scheffels 2016). In this publication, "legal risk" was defined as positive associations with having had sexual experiences that were regretted later and various difficulties in areas relating to the law. The odds of being male were non-significantly higher, as was "relationship risk", defined as positive associations with problems in close relationships, and also doing badly at school (Lund and Scheffels 2016). Furthermore, the occurrence of drinking episodes in the previous month was significantly higher among dual users compared to all other tobacco users: OR=1.06; 95% CI 1.00-1.13, $p < 0.05$ (Lund and Scheffels 2016).

According to a population-based cohort study wherein Swedish 14-15-year-olds were surveyed on tobacco use and other lifestyle choices, the prevalence of daily smoking and daily snus use were both significantly higher among those with smoking or snus-using parents, those living in an apartment, living in a single parent household, not participating in sports, and among those with lower parental SES (Hedman et al. 2015).

Two Swedish public reports captured dual use statistics among Swedish youth. In a survey of Swedish schoolchildren (aged 11, 13, and 15 years) with annual data from 2001/02 to 2013/14, the proportion of dual users was low and dropped among boys from 6% in 2001/02 to 3% in 2013/14

(Folkhalsomyndigheten 2014b). About 1% of girls reported using snus and smoking daily and has remained stable over the years (Folkhalsomyndigheten 2014b). Statistics Sweden (2016) collected data on dual use among 9th graders in 1985, 2000, and 2015. The prevalence of dual use peaked in 2000, with 17% of boys and 3% of girls reporting the habit. In 1985 and 2015, 1% of girls reported dual use of snus and cigarettes, and 8% and 4% of boys, respectively.

Newly identified studies presented similar gender-specific prevalence rates and smoking cessation intentions associated with dual use in recent years. The studies published since the 2014 MRTPA examined adolescents' dual tobacco habits and presented similar findings to those reported in 2014 including a higher prevalence of risky and negative behaviors among dual users. Snus use in Finland comprised 2% of those surveyed in a large school-based study and in a smaller study of 15-year-olds in Norway, dual use comprised 8.2%. Dual use in adolescents was more common among daily smokers than among daily snus users.

2.4.2 Transition patterns

Summary from 2014 MRTPA

Two authors examined transition patterns among adult dual users registered in the VIP cohort study (Lundqvist et al. 2009; Norberg et al. 2011). Of the total baseline of snus users who transitioned to smoking at the ten-year follow-up (6.1% males, 8.1% females), a majority of them were dual users, 5% males and 6.2% females (Norberg et al. 2011). In addition, among baseline smokers (n=1,104), 7.4% of men and 2.4% of women became dual tobacco users. Baseline smokers were most likely to become snus users or remain smokers; although, the authors reported that, for men, it was twice as common to stop smoking without becoming snus dependent than to switch to snus (Lundqvist et al. 2009). Furthermore, among dual tobacco users at baseline, a third of the men and a fourth of the women remained dual users at 10 years follow-up; baseline dual users were most likely to transition to snus use at follow-up (Norberg et al. 2011). The authors concluded that the increase in snus use was paralleled by a slight increase in dual use and that smoking prevalence does not appear to be influenced by snus. They concluded that dual use of cigarettes and snus appeared to be more frequent in Sweden with its high prevalence of snus use, and that it may contribute to continuation of smoking among some smokers.

In another follow-up study, Tillgren et al. (1996) examined the tobacco use patterns among participants aged 16-84 years in the Swedish Survey of Daily Living who responded in both 1980/81 and 1988/89. Most baseline mixed users (n=120) transitioned to snus use (31%) or remained mixed users (31%) at follow-up. The remaining 25% became cigarette smokers and 15% became non-tobacco users.

In a cross-sectional analysis, Furberg et al. (2005) assessed lifetime use or ever (daily or occasional) use of either snus and/or cigarettes. The authors found that compared to never snus users, the likelihood of being an ever smoker was lower among regular snus users (OR=0.2; 95% CI: 0.2 – 0.3) and "now and then" snus users (OR=0.5; 95% CI: 0.3 – 0.7). The literature includes other studies for which the primary purpose was not to describe dual use patterns. For example, in the Hergens et al. (2005) case-control study of myocardial infarction, of the 1,810 controls, 33% had never used tobacco, 5.2% were former smokers and current snus users and 3.3% used both forms of tobacco; however, less than 1% were former snus users and current smokers (Hergens et al. 2005).

Newly Identified Studies

In a Norwegian study of 6 pooled population-based cross-sectional studies from 2005-2010 that included data on 226 self-identified dual users, almost 75% of dual users started tobacco use with cigarettes (Lund and McNeill 2013). Less than a quarter of dual users began their tobacco use with snus. Transition to exclusive snus use was more common in those who initiated with snus use: more than half of snus initiators were exclusively snus users at the time of the survey (57.5%; 95% CI 46.2-68.8). However, a large proportion of those who initiated with cigarettes reported exclusive snus use at the time of the survey: 42.9% (95% CI 35.9-49.9) (Lund and McNeill 2013). Though these studies were population-based and captured data from over 3500 male participants between the ages of 16 and 74 years, the sample size of dual users was relatively small. Furthermore, the data was self-reported and due to the variable time in between survey and tobacco use start, potential recall bias is a limitation.

This study's findings are consistent with those published in the 2014 MRTPA in that the majority of dual users started tobacco use with cigarettes.

Transition patterns among youth

Summary from 2014 MRTPA

No clinical trials have been conducted among adolescent tobacco users. The gradual transition from smoking to snus observed in adults was not as apparent among adolescents. Experimentation with snus and smoking was common through teenaged years, with no inclination towards a tobacco type, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. Several authors emphasize the importance of psychosocial contributions which may impact an individual's decision to quit tobacco.

Grotvedt and colleagues (2013) grouped 16-year-old tobacco users into several sub-groups: occasional smokers with daily snus use, daily smokers with occasional snus use, those who used both products occasionally, and those who used both products daily. This categorization permitted the examination of patterns of use among dual users. Baseline snus users who were dual users at follow-up seemed to prefer using snus daily and cigarettes occasionally, OR= 7.42; 95% CI: 2.9 - 18.7, rather than daily smoking and occasional snus use (not significant) (Grotvedt et al. 2013). Likewise, baseline smokers who only became dual users at follow-up preferred to smoke daily and use snus occasionally. Overall, the results showed that for all tobacco users (whether daily or occasional users) who became dual users at follow-up, dual users were more likely to use either one of the products occasionally rather than to use of both products daily (Grotvedt et al. 2013). Compared to no tobacco use, snus use at baseline was associated with increased likelihood of dual use at follow-up (OR=3.49; 95% CI 1.8 to 6.8). Compared to snus-only users at follow-up, snus use at baseline was associated with increased likelihood of dual use at follow-up (OR=1.88; 95% CI 1.1 to 3.3). Additionally, baseline dual users had a high likelihood of remaining dual users (OR=9.28; 95% CI: 5.7-15.2) or becoming smokers only (OR=3.29; 95% CI: 1.8-6.0).

Galanti and colleagues assessed development of tobacco use among adolescents and young adults between the ages of 11 and 18 years participating in the BROMS cohort survey (Galanti et al. 2008). The study conducted six follow-up assessments to understand how the initiation of the use of snus, cigarettes or both led to the development of a tobacco habit. Assessment at follow-up showed that

69.5% (1,582) started by smoking cigarettes, 11.2% (256) by using snus, and 19.3% (439) started by using snus and cigarettes during the same year. Baseline mixed starters (i.e., users of snus and cigarettes) had a significantly higher risk for being a current smoker at follow-up (OR= 2.54; 95% CI: 1.68 – 3.91). In general, the risk of current smoking or tobacco use was significantly higher for mixed starters compared with snus starters.

Newly Identified Studies

Two observational studies, one of a Norwegian population and one of a Swedish population, reported on transition patterns among dual users (Pedersen and von Soest 2014; Joffer et al. 2014). Pedersen and von Soest (2014) conducted a school-based cross-sectional study of Norwegian 16-17 year-olds in 2002 and 2010, totaling 6,217 respondents. Due to the repetitive design, the trends in tobacco use are inferred. Daily smoking prevalence significantly decreased (23.6% in 2002, 6.8% in 2010, $p < 0.001$) and daily snus use prevalence significantly increased (4.3% in 2002, 11.9% in 2010, $p < 0.001$). The prevalence of dual use was 1% in both survey years. A significantly greater increase in the proportion of girls using snus from 2002 to 2010 was seen compared to the proportion of boys using snus over the same time period, suggesting that snus use was becoming more popular or accepted among adolescent girls. Less than 1% of girls and approximately 8% of boys used snus daily in 2002, which increased to 7.4% in girls and 16.1% in boys by 2010. Excluding non-tobacco users, significantly more ($p < 0.001$) snus was used on a non-daily or daily basis by non-daily smokers in 2010 (53.8%) than in 2002 (17.5%). The proportion of dual daily users among tobacco users remained similar (17.8% in 2002 and 15.2% in 2010) but the proportion of daily smokers who used snus daily or non-daily increased (31.8% in 2002 and 42.4% in 2010) (Pedersen and von Soest 2014). Overall, the prevalence of smoking (both daily and non-daily) decreased, while the relative proportion of non-daily smokers using snus tripled (Pedersen and von Soest 2014).

In a longitudinal study of Swedish adolescents aged 12-14 with follow-up at age 17-18, 8.1% had ever used snus at baseline and 37.5% had used snus at follow-up (Joffer et al. 2014). The study included students from three Swedish municipalities with 649 respondents to the follow-up survey. Snus use was more prevalent in boys than in girls, and boys also used snus more than cigarettes. Dual use increased with age: 2.8% of 12-14 year-old boys and 1.4% of 12-14 girls reported combined use (defined as smoking and ever-use of snus), and at age 17-18, 17.2% of boys and 19.1% of girls reported combined use. Based on multivariate logistic regression analysis, ever using snus was a significant independent predictive factor for smoking at follow-up: OR=3.43; 95% CI 1.78-6.62.

The newly identified studies support the findings reported in the 2014 MRTPA. Snus use was more prevalent among boys, and dual use increased with age. Those who used snus either experimentally or habitually were more likely to smoke later in life.

2.4.3 Tobacco consumption (amount of cigarettes and STPs used)

Summary from 2014 MRTPA

Actual tobacco consumption among dual users is often not reported or quantified. There is evidence that smokers who use snus smoke fewer cigarettes per day or smoke less often in a specified period than smokers who do not use snus.

