

FDA Briefing Document

April 9 -10, 2015

Meeting of the Tobacco Products Scientific Advisory Committee

Modified Risk Tobacco Product Applications
for ten General brand snus tobacco products (FDA Submission
Tracking Numbers MR0000020-MR0000029)
Swedish Match North America, Inc.

Office of Science
Center for Tobacco Products
Food and Drug Administration

DISCLAIMER STATEMENT

The attached briefing document contains briefing information prepared by the Food and Drug Administration (FDA) for the members of the Tobacco Products Scientific Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought Swedish Match North America, Inc.'s Modified Risk Tobacco Product Applications for multiple snus tobacco products to this Advisory Committee in order to gain the Committee's insights and opinions. Although the entire applications are referred to the Committee, this briefing package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process, and from the public comments, has been considered and all FDA reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting. The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.

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Draft Topics for Discussion

With respect to the relative health risks to individual users of the snus tobacco products that are the subject to the proposed modified risk tobacco product applications:

1. The relative health risks to individual users of the snus tobacco products that are the subject to the proposed modified risk snus tobacco products, particularly with respect to
 - a. gum disease or tooth loss
 - b. oral cancer
 - c. a comparison to risks of cigarette smoking
2. The behavioral aspects of snus use, particularly as they relate to
 - a. The likelihood that existing users of tobacco products who would otherwise stop using those products will switch to the snus tobacco products that are the subject to the proposed modified risk snus tobacco products
 - b. The likelihood that persons who do not use tobacco products will start using the snus tobacco products that are the subject to the proposed modified risk snus tobacco products
3. Comprehension of the modified risk information and perception of the product in the context of total health
4. Postmarket surveillance and studies
5. Other Recommendations regarding the modified risk tobacco product applications.



SUMMARY MEMORANDUM

DATE: March 13, 2015

FROM: RADM David L. Ashley, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration

TO: Members, Tobacco Products Scientific Advisory Committee

SUBJECT: Overview of the FDA Briefing Document for April 9-10, 2015 discussion of Swedish Match North America, Inc., MRTPAs for 10 snus products (FDA Submission Tracking Numbers MR0000020-MR0000029)

Introduction

We would like to thank the Tobacco Product Scientific Advisory Committee (TPSAC) in advance for their efforts to provide FDA recommendations on the modified risk applications submitted by Swedish Match North America, Inc. (SMNA).

On June 10, 2014, SMNA submitted modified risk tobacco product applications (MRTPAs) seeking risk modification orders under Section 911(g)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) for 10 smokeless snus tobacco products. Specifically, SMNA requests certain product-specific modifications to the health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products:

1. Maintain "WARNING: Smokeless tobacco is addictive."
2. Remove "WARNING: This product can cause gum disease and tooth loss."
3. Remove "WARNING: This product can cause mouth cancer."
4. Revise "WARNING: This product is not a safe alternative to cigarettes" to "WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes."

SMNA is not seeking any other claims or changes in marketing for these products, other than the modified warning statements.

Enclosed is the FDA's background package for your preparation for the meeting in which the ten snus products will be discussed. Although the entire applications are referred to the Committee, this background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Committee. This package does not contain a comprehensive review of the applications. Rather, the package contains a summary of the specific issues FDA identified during scientific review to date for which we seek recommendations from TPSAC, as well as the key issues and topics for discussion at the meeting.

This document contains statements of preliminary findings and interpretations of the data and information reviewed to date. It must be emphasized that these documents do not represent final findings, recommendations, or conclusions, and that no regulatory decision on the status of these applications has been made. Indeed, an important aspect of our thinking on these applications will be a full consideration of public comments and whatever advice the TPSAC provides on these important issues.

The focus of this Advisory Committee will be in regards to scientific topics as they relate to the proposed product-specific modifications to the health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for SMNA smokeless snus tobacco products.

Executive Summary

In the MRTPAs, SMNA has requested product-specific modifications of the warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act. In total, SMNA proposes to remove the following warnings:

- (1) “WARNING: This product can cause gum disease and tooth loss.”
- (2) “WARNING: This product can cause mouth cancer.”

and to revise the following warning:

- (3) “WARNING: This product is not a safe alternative to cigarettes.” to “WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes.”

Thus, the MRTPAs request that the ten specified products would bear only the following two rotating warnings:

- (1) “WARNING: Smokeless tobacco is addictive.”
- (2) “WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes.”