Evidence also suggests that tobacco consumption among dual tobacco users may be different from exclusive users of either product with respect to the amount of product used (Galanti et al. 2008; Gilljam and Galanti 2003; Rodu et al. 2002), and that dual users consume less tobacco than exclusive snus or cigarette users. In one study (Rodu et al. 2002), exclusive snus users reported average daily consumption of 0.41 packages among ex-smokers and 0.44 packages among never smokers. With regard to smoking, ex-snus users averaged 15.1 cigarettes daily and never users of snus smoked 16.0 cigarettes. In comparison, dual users consumed 0.25 packages of snus daily, about 40% less and smoked an average of 10.8 cigarettes daily, about 30% fewer (Rodu et al. 2002). Digard et al (2009) also investigated the frequency of cigarette use among daily snus users; all daily snus users who also smoked reported doing so at least once per week, and 53.5% of them did so daily. In the Malmö study, Janzon and Hedblad (2009) reported that the male dual users smoked significantly fewer cigarettes per day (12.3) than exclusive smokers (16.1 cigarettes per day). This was also observed among female dual users, who smoked on average 7.8 cigarettes per day compared to 12.9 cigarettes per day among exclusive smokers.

Similarly, Gilljam and Galanti (2003) reported that the proportion of current smokers smoking fewer than 10 cigarettes/day was nearly twice as high among users of snus than among non-users (44% versus 24%, respectively) (Gilljam and Galanti 2003).

Some evidence suggests slightly lower overall tobacco use among the dual users. One study reported that pouched snus users had a slightly higher prevalence of cigarette smoking compared to users of loose snus (Digard et al. 2009). Taken together, among adults and adolescents, the range of dual use appears to be less than 10% in the Swedish population of snus users and appears to mark a transitional period in tobacco use. Among adult tobacco users, baseline dual users were most likely to transition to snus use or remain dual users—whereas among adolescents, 38% of dual users transitioned to smoking. (Galanti et al. 2008).

Youth Behavior

Tobacco consumption among adolescents in the BROMS cohort was not significantly different among snus, cigarette, and mixed starters (Galanti et al. 2008). Similar results were also observed in the Finnish study of male military recruits (Hamari et al. 2013). However, mixed starters were over-represented in the highest category of tobacco consumption of 85 or more cigarettes and/or snus portions per week.

Newly Identified Studies

Five new studies reported findings regarding tobacco consumption among dual users (Lund and McNeil 2013; Lund et al. 2017; Kvaavik et al. 2014; Leon et al. 2016, Lund et al. 2014). A pooled population-based cross-sectional study (Lund and McNeil 2013) found that dual users of cigarettes and snus in Norway reported lower consumption of cigarettes (56.6 cigarettes/week, SD 53.86, n=226) than smokers who quit snus (79.6 cig/week, SD 61.47, n=108) and smokers with never-snus use (80.2 cig/week, SD 55.86, n=621). Among occasional snus users, a greater proportion smoked daily: 15.6% were occasional smokers and 40.9% were daily smokers. 43.3% of dual users (n=238) reported that the purpose of their snus use was to quit smoking and a greater percentage of daily snus users cited snus use for quitting smoking (53.6%, n=112) than of those who were occasional snus users (34.1%, n=126). Another study involving a nationally representative survey of 2010 and 2011 data on 8,700

participants, age 16-74 years from Statistics Norway reported that a higher proportion of occasional smokers used snus daily compared to daily smokers (17% vs. 3%, respectively) (Kvaavik et al. 2014).

Another nationally representative cross-sectional survey consisting of over 2,000 male ever-snus users from 2003-2015 also reported that dual users consumed fewer cigarettes than non-dual users (Lund et al. 2017). The average number of cigarettes smoked per week was significantly lower among dual users (57.0 cigarettes/week) than among current smokers who never used snus (80.9 cig/week) and current smokers who had quit snus (79.6 cig/week). Furthermore, a greater proportion of dual users (29.7%) reported that they had reduced from daily to occasional smoking than the proportion among current smokers who never used snus (14.6%) or who had quit snus (17.2%) (Lund et al. 2017). One study reported no significant difference in the number of cigarettes per day between snus users (13.3 cigarettes/day) and non-snus users (12.9 cigarettes/day) (Leon et al. 2016). However, this study had a smaller sample size of survey participants compared to the other studies cited above.

Lund and colleagues (2014) collected information from 3,401 exclusive cigarette smokers, 885 exclusive snus users, and 566 dual users of cigarettes and snus who responded to a survey stemming from a postal database in Norway. Exclusive smokers consumed 48% more cigarettes (as measured in grams per week) than dual users. Compared with dual users, the consumption of snus was 87% higher in exclusive snus users (Lund et al. 2014).

Similar to the findings from the 2014 MRTPA, three new studies reported that dual users tended to smoke fewer cigarettes than smokers not currently using snus. No new information related to youth behaviors was identified since the 2014 MRTPA.

2.5 Likelihood that users who may have otherwise quit using tobacco products will instead use snus

Summary from 2014 MRTPA

The clinical trials in which snus use was specifically used for smoking cessation support resulted in a success rate roughly equivalent to that of other NRTs. The available studies indicate that snus has been used more often than NRTs by Scandinavian males as an aid for smoking cessation, and that being a former smoker is common among snus users. These data have consistently shown that male snus users are more likely to quit smoking than smokers who do not use snus. The data also indicate that some smokers initiate use of snus specifically to aid in smoking cessation, and that they go on to successfully quit smoking. The SCENHIR report concluded that “observational data from Sweden indicate that snus has been used more often than pharmaceutical nicotine products by some men as an aid to stop smoking.” The data are consistent in demonstrating these male snus users are more likely to quit smoking than non-users (Lund et al. 2010; Lund et al. 2011; SCENIHR 2007; SCENIHR 2008). Subsequent clinical trials and two meta-analyses in Norway on the use of snus as a smoking cessation tool support this conclusion (Fagerstrom et al. 2012; Joksic et al. 2011; Lund et al. 2010; Lund et al. 2011; Sharp et al. 2008).

A number of observational studies reported evidence suggesting that snus is a fairly effective smoking cessation tool. However, causal inferences are not possible from the cross-sectional studies cited above. The temporality of exposure and cessation outcome is unknown and, in most cases, data on smoking cessation were self-reported and not biologically verified. In addition, the definition of tobacco-use categories varies across studies making it difficult to measure success rates for smoking

cessation. Moreover, several authors have discussed the importance of psychosocial contributions to smoking cessation and their impact on an individual's decision to quit tobacco.

Newly Identified Studies

Snus used with intent to quit smoking

Three studies investigated the proportion of people who used snus with the intent to quit smoking (Lund and McNeill 2013; Lund et al. 2017; Rutqvist 2012; Sohlberg 2015). Over half (53.6%) of dual users with daily snus use reported that the purpose of snus use was to quit smoking in a group of Norwegian men surveyed between 2005-2010 (Lund and McNeill 2013). The majority of dual users reported definitely or probably being smoke-free five years into the future: 74.4% (95% CI 68.8-80.0). The proportion of exclusive smokers reporting a similar intent to be smoke-free in five years was smaller: 61.3% (95% CI 57.6-65.0, n=658). Among those who smoked with occasional snus use (n=126), harm reduction strategies like smoking reduction (53.2%) and smoking substitution (55.6%) were significantly more prevalent reasons to use snus compared to attempting to achieve complete cessation of smoking (34.1%) (Lund and McNeill 2013). A second Norwegian study of repeated nationally representative cross-sectional surveys from 2003-2015 reported a significantly higher proportion of dual users (43.8%) affirming that they would definitely be smoke-free in five years than that of current smokers who had never used snus (32.2%) (Lund et al. 2017). However, when the question was posed for a shorter timeline (quitting smoking within 6 months), there was no significant difference in the proportion with the intent to quit in dual users (45.8%) compared with current smokers with no snus use (43.1%) (Lund et al. 2017).

These studies support the conclusions made in the 2014 MRTPA: that snus is commonly and intentionally used as a smoking cessation aid, particularly among male smokers.

Successful quitting

Several studies have presented evidence that snus use is more commonly linked with successful attempts in smoking cessation as opposed to other cessation tools, especially in men (Lund et al. 2017; Rutqvist 2012; Lund and Lund 2014; Lund et al. 2014; Ramstrom et al. 2016). In a survey of 2,067 male ever-snus users in Norway, 75.4% of dual users had utilized snus in their latest quit attempt. Among snus users who had successfully quit smoking, 82.7% reported using snus in the most recent quit attempt (Lund et al. 2017). When considering both genders together in an annual, nationally representative Norwegian survey (n=1,850 ever-smokers), snus was the most common aid (20.9%) followed by pharmacological nicotine products (14.8%) (Lund and Lund 2014). Overall, women were significantly more likely ($p < 0.001$) to attempt quitting without an aid (78%) than men (68%) based on a population-based sample of over 6,000 people in Sweden surveyed between 2008 and 2009 (Rutqvist 2012). In this large Swedish study, snus was reported to have helped "to a great extent" or "to some extent" in 77% of those who successfully quit smoking. Those who used snus as a smoking cessation aid had the greatest proportion of successful quitters: 81% of men and 72% of women (nonsignificant between genders, $p > 0.05$). Only 50-60% of people who used other cessation aids like pharmaceutical nicotine and counseling reported successful quitting of smoking (Rutqvist 2012). Rutqvist (2012) also reported that there was no difference in snus use for smoking cessation between the ages of 18-64; it ranged between 28-31%. However, only 13% of those in the oldest age group (65+ years) used snus to help quit smoking. Snus tended to be more popular as a quitting aid

among younger women than older women (4-12% of those aged 18-29, 30-44, and 45-54 years vs 2% in those aged 55-64 and 65+ years). One study of Norwegians reported a greater mean number of quit attempts among dual users (3.0, SD 6.0) than among exclusive smokers (2.8, SD 4.6) and exclusive snus users (1.3, SD 3.0) (Lund et al. 2014). In Lund and Lund's (2014) study of every-daily Norwegian smokers over 2003-2013, the daily smoking quit ratio (calculated as the number of former smokers out of the total number of ever-smokers) was significantly higher ($p < 0.001$) among those who used snus daily than among those who never used snus: 74.8 (95% CI 72.8-76.8) and 52.3 (95% CI 51.4-53.2), respectively.

These studies show that snus use is commonly linked with success in quitting smoking, consistent with findings presented in the 2014 MRTPA.