FDA is reviewing the scientific information submitted in the MRTPAs, which includes epidemiological data on the impact of other snus products on populations in Sweden and Norway, data from clinical trials on the effectiveness of snus for cessation, data from a clinical study on the impact of the warning statements on consumer comprehension and perception, as well as other scientific information. FDA is also reviewing public comments submitted in accordance with Section 911(e). FDA intends to bring the following matters for discussion with TPSAC:

1. The relative health risks to individual users of the snus tobacco products that are the subject to the proposed modified risk snus tobacco products, particularly with respect to
 - a. gum disease or tooth loss
 - b. oral cancer
 - c. a comparison to risks of cigarette smoking
2. The behavioral aspects of snus use, particularly as they relate to
 - a. The likelihood that existing users of tobacco products who would otherwise stop using those products will switch to the snus tobacco products that are the subject to the proposed modified risk snus tobacco products

- b. The likelihood that persons who do not use tobacco products will start using the snus tobacco products that are the subject to the proposed modified risk snus tobacco products
3. Comprehension of the modified risk information and perception of the product in the context of total health
4. Postmarket surveillance and studies
5. Other Recommendations regarding the modified risk tobacco product applications.

Background

The FD&C Act defines “modified risk tobacco product” as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. [Section 911(b)(1)]. Sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products means a tobacco product:

- (1) that represents in its label, labeling, or advertising, either implicitly or explicitly, that:
 - i. the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
 - ii. the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
 - iii. the tobacco product or its smoke does not contain or is free of a substance;
- (2) that uses the descriptors “light”, “mild”, “low”, or similar descriptors in its label, labeling, or advertising;¹ or
- (3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product’s label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [Section 911(b)(2)]

Before a modified risk tobacco product can be introduced into interstate commerce, an order from FDA under section 911(g) must be issued and in effect with respect to the tobacco product.

¹ While cigarettes had been marketed with such descriptors before the Tobacco Control Act was enacted, as of June 22, 2010, manufacturers were prohibited from manufacturing for sale or distribution any tobacco products for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, without an FDA order in effect under section 911(g) of the FD&C Act. Section 911(b)(3) of the FD&C Act. Furthermore, as of July 22, 2010, manufacturers, including importers of finished tobacco products, were prohibited from introducing into the domestic commerce of the United States any tobacco product for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, irrespective of the date of manufacture, without an FDA order in effect under section 911(g) of the FD&C Act. *Id.*

To request such an order from FDA, a person may file a MRTPA under section 911(d). The MRTPA should include information about the various aspects of the tobacco product, including information to enable FDA to assess the likely impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled “Modified Risk Tobacco Product Applications,” which discusses the submission of applications for a modified risk tobacco product under section 911 of the FD&C Act and considerations regarding studies and analyses to include in a modified risk tobacco product application. (See attached).

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two bases for FDA to issue an order.

FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

FDA has the authority to require with respect to tobacco products for which risk modification orders are issued that the product comply with requirements relating to advertising and promotion of the tobacco product. Section 911(h)(5) of the FD&C Act.

In the alternative, for products that cannot receive a risk modification order from FDA under section 911(g)(1) of the FD&C Act, FDA may issue an order under section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances, which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

In evaluating the benefit to health of individuals and of the population as a whole under sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

FDA Review Process

Draft guidance on Modified Risk Tobacco Product Applications was released for public comment in March 2012. The draft guidance discusses how to organize, submit, and file a modified risk tobacco product application, what scientific studies and analyses to submit, and what information to collect through post-market surveillance and studies if an FDA order authorizing the marketing of the product is issued. Since the release of this draft guidance, FDA has been meeting with manufacturers to discuss studies the manufacturers have proposed to provide, and the scientific evidence needed to demonstrate that the issuance of a MRTP order would be appropriate. FDA provided feedback on these proposed studies to manufacturers so that they can provide information to inform FDA's decisions about proposed modified risk products.

Once an MRTPA is submitted, FDA performs a preliminary administrative review to determine whether to accept and file it. In general, after filing an application, FDA can begin substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee. FDA intends to review and act on a complete MRTPA within 360 days of FDA receipt². FDA can issue an order authorizing the marketing of a product under section 911(g)(1) only if the evidence submitted in the application meets the requirements of section 911, including showing that the product, as actually used by consumers, will benefit the health of the population as a whole. An order permitting the sale of an MRTP refers to a single specific product, not an entire class of tobacco products (e.g. all smokeless products).