Gender differences in snus use and cessation

Based on an annual cross-sectional survey, Lund and Lund (2014) reported that 33.8% of men who had attempted to cease smoking used snus as a method but only 8% of women who tried to quit used snus. In a nationally representative sample of Swedish former daily smokers who had successfully quit for at least one year, 35.1% of men and 9% of women ($p = 0.000$) used snus in the cessation process (Sohlberg 2015). In a large Swedish cross-sectional study, 63% of men who used a smoking cessation aid during a quit attempt used snus compared to 22% of women that did so. Larger proportions of women utilized counseling (36%) or pharmaceutical nicotine (gum 35%, patch 22%) than snus (Rutqvist 2012). Among men who successfully quit smoking, the proportion who used snus was significantly larger than those who used other methods ($p < 0.001$) (Rutqvist 2012). Ramstrom and colleagues (2016) reported very similar proportions in successful smoking cessation attempts in men (snus only 64%, nicotine gum 12%, patch 7%) and women (snus only 20%, nicotine gum 33.8%, patch 17.7%) in their population-based Swedish study of daily tobacco users.

Consistent with findings presented in the 2014 MRTPA report, multiple studies reported that men were significantly more likely to use snus in the cessation process (Sohlberg 2015, Rutqvist 2012, Lund and Lund 2014).

Snus use among former/current smokers

The successful use of snus as a smoking cessation aid has become more prevalent in recent years, as reported in three observational studies (Lund et al. 2017; Lund and Lund 2014; Sohlberg 2015). In a nationally-representative cross-sectional study of Norwegian males in 2003-05 and repeated in three-year periods until 2012-15, the prevalence of current snus users who had quit smoking increased from 14.5% to 25.1% by 2012-15. However, the proportion of men who had quit both snus and smoking remained stable at around 11% over the repeated surveys. Another reflection of snus use becoming more popular and cigarettes less so: the proportion of men who continued to smoke but quit using snus decreased over time from 22.4% (95% CI 18.7-26.1) in 2003-05 to 8.1% (95% CI 6.2-10.1) in 2012-15 (Lund et al. 2017). Based on market data in Norway, the prevalence of daily or occasional smoking among 16-30 year-old men was 50% in 1985 and 21% in 2013 and the prevalence of snus use increased from 9% to 33% (Lund and Lund 2014). Regardless of gender, it was common for individuals to continue to use snus after quitting smoking, though men were significantly more likely to continue to use snus after quitting smoking ($p = 0.000$): 52.5% of men and 39.3% of women who had been smoke-free for at least one year at the time of survey (Sohlberg 2015).

Four studies explore the phenomenon that snus use is common among former or current smokers, and even more common among male tobacco users (Leon et al. 2016; Rodu et al. 2013; Ramstrom et al. 2016; Kvaavik et al. 2016). In a nationally representative sample of 1,000 Swedes, snus use was more common in current (16.6%) or former smokers (18.3%) than in those who never smoked (8.7%). Current and former smokers were also more likely to be current users of snus compared with never smokers: OR=1.96 (95% CI 1.15-3.34) and OR=2.67 (95% CI 1.66-4.29) (Leon et al. 2016). In another Swedish cross-sectional study (Rodu et al. 2013), 52% of men who quit smoking had ever used snus whereas 19% had never used snus. The proportion of snus use among women who had quit smoking was predictably lower with 21% having ever used snus and 51% never used snus (Rodu et al. 2013). Furthermore, the proportion of male smokers who take up secondary daily snus use is increasing, evidenced by nationally representative longitudinal data over the decades (Ramstrom et al. 2016): 34% in the 1940s birth cohort, 41% in the 1960s birth cohort, and 46% in the 1980s birth cohort. Snus use was also linked to smoking cessation success in this population, regardless of birth cohort. Among men and women who began secondary daily snus use, a large majority completely quit smoking (76.3% of men, 86.4% of women), with some quitting tobacco altogether (31.5% of men, 28.6% of women) (Ramstrom et al. 2016). Among those who did not take up secondary daily snus, smaller proportions completely quit smoking (55.3% of men, 53.6% of women). A large population-based study of Norwegian women reported that among older women (up to 45 years of age) most snus users were former smokers or dual users; the proportion of former smokers among current snus user generally increased with increasing age: 15.5% of 18-19 year-olds, 26.5% of 20-29 year-olds, 45.9% of 30-39 year-olds, 40.2% 40-45 year-olds. (Kvaavik et al. 2016).

Consistent with findings presented in the 2014 MRTPA, snus use is commonly used as an effective smoking cessation aid, with increasing prevalence during recent years. Former or current smokers frequently use snus, and it is more common among male tobacco users than females. One large set of longitudinal data of Swedes reported that over three-quarters of smokers who picked up snus as a secondary daily tobacco product completely quit smoking. Among those who tried to quit smoking without the aid of snus, only half were successful (Ramstrom et al. 2016).

2.5.1 Youth behaviors

No new studies regarding smoking cessation in youth were identified since the 2014 MRTPA.

Summary from 2014 MRTPA

No clinical trials investigating snus use as a smoking cessation aid have been conducted among adolescent tobacco users. Several cohort studies have evaluated youth tobacco use behaviors, but overall, smoking cessation was not evaluated or was not a priority among the youth populations studied in the publications described in the 2014 MRTPA. Experimentation with snus and cigarettes was common through teenage years, without an inclination towards a tobacco type, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. Overall, both cigarette only and snus only users at baseline were more likely to remain in their baseline category or become a mixed user (Galanti et al. 2001). In another study of male youth, Grotvedt et al (2013) examined patterns of tobacco use among 16-year old Norwegian students (n=1,440) followed for three years. In this cohort, baseline smokers were more likely to remain smokers or become dual users at follow-up, while the likelihood of switching from smoking only to snus only were not significant (OR=1.53; 95% CI: 0.71 - 3.31).

2.6 Likelihood that consumers will use snus as intended or designed

No new studies investigating correct consumer use of snus were identified since publication of the 2014 MRTPA.

Summary from 2014 MRTPA

Understanding the frequency, amount, and duration of snus use and the degree of variability among individuals and trends over time is an important part of examining STP use and the potential health effects of snus. However, there are inconsistencies among the studies as to the manner of information collection, the units of time, and the frequency of use. The most common method of snus use is to deposit one to two grams of loose product or a pouch of pre-portioned packaged snus in the vestibular area inside the upper lip (Andersson 1991); Digard and colleagues (2009) reported that 96% of pouched users and 99% of loose snus users placed the snus at that site, though approximately one-third of pouched users and one-fifth of loose snus users move the portion around the mouth during use.

The most recent and comprehensive assessment of Swedish snus exposure patterns was reported by Digard and colleagues (2009). The authors conducted a telephone survey of daily snus users to quantify tobacco consumption among 2,914 snus users between the ages of 18 and 72 years and reported that female snus users (n=359) were more likely to use pouched snus (92.8%) than loose snus (6.4%) and 0.8% used both. Snus use among males (n=2,555) was more evenly distributed, as 54% reported pouched snus use, 42.1% used loose snus and a minority reported use of both. Both men and women consumed about 30 grams of snus regardless if it was in packages or portions. The length of time using snus per day was, on average, 12.7 hours for men and 14.6 hours for women and the average length of time in mouth was longer for men (69.6 minutes) than for women (56.1 minutes) (Digard et al. 2009). There was an increase in the prevalence of the use of packaged snus in this study compared to a 1992 report (date of data collection unknown) which indicated that 73% of snus users consume only loose snus, 13% only snus pouches, and 14% use both (Svenska Tobaks AB, Basdata om tobakskonsumtion 1992, TEMO AB, reported by Andersson et al. 1994).

The Norwegian Tobacco statistics reported average consumption of 9.5 pinches of snus per day for daily Norwegian snus users, and 3.6 pinches per week for occasional users (Lund and Lindbak 2007). A pinch is typically considered 2.5 grams; using this conversion, the average consumption for Norwegian snus users was 23.75 g/day. The authors noted that it was extremely difficult to measure self-reported consumption of snus, both because it can be difficult to remember and because the size of a pinch may vary. The authors reported that, as of 2003, the loose form of snus was used by 63% of the Norwegian male snus users, and the remainder used portioned snus. By 2006, the type of snus used was more evenly divided between loose snus and portioned snus. However, those who used snus daily were typically loose snus users (70%).

The amount of snus use reported in other studies is highly variable though the results are generally consistent with those observed more recently by Digard et al (2009).

2.7 Dependence in Swedish snus users

No new studies were identified since publication of the 2014 MRTPA.

Summary from 2014 MRTPA

Most forms of tobacco use may result in dependence, likely because of their nicotine content, and STPs such as Swedish snus are no exception. The broad range of different methods to assess dependence of products containing tobacco along with difficulties in comparing dependence between product categories, and the paucity of such studies of users of STPs, make an overall conclusion on Swedish snus and dependence difficult. However, the data reviewed herein would indicate that, for a number of reasons (e.g. "fewer behavioral components", different nicotine delivery profile, and components with addictive potential other than nicotine in tobacco smoke) dependence in users of Swedish snus is probably less than the dependence to cigarettes.

Clinical trials indicate that Swedish snus as well as some novel snus-like products generally are associated with a somewhat faster absorption of nicotine than that from pharmaceutical gum, and a corresponding faster onset of subjective symptoms. Although because of the oral route of administration, nicotine delivery to the brain can never be as fast with Swedish snus as with cigarette smoking. The SCENIHR Report (SCENIHR 2008) posited that the speed of delivery of nicotine to the brain was an important determinant of dependence. Given the difference in nicotine delivery with cigarettes compared to STPs, the committee hypothesized that non-inhaled forms of nicotine delivery to be proportionally less addictive than inhaled tobacco smoke.

This assumption of less dependence with STPs compared to cigarettes smoke is supported by observations from clinical trials. There is probably a "continuum of dependence" from cigarettes (high dependence) to pure nicotine (NRT, low dependence). The dependence to Swedish snus is probably intermediate between the two (Fagerstrom and Eisenberg 2012).

3. EFFECT ON TOBACCO USE INITIATION AMONG NON-USERS

A critical population health consideration under section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C Act is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users (including never users and former users). An MRTPA must contain scientific evidence regarding the effect the product and its marketing will have on increasing the likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application.

These studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

- The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco products;
- The likelihood that non-users who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk; and
- The likelihood that former users of tobacco products will re-initiate use with the tobacco product.

Six new studies that investigated Swedish snus use initiation among non-tobacco users were published since the 2014 MRTPA as of July 28, 2017 (two publications focusing on a Swedish population: Leon et al. 2016 and Ramstrom et al. 2016; and four publications with a Norwegian population: Kvaavik et al. 2016, Lund and McNeill 2013, Lund and Scheffels 2014b, and Lund et al. 2017).

3.1 Likelihood that non-users, particularly youth and young adults, will initiate use of the tobacco product

Summary from 2014 MRTPA

Several studies focused on snus uptake, some of which focus specifically on adolescents (Edvardsson et al. 2009; Galanti et al. 2001; Galanti et al. 2008; Ramström and Foulds 2006). Tobacco uptake is often initiated at an early age. Smoking is generally initiated between 10 and 13 years of age, with a rapid increase occurring between the ages of 14 through 15 years (Edvardsson et al. 2009; Furberg et al. 2008; Galanti et al. 2008). Adolescent males surveyed as part of the BROMS cohort initiated snus at the median age of 15 years; while females exhibited snus use at 18 years (Galanti et al. 2008). Overall, snus uptake seems to occur between ages 15 through 18 years (Furberg et al. 2008; Post et al. 2010; Wium and Aaro 2011). In Sweden and Norway, uptake of snus occurred across all age categories compared to cigarette uptake which appeared to occur more frequently at a younger age. In addition, tobacco initiation was shown to be gender-dependent, as males were more likely to initiate snus while females more likely to initiate cigarette smoking. Studies in Sweden and Norway have shown that snus initiation was more prevalent among former cigarette smokers than among non-tobacco users (Furberg et al. 2005; Furberg et al. 2006; Lund et al. 2010; Lund et al. 2011).

Newly Identified Studies

Five new studies reported findings regarding the likelihood that non-users will initiate snus use (Lund and McNeill 2013, Lund et al. 2017, Leon et al. 2016, Kvaavik et al. 2016, Ramstrom et al. 2016).

Though snus has gained popularity in recent decades, the majority of individuals with dual use in a Norwegian pooled cross-sectional study surveyed between 2005-2010 began tobacco use with cigarettes (75%) compared to snus use (24%) (Lund and McNeill 2013). In the repeated nationally representative cross-sectional surveys (Lund et al. 2017, described above in section 2.1.1: Swedish Usage Rates) snus use increased among never-smokers. From the period 2003-2005 to 2012-2015, current snus users/never smokers among ever snus users increased from 16.0% to 24.9%. The linear trend was a 6.2% increase per year in snus use. The linear trend of never smokers who were former snus users was 10.1% per year over the period of the study. Increases in snus uptake among never smokers was seen in later years: 36.6% of ever-snus users in 2012-15 compared to 21.2% in 2003-05. The majority of those surveyed who had lifetime use of tobacco had initiated use with cigarettes: 67.6%-77.4% initiated with cigarettes and 19.6%-29.8% initiated with snus (Lund et al. 2017).

Leon and colleagues (2016) reported that the mean age at beginning regular snus use was 23.6 years (23.1 years for men and 26.1 years for women) based on a nationally representative cross-sectional survey in Sweden. Two observational studies reported that the average age of initiating tobacco use with snus increased with current age of individuals surveyed; i.e., initiating tobacco use with snus was more common in recent decades and younger birth cohorts (Kvaavik et al. 2016, Ramstrom et al. 2016). Kvaavik and colleagues (2016) focused on snus trends in over 13,000 Norwegian women, reporting that 18-19-year-old daily users, on average, started snus around age 16. In contrast, among 40-45-year-old daily users, the average age at snus initiation was 34 years. In the group of women surveyed, the average age at initiation of regular smoking was under 19 years for all age groups and under the average age of snus initiation at every age group surveyed. Ramstrom and colleagues (2016) had a robust dataset of over 60,000 Swedish adults born in the 1940s and later from the Swedish "Your Country and Your Life" longitudinal survey. Among boys, a larger proportion initiated tobacco use with snus compared with the proportion of girls through the decades. Only a very small proportion of girls initiated tobacco use with snus through the decades, with slightly more in the 1970s and 1980s birth cohorts. This overall increase in snus use was accompanied by a decline in primary initiation of smoking; the proportion of those who initiated tobacco use with smoking dropped through the decades, with greater proportions among girls than among boys (since a greater proportion of boys initiated with snus). Among boys, 55% of the 1940s birth cohort initiated with smoking and 10% initiated with snus. In the more recent 1980s birth cohort of boys, 18% initiated with smoking and 30% initiated with snus (Ramstrom et al. 2016). Overall, there were fewer tobacco users in recent years compared with the 1940s birth cohort (Ramstrom et al. 2016).

Two qualitative focus group studies (Edvardsson et al. 2012, Scheffels and Lund 2017) reported on adolescents' reasons for starting snus use. Edvardsson and colleagues (2012) interviewed 27 regular snus users aged 17-19 years old about the views, attitudes, opinions, and arguments regarding snus use. Snus use was cited as a masculine habit and Swedish pastime, linking adolescent boys to their identities as Swedish men. The group of girls interviewed noted that they used snus partly to convey independence and make them different (Edvardsson et al. 2012). The second focus group study interviewed 35 tobacco users and non-users aged 15-17 years old. In these interviews, the non-users speculated that the wide variety in brands and attractive packaging could lead other non-users to try snus (Scheffels and Lund 2017).

As reported in the 2014 MRTPA, snus uptake is more frequent among younger populations, and males are more likely to initiate tobacco use with snus. The newly identified studies also reported an increase

in snus uptake in recent years, regardless of age or gender. Furthermore, the proportion of snus users who had never smoked has increased and more women are taking up snus compared to previous decades.

3.2 Likelihood that non-users who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk

Summary from 2014 MRTPA

Longitudinal and cross-sectional studies conducted on snus use in Sweden and other Scandinavian countries provide little evidence that prior snus use leads to daily cigarette smoking among adults. Rather, these studies show that, as compared to non-tobacco users or those who start using tobacco as smokers, snus use is associated with a reduced risk of becoming or continuing to be a regular cigarette smoker, demonstrating an inverse relationship between snus use and the initiation of cigarette smoking. Longitudinal studies also provide evidence that smokers tend to transition from cigarettes to snus rather than switching from snus use to cigarette smoking. Studies of adolescents in Sweden, Norway and Finland showed that (i) baseline snus use was not a precursor to exclusive cigarette smoking and (ii) tobacco initiation with snus or current snus use was not a predictor of future cigarette smoking. According to the 2007 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) report, "the Swedish data, with its prospective and long-term follow-up do not lend much support to the theory that smokeless tobacco (i.e. Swedish snus) is a gateway to future smoking." Several additional studies published since the SCENIHR report supports this conclusion. (Grotvedt et al. 2013; Lundqvist et al. 2009; Stenbeck et al. 2009).

Using the Swedish Level of Living Survey (ULF) from 1988-89 and 1996-97, Stenbeck et al. (2009) reported that, compared to non-snus users at baseline, younger participants who were considered "snus beginners" and those who were consistent snus users were more likely to stop smoking compared to those who initiated with smoking. Among older participants and compared to non-snus users, those who began snus use in the follow up period had nearly equal odds of either initiating or quitting cigarette smoking (OR=8.2 vs. 6.6). Snus use during follow-up in the 1990s was associated with a greater incidence of smoking cessation than smoking initiation. Smokers who started using snus were much more likely than non-snus using smokers to quit smoking.

Several cross-sectional studies on the relationship between snus use and cigarette smoking support some of the findings observed in the longitudinal studies (Furberg et al. 2005; Ramström and Foulds 2006). Furberg et al. (2005) evaluated the association between snus use and subsequent smoking initiation among adult males as part of the Swedish SALT twins study. Men who had used snus before they started smoking were compared to men who had never used snus in relation to any lifetime smoking while adjusting for age and other variables associated with smoking initiation. Results from this study suggested that "regular" and "now and then" snus use was inversely associated with smoking initiation. Ramstrom and Foulds (2006) analyzed retrospective data from a cross-sectional survey completed by adult males participating in the Sweden Your Country and Your Life national survey. This data showed that male primary snus users had a decreased likelihood of initiating smoking compared to non-snus users (OR= 0.28; 95% CI: 0.22 - 0.36). The authors concluded that the likelihood of initiating daily smoking was significantly lower for those who had started using snus than for those who had not. Among primary snus users who started secondary smoking (potential

gateway subjects), 74% later ceased daily smoking, 56% returned to exclusive daily snus use and 18% had, by the time of the survey, quit tobacco use altogether.

Newly Identified Studies

One longitudinal cohort study and one cross-sectional study reported here investigated the likelihood of never-smoking snus users of switching to smoking later on (Ramstrom et al. 2016; Lund et al. 2017). Ramstrom and colleagues (2016) analyzed a cohort of almost 29,000 Swedes surveyed in a nationally representative long-term study from 2003-2011 ("Your Country and Your Life") with daily tobacco use (either cigarettes or snus or both, paired with or without occasional use of the other product). Those with primary snus use were much less likely to initiate daily smoking than those who had secondary snus use. This trend was seen in both men [17.6% of primary snus users (95% CI 16.4%-18.6%) vs. 45.9% of non-primary snus users (95% CI 45.3%-46.5%)] and in women [8.2% of primary snus users (95% CI 5.8%-10.5%) vs. 40.2% of non-primary snus users (95% CI 39.7%-40.7%)]. In total, 11,557 men initiated daily smoking, and 7.6% (95% CI 7.1-9.10) reported daily smoking initiation following daily snus use. Among the 12,798 women who ever initiated daily smoking, <0.1% began daily smoking from primary daily snus use (Ramstrom et al. 2016). Furthermore, among men, the proportion of primary snus users becoming smokers decreased through the decades: 22.8% among the 1950s birth cohort and 14.3% in the 1980s birth cohort (Ramstrom et al. 2016). Data from repeated cross-sectional studies of Norwegian men aged 15-79 years from 2003-2015 showed that those who used snus before cigarettes were in the minority. The marginal mean probability of having used snus before cigarettes among dual users was 25.7%, whereas the probability of having used cigarettes before snus was 70.3%. This trend in order of tobacco product uptake was seen in all groups: current snus users who used to smoke, current smokers who formerly used snus, and former users of both products (Lund et al. 2017).

Similar to the findings presented in the 2014 MRTPA, the proportion of snus users who picked up smoking habits among snus users was small compared to the proportion of smokers who then added snus use as a habit. Furthermore, those who started daily tobacco use with snus had a lower probability of acquiring a daily smoking habit compared to those who did not initiate daily tobacco use with snus, based on data from the nationally representative longitudinal study "Your Country and Your Life" 2003-2011 in Sweden (Ramstrom et al. 2016).