An FDA order permitting marketing of an MRTP is not permanent; it is for a fixed period of time that will be determined by FDA and specified in the order. To continue to market a modified risk tobacco product after the set term, an applicant would need to seek renewal of the order and FDA would need to determine that the findings continue to be satisfied. Also, if at any time FDA determines that it can no longer make the determinations required for an MRTP order, FDA is required to withdraw the order. Before FDA withdraws an MRTP order, it will provide an opportunity for an informal hearing as required under the law.

Regulatory History

On June 10, 2014, FDA received applications from Swedish Match North America, Inc. SMNA is requesting modified risk tobacco products orders under section 911(g)(1) of the FD&C Act for the following tobacco products listed by the FDA Submission Tracking Numbers:

- MR0000020: General Loose, smokeless tobacco, loose snus, 1.59 oz (45g), cardboard can (SKU 4852);
- MR0000021: General Dry Mint Portion Original Mini, smokeless tobacco, snus portions, 0.21 oz (6g), 20 – 0.3g portions, plastic can (SKU 4800);
- MR0000022: General Portion Original Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24—1g portions, plastic can (SKU 4880);
- MR0000023: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can (SKU 4877);
- MR0000024: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can (SKU 4878);
- MR0000025: General Mint Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4352);
- MR0000026: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can (SKU 4876);

² This timetable is FDA's best estimate from November 2009 draft guidance, but it is based on limited information as FDA has limited experience with MRTPAs and the statute includes novel requirements, including public availability of the application and solicitation of comments.

- MR0000027: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can (SKU 4875);
- MR0000028: General Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4881); and
- MR0000029: General Wintergreen Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4882).

FDA also received the following amendments to each of the ten original applications:

- July 31, 2014, containing the (b)(4) raw data
- August 1, 2014, containing HPHC raw data
- August 5, 2014, containing background information related to cognitive testing for the premarket consumer perception study
- August 15, 2014, containing the raw data for the consumer perception study
- December 3, 2014, containing responses to the November 12, 2014 FDA’s Advice/Information Request for clarifying information
- December 9, 2014, containing responses to the November 25, 2014 Office of Compliance and Enforcement Request
- January 27, 2015, containing responses to FDA’s request for clarifying information in the January 9, 2015 teleconference
- February 20, 2015, containing responses to the February 6, 2015 Office of Compliance and Enforcement teleconference meeting

Pursuant to Section 911(e) of the FD&C Act, SMNA’s MRTPAs and amendments are available to the public (except matters in the application which are trade secrets or otherwise confidential, commercial information) for 10 tobacco products. The notice of availability for these applications appeared in the Federal Register of August 27, 2014. In that notice, FDA requested public comments on the 10 MRTPAs that are posted on regulations.gov and FDA’s website³. FDA received many comments in response to that request, and is continuing to review them.

What follows is a discussion of some specific issues FDA identified during scientific review of the application for which FDA seeks recommendations from TPSAC.

Preliminary FDA Review Findings

I. Epidemiological Evidence Related to SMNA Snus and Gum Disease and Tooth Loss

The applicant submitted published epidemiological studies of snus and gum disease or tooth loss to support the request to remove “WARNING: This product can cause gum disease and tooth loss.” The application included 12 studies on the association between snus and outcomes related to gum disease and tooth loss (11 cross-sectional-studies and 1 case-control study). FDA

³ FDA will post further amendments (except for matters in the amendment that are trade secrets or otherwise confidential, commercial information) to the docket as they are received.

conducted an independent systematic search for published epidemiologic studies of snus use and disease risk and did not identify any additional studies that pertained to gum disease and tooth loss.

The applicant reported that “No effects of snus use on gingivitis, gingival recessions, and other dental conditions were consistently identified among studies that controlled for important confounders such as socioeconomic status (SES) and oral hygiene habits. The use of snus is not associated with periodontal disease or any individual indicators of periodontal disease based on the results of seven studies, five of which accounted for the potential confounding effects of SES or oral hygiene habits.” (page 442 section 6.1.1.7 of the application).