3.2.1 Youth Behaviors

Summary from 2014 MRTPA

Galanti and colleagues (2001; 2008) assessed tobacco initiation among adolescents between the ages of 11 and 18 years in 5th grade through three years post-compulsory school (n=2,938). At one-year follow-up (6th grade), the authors reported that 36% of baseline snus (referred to as snuff) users (n=52) had also smoked while the others remained snus-only users; among baseline cigarette smokers (n=419), 18% used snus at follow-up (Galanti et al. 2001). The authors reported that, compared to non-tobacco users, baseline snus users were not more likely to become cigarette smokers at follow-up (OR=1.95; 95% CI: 0.96-3.8); and that exclusive cigarette users (OR=2.89; 95% CI: 2.25-3.71) and mixed starters (OR= 4.81; 95% CI: 3.09-7.5) were more likely to smoke cigarettes at the end of follow-up. The likelihood of being a current smoker at end of follow up was higher, but not significantly so, for cigarette starters compared with snus starters (OR=1.42; 95% CI: 0.98-2.1), and those who were mixed starters (cigarette and snus) were more likely to smoke at

follow-up (OR=2.54; 95% CI: 1.68–3.91) (Galanti et al. 2008). Among Finnish students participating in a 3-year longitudinal study, boys who had tried snus but were not regular smokers in 7th grade had a higher risk for smoking in 8th grade. Experimenting with snus in 8th grade predicted weekly smoking at the start of 9th grade (Haukkala et al. 2006). The impact of snus experimentation upon later smoking experimentation was smaller than vice versa which the authors attributed to the greater prevalence of smoking experimentation than snus experimentation (Haukkala et al. 2016). Another longitudinal study of Norwegian 16-year-old boys reported that baseline snus use was not associated with increased likelihood of smoking only at follow-up after adjusting for “previous smoking” experience (Grotvedt et al. 2013). Grotvedt and colleagues (2013) concluded that snus use at baseline increased the risk of being a dual user.

Newly Identified Studies

One set of repeated cross-sectional studies investigated snus use in youth and the adoption of smoking after snus initiation (Lund and Scheffels 2014b). Those who began snus use in early adolescence (aged 16 years or younger) were more likely to smoke later in life (Lund and Scheffels 2014b). Based on data from annual repeated nationally representative surveys in Norway, 5.9% of late snus initiators were current smokers compared to 22.9% of early snus initiators (Lund and Scheffels 2014b). The unadjusted odds ratio of being a lifetime smoker was 3.1 ($p < 0.001$) among those who began using snus (experimental use or more frequently) before the age of 16. The unadjusted odds ratio was 2.3 ($p < 0.001$) among those who began using snus at age 20 years or earlier. This trend remained after adjustment for age (Lund and Scheffels 2014b).

This study adds additional evidence that those who began snus earlier were more likely to be smokers later on, though the overall picture is mixed, with other studies showing no increased likelihood of snus users becoming a smoker compared to non-users of tobacco at baseline.

3.3 Likelihood that former users of tobacco products will re-initiate use with snus

Summary from 2014 MRTPA

The clinical trials in which snus use was specifically used for smoking cessation support resulted in a success rate roughly equivalent to other NRTs. However, since there was no long-term follow-up beyond the 6-month trial, relapse rates are unknown. Data from Scandinavian cohorts have further shown that being a former smoker is common among snus users (Lund et al. 2010; Lund et al. 2011; SCENIHR 2008; Scheffels et al. 2012), although there is some suggestion that there are low rates (5%) of relapse among former smoking snus users (Lundqvist et al. 2009). Additional evidence that former tobacco users are not likely to re-initiate tobacco use or purchase products based on modified risk claims comes from the Swedish Match Consumer Perception Study. In this study, modified risk product claims did not encourage former tobacco users to re-initiate use of this tobacco product or motivate them to purchase snus. As with the other non-users of tobacco, the modified risk claims were less likely to deter former users from using or purchasing snus.

Newly Identified Studies

One set of repeated cross-sectional studies in Norway (conducted over 3-year periods from 2003 until 2015) reported that the proportion of men who quit both snus and cigarettes remained stable over the study years, which was 11.2% in 2013-2015 when the study ended (Lund et al. 2017). Current snus users who had quit smoking increased from 14.5% to 25.1% from 2003-2005 to 2012-2015, based on

data from nationally representative cross-sectional studies in Norway. No direct data was reported on those who ceased tobacco use and then re-started tobacco use with snus. However, of those who currently used snus following successful cessation of smoking, 82.7% reported that snus was used in the final attempt to quit smoking. The proportion of former snus users who currently smoked steadily decreased (negative linear trend -12.2% per year) over the study periods: 22.4% in 2003-2005 to 8.1% in 2012-2015 (Lund et al. 2017).

The likelihood that former tobacco users would re-initiate tobacco use with snus was not directly captured in any observational studies since the 2014 MRTPA, nor were there clinical trials investigating this phenomenon. However, there was a downward trend in the prevalence of former snus users who currently smoked.

4. CONSUMERS' BELIEFS ABOUT THE HEALTH RISKS OF USING SWEDISH SNUS

This section of the report summarizes the available scientific literature describing studies that assessed current perceptions of risk about Swedish snus. We identified a total of five published product-specific studies which provided information on consumers' beliefs about the health risks of using snus.

Summary from 2014 MRTPA

The data showed that adults generally, and smokers in particular, had an exaggerated perception of the health risks related to snus use. Participants often overrated the harmfulness of snus compared to other tobacco types, and this same trend was also observed in the one available study on this topic in adolescents. Factors that were associated with exaggerated beliefs were male gender, young age, and a higher degree of dependency. Those with beliefs more closely aligned with facts related to the relative risks of snus and cigarettes were more likely to be snus users or to have tried the product.

In studies that provided tobacco health facts to participants, findings suggest that participants were able to understand comparative tobacco risk information. However, no studies of sufficient duration or design were identified to determine whether imparting tobacco health facts resulted in changes in established tobacco habits.

Most of the studies were conducted among tobacco users. One drawback of the available studies is the limited information on tobacco-related knowledge and beliefs among non-smokers and non-users of tobacco. Also, only one of the identified studies was a prospective design (among adolescents) to examine changes in perceptions and tobacco-related behaviors over time, and perceptions on tobacco harmfulness did not appear to predict future tobacco use.

4.1 Ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health

Summary from 2014 MRTPA

One study addressed consumers' ability to understand modified risk claims for Swedish snus by providing factual information on the relative harms of STPs and NRTs compared to smoking tobacco (Borland et al. 2012). Borland and colleagues (2012) observed that the knowledge on the mechanisms of tobacco-related harms became more accurate among smokers in Sweden as well as other countries in the study, including the U.S., Australia, and the U.K. Before the fact sheet was provided, smokers had little knowledge about the harmfulness of different nicotine delivery products. The increased knowledge levels on the relative harmfulness of STP/NRT compared to cigarettes increased participants' interests in using NRT as a cessation aid and/or trying STPs as a substitute for cigarette smoking.

Newly Identified Studies

Rodu and colleagues (2016) conducted an independent analysis of the Swedish Match-sponsored U.S. consumer perception survey wherein participants viewed four current warning labels and two proposed relative-risk (lower risk and substantially lower risk) labels for Swedish snus. The four current labels state the following: "This product can cause mouth cancer;" "This product can cause gum

disease and tooth loss;" "This product is not a safe alternative to cigarettes;" and "Smokeless tobacco is addictive." The two proposed labels stated the following: "No tobacco product is safe, but this product presents lower risks to health than cigarettes," and "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes." Believability, perception of harmfulness, motivation to use, and likelihood of buying snus were evaluated. 4,324 daily exclusive cigarette smokers, 1,033 daily smokeless tobacco users, 1,205 daily users of other tobacco products, 726 former tobacco users, and 5,915 triers/never users (used once or twice, or never) were assigned to view one of these six labels. Participants were randomly assigned to view labels according to sex, age, race/ethnicity, income and geographic location so there were no differences in tobacco status among those viewing different labels.

Believability and perception of harm: Among smokers, more than 80% of those who viewed the current warning label reported they were believable; about 60% of those who viewed the proposed relative-risk labels reported believability. Regardless of the label viewed, about 90% of smokers reported that they perceived snus as harmful. Compared to the smokers' responses, smaller proportions of ST users believed the current warnings (73-89%), and significantly higher proportions believed the proposed labels (70-72%). Significantly smaller proportions of ST users perceived snus as harmful regardless of the type of label (78-89%). Participants who used other tobacco (neither cigarettes nor ST) had similar responses to smokers regarding believability and perceived harm after viewing current or proposed labels. Similar to smokers, 80-97% of former users reported that the current warnings were believable and about 60% thought the proposed relative-risk labels believable. Over 90% of triers/never users perceived snus as harmful, and 73-85% believed the current warnings whereas 48-49% believed the proposed labels (Rodu et al. 2016).

Motivation to use or buy snus: Among smokers, 10-13% of those who viewed the current warnings said they would be more likely to use snus compared to 21-23% of those who viewed the proposed labels. Compared to smokers, significantly larger proportions of ST users reported they were likely to use snus and were motivated to buy snus after viewing any of the six labels (35-45% of those who viewed the current labels, 48-65% of those who viewed the proposed labels). Among other tobacco users, 23-25% of those who viewed current labels and 14-23% of those who viewed proposed labels reported they were likely to use snus; 14-23% of those who viewed current labels and 31-35% of those who viewed proposed labels reported they were motivated to buy snus. Former users were the least likely to use or buy snus, regardless of which label was viewed (4-11% reported they were likely to use, 3-7% reported they were likely to buy). A slightly higher proportion of triers/never users reported they were likely to use snus (10-14%) or buy snus (6-11%) compared to former users (Rodu et al. 2016).

Rodu and colleagues (2016) also performed logistic regression analyses on outcomes comparing those who viewed proposed warning labels with those who viewed the current not-safe-alternative label, stratified by tobacco status and adjusted for sex, age, race/ethnicity, income, region, education and marital status. The two proposed relative-risk labels had lower odds of believability among all groups. The vast majority of all respondents, with minimal variation according to labels, also perceived that using snus is harmful. The odds of perceived harm were mostly lower in relation to the proposed labels, but these differences weren't always statistically significant. The odds of being motivated to buy snus after viewing the two proposed labels compared to the not-safe-alternative label were greater than 1 (i.e. they were more likely to report being motivated to buy snus) for all tobacco user

categories except for former tobacco users. However, the odds of buying snus were significantly greater among smokers (OR=3.50 and 4.0), ST users (OR=1.92 and 2.15), and other tobacco users (OR=1.93, substantially lower risk label only). Among triers/never users, those who viewed the two proposed labels had greater odds of reporting motivation to buy snus, with significantly greater odds among those who viewed the substantially lower risk label (OR=1.88). The likelihood to use snus after viewing the relative-risk labels was similar among these groups. Former tobacco users were the only group who reported being less likely to buy or use snus after viewing the proposed labels, though this trend was not significant (Rodu et al. 2016).

4.1.1 Youth Behaviors

Summary from 2014 MRTPA

In an intervention study with male ice-hockey players in Sweden, participants listened to a 15-minute anti-tobacco information session conducted by two dental hygienists (Rolandsson and Hugoson 2000). Post-intervention, the authors noted that knowledge of tobacco and its harmful effects increased significantly; however, in spite of knowledge, tobacco use habits remained the same. With regards to differences between tobacco use groups, no significant difference could be observed among those snus users and non-users concerning their knowledge of the harmful effects of tobacco (Rolandsson and Hugoson 2000).

Newly Identified Studies

No new studies regarding youth consumers' understanding of modified risk claims regarding Swedish snus were identified since the 2014 MRTPA.

4.2 Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products

Summary from 2014 MRTPA

Five cross-sectional studies investigated the perception of health risks related to snus use among adults (Bolinder et al. 2002; Borland et al. 2012; Lund and Scheffels 2012; Lund and Scheffels 2014a; Lund 2012). These studies reported that Scandinavians had an exaggerated perception of the health risks associated with snus use. Among Norwegian adults who were either current or former tobacco users, a majority of smokers believed snus users had a higher or equal risk for all tobacco-related cancers except lung cancer (Lund and Scheffels 2014a). Another study in Norway presented similar conclusions with both former and current adult smokers inaccurately reporting that harm from snus was only somewhat less risky (Lund 2012). Smokers with a history of snus were more likely to correctly predict that daily snus use was far less risky than daily cigarette smoking (Lund 2012). In Sweden and other locations worldwide, Borland and colleagues (2012) provided factual information on the relative harms of STP/NRT compared to smoked tobacco and reported that after reading all or some of this fact sheet, the knowledge on mechanisms of tobacco-related harms became more accurate and perceived that STPs were less harmful.

Two of the five cross-sectional studies observed that a significant percentage of the medical community hold beliefs that conflict with scientific consensus on the health risks of snus (Bolinder et al. 2002; Lund and Scheffels 2012). Half of doctors surveyed believed that snus use probably increases the risk of oral cancer, hypertension, and some heart diseases (Bolinder et al. 2002) and

some doctors reported that they never or seldom recommended snus as a cessation aid (Bolinder et al. 2002; Lund and Scheffels 2012).

Among Norwegian snus users and cigarette smokers, a majority believed that snus users and smokers were more or less at the same risk of becoming addicted to nicotine. Current dual users, compared to other tobacco user groups, believed that snus users ran the highest risk to be addicted to nicotine (Lund and Scheffels 2014a).

Certain factors were found to be correlated with the belief that snus was less harmful than cigarettes. Men and adults younger than 30 years old tended to have more accurate perceptions of snus compared to women and those older than 60 years (Wikmans and Ramstrom 2010). Furthermore, snus users or former snus users correctly believed that daily snus use was less risky than daily cigarette smoking compared to those who did not use snus (Lund 2012). Those who believed that STP was less harmful than cigarettes had more interest in trying STP (Borland et al. 2012; Lund 2012) and, if already using, tended to have higher nicotine dependency and had previously tried to quit cigarettes using snus (Wikmans and Ramstrom 2010).

Newly Identified Studies

Mays and colleagues (2016) conducted a randomized controlled study in which young adults viewed one of four warning labels associated with Swedish snus or a control with no warning label. The convenience sample consisted of 517 adults aged 18-30 years living in the United States. 33% of the sample were smokers, and approximately half were men. One warning conveyed the addictiveness of snus, the second warning discussed the potential harms of snus, the third warning communicated the potential-reduced harms of snus compared with cigarettes, and the fourth warning label conveyed the potential-reduced harms of snus when switching completely from cigarettes to snus. Those who viewed the harm reduction label or the harm reduction/complete switch label were significantly more likely than the control group to perceive snus as less harmful than cigarettes ($p < 0.001$). They were also more likely to perceive snus as less harmful than cigarettes than the groups who viewed the addiction or harm labels. Nonsmokers who saw the harm reduction label reported fewer thoughts about not using snus than nonsmokers who saw the label only discussing the potential harms of snus.

4.2.1 Youth Behaviors

Summary from 2014 MRTPA

Six studies examined tobacco-related knowledge, attitudes and beliefs among adolescents and/or young adults. Two were prospective studies and four were cross-sectional in design. High schoolers were assessed for knowledge of tobacco effect and surveyed annually from sixth through ninth grade (Rosendahl et al. 2005). The authors reported that acquired knowledge often did not predict future tobacco use; no association was observed between this score and subsequent tobacco use, and it did not predict future tobacco use (Rosendahl et al. 2005). Rosendahl and colleagues (2008) modeled the development of behavior in adolescents up to age 18 and observed gender differences: rapid escalation for snus use was seen in boys and high consumption of cigarettes was seen in girls. Dual users had a trajectory of steeper and more prolonged increase in tobacco consumption than exclusive users (Rosendahl et al. 2008).

Four cross-sectional studies evaluated knowledge, attitudes and beliefs among Scandinavian adolescents and young adults (Nilsson et al. 2009; Overland et al. 2008; Wium et al. 2009; Wium et al. 2011). Both cigarette smoking and snus use were considered to be unattractive; however, snus was reported to be trendier than smoking. Males generally considered snus use to be more attractive and trendier than did females, and use was more common among males than females. According to a cross-sectional study conducted by Nilsson et al. (2009), a majority of Swedish adolescents (85%) expected their parents to try to make them stop using snus, suggesting that these adolescents on some level consider snus use to be a habit of which their parents would not approve. Overland and colleagues (2008) had adolescents aged 16-20 years rank tobacco products in order of harm. Overall, cigarettes were rated as more harmful than snus, but 41% rated snus as equally or more harmful than cigarettes.

Newly Identified Studies

A focus group study explored the knowledge of snus-related health risks among Swedish adolescents (Edvardsson et al. 2012). The focus group consisted of 27 Swedish 17-19 year-olds, and reported that using snus was not considered a risk. Health risks of using snus were considered uncommon and knowledge of risks was low (Edvardsson et al. 2012). This group emphasized snus as a national Swedish pastime and boys strongly identified with snus use as a masculine pastime (Edvardsson et al. 2012).

Another qualitative focus group study assessed the perceptions of snus packaging among adolescents in Norway (Scheffels and Lund 2017). The 35 participants were between 15 and 17 years of age and self-defined as smokers, snus users, or non-users. Many of the tobacco users had tried or occasionally use the other product type. Snus packaging and flavor additives were associated with perceived harm of the product. Snus packaged in smaller, lighter colored, or round-edged packaging was perceived as less strong than that packaged in darker, sharp-edged boxes. In particular, one participant commented that General Snus (Classic Loose) with its dark color theme and sharp edges looked like it could "destroy you." Colorful boxes and flavoring were perceived as less dangerous; white, sterile-looking packaging was associated with medicine (Scheffels and Lund 2017). During group discussions, non-users expressed resolve in abstaining from tobacco and that nice packaging would not change their behavior. However, in qualitative interviews, non-users had more ambiguous views and expressed curiosity in trying flavored products (Scheffels and Lund 2017).

4.3 Consumer beliefs about the health risks of (i) using the product relative to cessation aids and (ii) using the product relative to quitting all tobacco use

Summary from 2014 MRTPA

Borland and colleagues (2012) reported that the knowledge levels on relative harmfulness of STPs or NRTs compared to cigarettes increased participants' interests in using either NRTs or STPs as a substitute for cigarette smoking among adult smokers. In a national survey of Norwegian adults, the accurate perception of relative risk of snus and cigarettes correlated positively with having used snus when quitting smoking (Lund 2012). Based on a mail-in questionnaire for Norwegian general practitioners, snus was less likely to be recommended as a cessation tool compared to NRTs (Lund and Scheffels 2012).

Newly Identified Studies

In a cross-sectional survey of almost 5000 adult Norwegian tobacco users (3,401 exclusive cigarette smokers, 885 exclusive snus users, and 556 dual users of cigarettes and snus), the health benefits of quitting smoking as reported by surveyed smokers were much greater ($M=3.92$, $SD 0.79$) than the health benefits of quitting snus as reported among snus users ($M=2.71$, $SD 0.85$) (Lund et al. 2014). The effect size between exclusive smokers' perceived benefit from quitting cigarettes and exclusive snus users' perceived benefit from quitting snus was 1.47 (Cohen's d). A similar effect size was seen between dual users' perceived benefit from quitting cigarettes and quitting snus (Cohen's $d=1.50$) (Lund et al. 2014). This difference in perceived benefit in quitting cigarettes compared with that in quitting snus may indicate that snus users regard the use of snus as having fewer health risks than smoking cigarettes (Lund et al. 2014).

4.3.1 Youth Behaviors

Summary from 2014 MRTPA

No studies on youth consumer beliefs about health risks of snus relative to cessation aids and quitting tobacco altogether were previously included in the 2014 MRTPA.

Newly Identified Studies

No studies on youth consumer beliefs about health risks of snus relative to cessation aids and quitting tobacco altogether were identified.

5. REFERENCES

- Andersson G. 1991. Snuff-induced changes associated with the use of loose and portion-bag-packed Swedish moist snuff. A clinical, histological and follow-up study. *Swed Dent J Suppl* 75:1-89.
- Andersson G, Bjornberg G, and Curvall M. 1994. Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: a comparative study. *J Oral Pathol Med* 23:161-167.
- Bolinder G, Himmelmann L, and Johansson K. 2002. [Swedish physicians smoke least in all the world. A new study of smoking habits and attitudes to tobacco]. *Lakartidningen* 99:3111-3117.
- Borland R, Li L, Cummings KM, O'Connor R, Mortimer K, Wikmans T, Ramstrom L, King B, and McNeill A. 2012. Effects of a Fact Sheet on beliefs about the harmfulness of alternative nicotine delivery systems compared with cigarettes. *Harm Reduct J* 9:19.
- Colilla SA. 2010. An epidemiologic review of smokeless tobacco health effects and harm reduction potential. *Regul Toxicol Pharmacol* 56:197-211.
- Digard H, Errington G, Richter A, and McAdam K. 2009. Patterns and behaviors of snus consumption in Sweden. *Nicotine Tob Res* 11:1175-1181.
- Edvardsson I, Lendahls L, and Hakansson A. 2009. When do adolescents become smokers? Annual seven-year population-based follow-up of tobacco habits among 2000 Swedish pupils--an open cohort study. *Scand J Prim Health Care* 27:41-46.
- Edvardsson I, Troein M, Ejlertsson G and Lendahls L. 2012. Snus user identity and addiction: a Swedish focus group study on adolescents. *BMC Public Health*, 12(1471–2458 (Electronic)): 975.
- Fagerstrom K, Rutqvist LE, and Hughes JR. 2012. Snus as a smoking cessation aid: a randomized placebo-controlled trial. *Nicotine Tob Res* 14:306-312.
- Fagerstrom K and Eissenberg T. 2012. Dependence on tobacco and nicotine products: a case for product-specific assessment. *Nicotine Tob Res* 14:1382-1390.
- Folkehelseinstituttet (FHI). 2013. [Use of tobacco, drugs and addictive drugs in Norway – main findings from the SIRUS population survey in 2012, the Norwegian Institute for Drug Research (SIRUS)]. Published June 2013. <https://fhi.no/publ/2013/bruk-av-tobakk-rusmidler-og-vanedannende-legemidler-i-norge---hovedfunn-fra/> Accessed 28 July 2017.
- Folkehelseinstituttet (FHI). 2017. "Røyning og snusbruk." Published 30 June 2014, Updated 14 May 2018. Folkehelseinstituttet. <https://fhi.no/nettpub/hin/levevaner/royking-og-snusbruk-i-noreg/#tobakk-og-hjarte-og-karsjukdomar> Accessed 28 July 2017.
- Folkhalsomyndigheten. 2014a. Fewer smokes every day. Folkhalsomyndigheten. <https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2014/mars/farre-roker-varje-dag-/> Accessed 28 July 2017.