Periodontal disease (gum disease), is an inflammatory disease caused by bacteria, often presenting in bacterial biofilm (plaque) (Laudenbach and Simon, 2014). Epidemiologic studies often examine signs of gum disease such as gingivitis, gingival recession, probing pocket depths clinical attachment loss or bone loss (Irfan, et al., 2001). In later stages, gum disease may also lead to tooth loss; however, tooth loss may be caused by other factors such as caries (Laudenbach and Simon, 2014).

The underlying assumption of SMNA’s ten MRTPAs, is that the snus products included in the studies are comparable to the snus products that are the subject of the MRTPAs. In support of this assumption, SMNA states in section 2 (page 90) of the main portion of the applications that during the period of study, SMNA products dominated the Scandinavian snus market: “There were no snus manufacturers other than Swedish Match North America, Inc. in Sweden until the 1990s. Since then, Swedish Match North America, Inc. has historically maintained a market share of more than 80-90%. In Norway, the Swedish Match North America, Inc. volume market share was above 90% until 2005, and ranged from 70-90% from 2006-2011” (page 90).

Here, we summarize FDA’s preliminary findings regarding the studies, including design characteristics, results, and study quality, and potential threats to validity across studies.

Study Populations

The application included 12 studies that examined the association between snus and outcomes related to gum disease or tooth loss; 11 cross-sectional studies and 1 case-control study. Table 1 summarizes the design and main findings of each study.

All of the studies took place in Sweden. Two of the studies (Hugoson et al., 2012; Hugoson and Rolandsson, 2011) used the same study population, a group of three cross-sectional studies conducted in 1983, 1993, and 2003. Other studies were conducted from prior to 1980 (Modeer et al., 1980) through the 2000’s. In one study, the date was not given (Monten et al., 2006).

Six cross-sectional studies of adult participants had sample sizes ranging from 84 to 1,674. Only one adult study compared more than 50 snus users to non-users per cross-sectional comparison. The number of snus users was not presented in one adult study and one adult study included only snus users and no non-users.

Five cross-sectional studies only included youth and young adults age 25 years or younger. Sample sizes in these studies ranged from 103 to 2,145 total participants, but only two included more than 50 snus users.

The only case-control study included 137 young adults (under age 25) but did not classify the number of snus users and non-users.

Exposure and Outcome Definitions

Definitions of the exposure varied among studies. Some of the cross-sectional studies classified snus users by lifetime exposure. Other cross-sectional studies classified snus users by the frequency of snus use such as daily snus use, nearly daily snus use, or regular snus use. The remaining studies measured exposure as a ‘yes/no’ response. Andersson and Axell (1989) included only snus users in their study and compared loose snus users to portion-bagged snus users.

The outcome measures and the definitions of each outcome varied between studies. Three studies included an aim to examine dental outcomes such as caries or tooth wear. Five studies included an aim to examine gum disease (periodontal disease) or precursors of gum disease. Four studies included broad aims to examine outcomes such as periodontal or oral health. Of these four studies with broad aims, two presented adjusted analyses on precursors of periodontal disease such as gingival index or gingival recessions. Hugoson and Rolandsson 2011 presented adjusted analyses both for the association between snus and severity of periodontal disease and the association between snus and gingival index, probing pocket depth and bone level index. Rolandsson et al., 2005 presented adjusted analyses only for risk factors for oral lesions within snus users. All of the studies with both broad and specific aims presented numerous unadjusted analyses in addition to the primary aim or primary adjusted analyses.

Results of Studies

In the applications, dental outcomes included plaque, caries, tooth wear or tooth loss. Of the two studies designed to evaluate caries, one found an association between snus and caries in unadjusted analyses (Hirsch et al., 1991), while the other found no association between snus and caries in adjusted analyses (Hugoson et al., 2012). The only study to evaluate the association between snus and tooth wear found a positive association between the two. (Ekfeldt et al., 1990) Other studies in the application provided data on the association between snus and dental outcomes but many of these were not designed to evaluate these specific outcomes or only presented unadjusted analyses for dental outcomes (See Table 1).

For periodontal disease and precursors of periodontal disease, the results were mixed by outcome. Of the three studies designed to examine periodontal disease or periodontal bone loss, none found an association between snus and periodontal disease, incipient alveolar bone loss, or distance between the cement-enamel junction and periodontal bone crest. In adjusted analyses, Hugoson and Rolandsson (2011) found no association between snus and severity of periodontal disease in any of the three years examined and only found a significant association between snus and probing pocket depth in 1983 but not 1993 or 2004.