Folkhalsomyndigheten. 2014b. [Schoolchildren's health habits in Sweden 2013/14]. Folkhalsomyndigheten.

Furberg H, Bulik CM, Lerman C, Lichtenstein P, Pedersen NL, and Sullivan PF. 2005. Is Swedish snus associated with smoking initiation or smoking cessation? *Tob Control* 14:422-424.

Furberg H, Lichtenstein P, Pedersen NL, Bulik C, and Sullivan PF. 2006. Cigarettes and oral snuff use in Sweden: Prevalence and transitions. *Addiction* 101:1509-1515.

Furberg H, Lichtenstein P, Pedersen NL, Thornton L, Bulik CM, Lerman C, and Sullivan PF. 2008. The STAGE cohort: A prospective study of tobacco use among Swedish twins. *Nicotine Tob Res* 10:1727-1735.

Galanti MR, Rosendahl I, and Wickholm S. 2008. The development of tobacco use in adolescence among "snus starters" and "cigarette starters": An analysis of the Swedish "BROMS" cohort. *Nicotine Tob Res* 10:315-323.

Galanti MR, Rosendahl I, Post A, and Gilljam H. 2001. Early gender differences in adolescent tobacco use--the experience of a Swedish cohort. *Scand J Public Health* 29:314-317.

Gilljam H and Galanti MR. 2003. Role of snus (oral moist snuff) in smoking cessation and smoking reduction in Sweden. *Addiction* 98:1183-1189.

Grotvedt L, Forsen L, Stavem K, and Graff-Iversen S. 2013. Patterns of snus and cigarette use: a study of Norwegian men followed from age 16 to 19. *Tob Control* 22:382-388.

Hamari AK, Toljamo TI, Kinnula VL, and Nieminen PA. 2013. Dual use of cigarettes and Swedish snuff (snus) among young adults in Northern Finland. *Eur J Public Health* 23:768-771.

Haukkala A, Vartiainen E, and de Vries H. 2006. Progression of oral snuff use among Finnish 13-16-year-old students and its relation to smoking behaviour. *Addiction* 101:581-589.

Hedman L, Andersson M, Stridsman C and Ronmark E. 2015. Evaluation of a tobacco prevention programme among teenagers in Sweden. *BMJ open*, 5(5): e007673.

Helsedirektoratet. 2017. "Statistics on smoking, snus and e-cigarettes." Helsedirektoratet. Updated 6 July 2017. <https://helsedirektoratet.no/folkehelse/tobakk-royk-og-snus/statistikk-om-royking-bruk-av-snus-og-e-sigaretter#tall-om-snus-og-ungdom> Accessed 28 July 2017.

Hergens MP, Ahlbom A, Andersson T, and Pershagen G. 2005. Swedish moist snuff and myocardial infarction among men. *Epidemiology* 16:12-16.

Janzon E and Hedblad B. 2009. Swedish snuff and incidence of cardiovascular disease. A population-based cohort study. *BMC Cardiovasc Disord* 9:21-27.

Joksic G, Spasojevic-Tisma V, Antic R, Nilsson R, and Rutqvist LE. 2011. Randomized, placebo-controlled, double-blind trial of Swedish snus for smoking reduction and cessation. *Harm Reduct J* 8:25.

Joffer J, Burell G, Bergström E, Stenlund H, Sjörs L and Jerdén L. 2014. Predictors of smoking among Swedish adolescents. *BMC Public Health*, 14(1).

Kvaavik E, Scheffels J and Lund M. 2014. [Occasional smoking in Norway]. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke*, 134(2): 163–167.

Kvaavik E, Lund I, Nygard M and Hansen BT. 2016. Lifestyle Correlates of Female Snus Use and Smoking: A Large Population-Based Survey of Women in Norway. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 18(4): 431–436.

Lager A, Berlin M, Heimerson I, and Danielsson M. 2012. Young people's health: Health in Sweden: The National Public Health Report 2012. Chapter 3. *Scand J Public Health* 40:42-71.

Leon ME, Lugo A, Boffetta P, Gilmore A, Ross H, Schuz J, La Vecchia C and Gallus S. 2016. Smokeless tobacco use in Sweden and other 17 European countries. *European journal of public health*, 26(5): 817–821.

Lindahl B, Stegmayr B, Johansson I, Weinehall L, and Hallmans G. 2003. Trends in lifestyle 1986-99 in a 25- to 64-year-old population of the Northern Sweden MONICA project. *Scand J Public Health Suppl* 61:31-37.

Lindroth M, Lundqvist R, Lilja M and Eliasson M. 2014. Cardiovascular risk factors differ between rural and urban Sweden: The 2009 Northern Sweden MONICA cohort. *BMC Public Health*, 14(1).

Lindstrom M and Isacsson SO. 2002a. Long term and transitional intermittent smokers: a longitudinal study. *Tob Control* 11:61-67.

Lindstrom M and Isacsson SO. 2002b. Smoking cessation among daily smokers, aged 45-69 years: a longitudinal study in Malmo, Sweden. *Addiction* 97:205-215.

Lund KE. 2012. Association between willingness to use snus to quit smoking and perception of relative risk between snus and cigarettes. *Nicotine Tob Res* 14:1221-1228.

Lund M and Lindbak R. 2007. Norwegian Tobacco Statistics 1973-2006. Norwegian Institute for Alcohol and Drug Research, Oslo, Norway.

Lund I and Lund KE. 2014. How has the availability of snus influenced cigarette smoking in Norway? *International journal of environmental research and public health*, 11(11): 11705–11717.

Lund KE and McNeill A. 2013. Patterns of dual use of snus and cigarettes in a mature snus market. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 15(3): 678–684.

Lund I and Scheffels J. 2012. Perceptions of the relative harmfulness of snus among Norwegian general practitioners and their effect on the tendency to recommend snus in smoking cessation. *Nicotine Tob Res* 14:169-175.

- Lund I and Scheffels J. 2014a. Perceptions of relative risk of disease and addiction from cigarettes and snus. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*, 28(2): 367–375.
- Lund I and Scheffels J. 2014b. Smoking and snus use onset: Exploring the influence of snus debut age on the risk for smoking uptake with cross-sectional survey data. *Nicotine and Tobacco Research*, 16(6): 815–819.
- Lund I and Scheffels J. 2016. Adolescent tobacco use practices and user profiles in a mature Swedish moist snuff (snus) market: Results from a school-based cross-sectional study. *Scandinavian Journal of Public Health*, 44(7): 646–653.
- Lund KE, McNeill A, and Scheffels J. 2010. The use of snus for quitting smoking compared with medicinal products. *Nicotine Tob Res* 12:817-822.
- Lund KE, Scheffels J, and McNeill A. 2011. The association between use of snus and quit rates for smoking: results from seven Norwegian cross-sectional studies. *Addiction* 106:162-167.
- Lund M, Lund KE and Halkjelsvik T. 2014. Contrasting smokers' and snus users' perceptions of personal tobacco behavior in Norway. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 16(12): 1577–1585.
- Lund KE, Vedøy TF and Bauld L. 2017. Do never smokers make up an increasing share of snus users as cigarette smoking declines? Changes in smoking status among male snus users in Norway 2003–15. *Addiction*, 112(2): 340–348.
- Lundqvist G, Sandstrom H, Ohman A, and Weinehall L. 2009. Patterns of tobacco use: a 10-year follow-up study of smoking and snus habits in a middle-aged Swedish population. *Scand J Public Health* 37:161-167.
- Mays D, Moran MB, Levy DT and Niaura RS. 2016. The Impact of Health Warning Labels for Swedish Snus Advertisements on Young Adults' Snus Perceptions and Behavioral Intentions. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 18(5): 1371–1375.
- Nilsson M, Weinehall L, Bergstrom E, Stenlund H, and Janlert U. 2009. Adolescent's perceptions and expectations of parental action on children's smoking and snus use; national cross sectional data from three decades. *BMC Public Health* 9:74.
- Norberg M, Lundqvist G, Nilsson M, Gilljam H, and Weinehall L. 2011. Changing patterns of tobacco use in a middle-aged population: the role of snus, gender, age, and education. *Glob Health Action* 4:5613.
- Overland S, Hetland J, and Aaro LE. 2008. Relative harm of snus and cigarettes: what do Norwegian adolescents say? *Tob Control* 17:422-425.
- Pedersen W and von Soest T. 2014. Tobacco use among Norwegian adolescents: From cigarettes to snus. *Addiction*, 109(7): 1154–1162.

Post A, Gilljam H, Rosendahl I, Bremberg S, and Rosaria GM. 2010. Symptoms of nicotine dependence in a cohort of Swedish youths: a comparison between smokers, smokeless tobacco users and dual tobacco users. *Addiction* 105:740-746.

Ramström LM and Foulds J. 2006. Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tob Control* 15:210-214.

Ramström L, Borland R, Wikmans T, Ramstrom L, Borland R and Wikmans T. 2016. Patterns of smoking and SNUS use in Sweden: Implications for public health. *International Journal of Environmental Research and Public Health*, 13(11).

Rodu B, Stegmayr B, Nasic S, and Asplund K. 2002. Impact of smokeless tobacco use on smoking in northern Sweden. *J Intern Med* 252:398-404.

Rodu B, Stegmayr B, Nasic S, Cole P, and Asplund K. 2003. Evolving patterns of tobacco use in northern Sweden. *J Intern Med* 253:660-665.

Rodu B, Jansson JH and Eliasson M. 2013. The low prevalence of smoking in the Northern Sweden MONICA study, 2009. *Scandinavian Journal of Public Health*, 41(8): 808–811.

Rodu B, Plurphanswat N, Hughes JR and Fagerstrom K. 2016. Associations of Proposed Relative-Risk Warning Labels for Snus with Perceptions and Behavioral Intentions Among Tobacco Users and Nonusers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, 18(5): 809–816.

Rolandsson M and Hugoson A. 2000. Knowledge and habits of tobacco among ice-hockey-playing boys. An intervention study. *Swed Dent J* 24:59-70.

Rosendahl KI, Galanti MR, Gilljam H, and Ahlbom A. 2005. Knowledge about tobacco and subsequent use of cigarettes and smokeless tobacco among Swedish adolescents. *J Adolesc Health* 37:224-228.

Rosendahl KI, Rosaria GM, and Gilljam H. 2008. Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: Differences and implications. *Nicotine Tob Res* 10:1021-1027.

Rutqvist LE. 2012. Population-based survey of cessation aids used by Swedish smokers. *Harm Reduction Journal*, 9.

Scheffels J and Lund I. 2017. Cute as candy: A qualitative study of perceptions of snus branding and package design among youth in Norway. *BMJ Open*, 7(4).

Scheffels J, Lund KE, and McNeill A. 2012. Contrasting snus and NRT as methods to quit smoking. an observational study. *Harm Reduct J* 9:10.

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). 2007. Health Effects of Smokeless Tobacco Products Preliminary Report. European Commission, Brussels.

Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR). 2008. Scientific opinion on the health effects of smokeless tobacco products. European Commission, Brussels.

Sharp L, Johansson H, Fagerstrom K, and Rutqvist LE. 2008. Smoking cessation among patients with head and neck cancer: cancer as a 'teachable moment'. *Eur J Cancer Care (Engl)* 17:114-119.

Skogen JC, Bøe T, Sivertsen B and Hysing M. 2016. Use of alcohol, tobacco and illicit drugs among ethnic Norwegian and ethnic minority adolescents in Hordaland county, Norway: the youth@hordaland-survey. *Ethnicity and Health. Alcohol and Drug Research Western Norway*, Stavanger University Hospital, Stavanger, Norway: Routledge.

Sohlberg T. 2015. Smoking cessation and gender differences - Results from a Swedish sample. *NAD Nordic Studies on Alcohol and Drugs*, 32(3): 259–276.

Official Statistics of Finland (Statistics Finland). 2008. *Statistics Finland 2007*. Helsinki, Finland.

Statistics Sweden. 2016. Tobacco habits, perception, and mortality [no formal title]. Statistics Sweden. <https://www.scb.se/en> Accessed on 28 July 2017.

Stegmayr B, Eliasson M, and Rodu B. 2005. The decline of smoking in northern Sweden. *Scand J Public Health* 33:321-324.

Stenbeck M, Hagquist C and Rosén M. 2009. The association of snus and smoking behaviour: a cohort analysis of Swedish males in the 1990s. *Addiction (Abingdon, England)*, 104(9): 1579–85.

Swedish Match. June 6, 2014. Modified Risk Tobacco Product Application for Swedish Match North America Snus Products.

Tillgren P, Haglund BJ, Lundberg M, Romelsjö A. 1996. The sociodemographic pattern of tobacco cessation in the 1980s: results from a panel study of living condition surveys in Sweden. *Journal of Epidemiology & Community Health*. 50(6):625-30.

Tseveenjav B, Pesonen P and Virtanen JI. 2015. Use of snus, its association with smoking and alcohol consumption, and related attitudes among adolescents: The Finnish National School Health Promotion Study. *Tobacco Induced Diseases*, 13(1).

U.S. Department of Health and Human Services (USDHHS). 2012. Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Wiiium N and Aaro LE. 2011. Outcome expectations and use of smokeless tobacco (snus): a cross-sectional study among young Norwegian snus users. *Scand J Psychol* 52:64-70.

Wiiium N, Aaro LE, and Hetland J. 2009. Subjective attractiveness and perceived trendiness in smoking and snus use: a study among young Norwegians. *Health Educ Res* 24:162-172.

Wiium N, Overland S, and Aaro LE. 2011. Smoking cessation among Norwegian adolescents and young adults: preferred cessation methods. *Scand J Psychol* 52:154-160.

Wikmans T and Ramstrom L. 2010. Harm perception among Swedish daily smokers regarding nicotine, NRT-products and Swedish Snus. *Tob Induc Dis* 8:9.

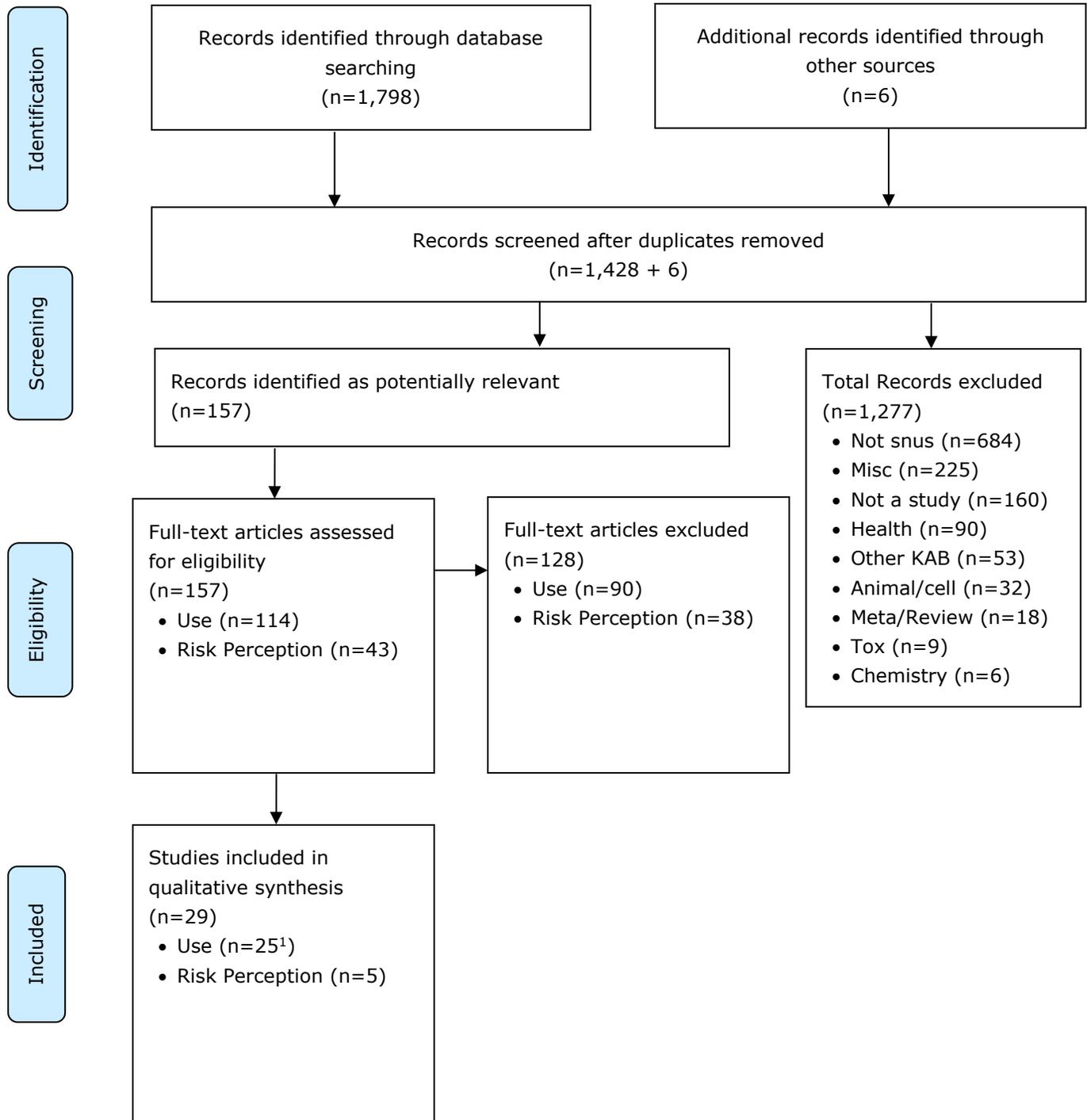
Appendix A: Search Results Tracking Table

The following search terms seek to be as inclusive as possible, and consequently focus on the exposure of interest for Research Topics 1-4 (Table B1). Table B2 presents the search terms and results that were used in the retrospective literature search of the health effects studies on Swedish snus through December 1, 2012. Given the relatively unique scope of Research Topic 5, different search terms were used to identify literature for this research question (Table B3).

Table B1: Update Searches				
Search No.	Source	Date	Search terms	Results (#)
1	PubMed	7/28/2017	snus OR snuff Filter: December 1, 2012 to present	1,194
2	Scopus	7/28/2017	TITLE-ABS-KEY(snus OR snuff) AND PUBYEAR > 2011 Filter: January 1, 2012 to Present	578
4	Clinicaltrials.gov	7/28/2017	snus OR snuff Filter: Limited to studies that have been "completed" and "with results." Terms entered into the "other terms" field. No year limits available.	26 total results (includes studies from all years) 0 relevant studies conducted after 2012.
5	http://www.scb.se/	7/28/2017	snus, snuff, tobacco	Snus: 249 "pages and documents," 1 "statistical database" (1 potentially relevant article) Snuff: 17 "pages and documents," 2 "statistical databases" (1 relevant; same as previous search) Tobacco: 548 "pages and documents," 2 "statistical databases" (0 relevant)
6	www.socialstyrelsen.se	7/28/2017	snus, snuff, tobacco	Snus: 8 (1 potentially relevant) Snuff: 3 (0 potentially relevant) Tobacco: 28 (0 potentially relevant)
7	www.folkhalsomyndigheten.se	7/28/2017	snus, snuff, tobacco	Snus: 103 (4 potentially relevant)

				Snuff: 18 (2 potentially relevant) Tobacco: 122 (0 potentially relevant)
8	www.helsedirektoratet.no	7/28/2017	snus, snuff, tobacco	Snus: 70 (5 potentially relevant) Snuff: 1 (0 potentially relevant) Tobacco: 40 (0 new potentially relevant)
9	www.fhi.no	7/28/2017	snus, snuff, tobacco	Snus: 78 (7 potentially relevant) Snuff: 4 (1 potentially relevant) Tobacco: 30 (1 potentially relevant)

Appendix B: Adapted PRISMA Literature Inclusion/Exclusion Diagram



¹ One study overlapped with "Risk Perception," and was identified from that literature during full-text review (Lund et al. 2014).