The only adjusted study to examine the association between snus and gingival index found an association in 12-13 year olds. One case-control study that examined the outcome of buccal attachment loss found no association with snus but another study found an association between snus and gingival recession in adjusted analyses of adolescents. In addition, Andersson and Axell 1989 found gingival recessions were more common in loose snus users compared to portion-bagged snus users.

Other studies reported unadjusted analyses for periodontal disease and precursors of periodontal disease (See Table 1).

Select Methodological Issues

Study Design. Eleven of the twelve studies included in the application were cross-sectional, which limits the ability to establish temporality between exposure and outcome and provides limited evidence to infer causality. Tooth loss cannot be evaluated in cross-sectional studies; therefore the only information provided in the application is on the number of teeth in cross-sectional studies. Definitions of both exposure and outcome varied across the studies, making comparisons across studies difficult. Longitudinal studies could better track whether snus users quit due to oral health problems, and in cross-sectional studies, lifetime history of snus should be measured but only two studies included in the applications provided history of snus use (Wickholm et al., 2004; Bergstrom et al., 2006). Even when studies measured similar outcomes, the outcomes were measured in different ways. Two studies (Julihn et al., 2008; Kallestal and Uhlin 1992) were designed to identify numerous factors related to the outcome of interest, and as a result, information on the association between snus and the outcome was incomplete, as was the definition of snus use.

Many oral health outcomes are not seen until later in life; studies of these outcomes in adolescents may not apply to older adults and/or adults who have been using the product longer. In the United States, prevalence of periodontal disease increases with age (National Institute of Dental and Craniofacial Research, 2015). The applicant presents 6 studies that included only adolescents or young adults under the age of 25. One of the studies of young adults included in the application states that periodontal disease rarely appears before age 40 (Rolandsson et al., 2005). Relying too heavily on studies of adolescents to determine causality may be inappropriate for periodontal disease, as the studies may simply be conducted too early, before the outcome is present.

Other areas of concern include the replication of studies in different parts of the dental outcomes and periodontal disease section of the applications, including outcomes not related to the main aim of the study or not the principle analysis, outcomes that are more descriptive than definitive.

Precision. Small study samples and few snus users may harm the power to detect statistically significant differences. Most of the studies had less than 50 snus users, only three studies comparing outcomes between more than 50 snus users compared to non-users (Hirsch et al., 1991, Julihn et al., 2008, Wickholm et al., 2004). Two studies did not mention number of snus users making the determination of precision difficult.

Confounding and bias. Although some studies restricted by gender or restricted samples to age groups within a 5 year age range, not all studies adjusted for gender when the study included both genders or age when the study contained participants with age differences of greater than a year. The only studies that adjusted for socioeconomic status were Hugoson and Rolandsson, 2011, Hugoson et al., 2012, Wickholm et al., 2004, and Julihn et al., 2008. The case-control study did not clearly state if the analyses of the relationship between snus and buccal attachment loss were adjusted for confounding. None of the studies adjusted for health status, comorbid diseases, nutrition or medications and few adjusted for other factors or indicators of general dental health. Only a few studies excluded dual users from the analysis in the design phase of the study (Hugoson et al., 2012, Hugoson and Rolandsson, 2011, and Monten et al., 2006), and only Wickholm et al., 2004 adjusted for smoking status for specific outcomes. The significant associations seen in some studies may have been due to dual use of snus and smoking, just as the lack of significant associations may have been because the non-snus users' comparison group included smokers. Most studies also only adjusted for confounding for one outcome, not the multiple outcomes presented in the application. In addition, many of the studies included select populations that might be related to dental status such as ice hockey players (Rolandsson et al. 2005) or shipyard workers (Andersson and Axell 1989).

Summary Discussion of Epidemiological Evidence on the Use of Snus and the Risk of Gum Disease and Tooth Loss

Based on the information provided, FDA seeks input from TPSAC on the strength of the body of evidence related to the association between snus products included in the MRTPAs and gum disease or tooth loss. FDA's preliminary assessment of the epidemiologic evidence identified issues that raise questions about the quality of the studies and the sufficiency of the evidence on the association between snus use and gum disease and tooth loss. In particular, almost all of the studies presented were cross-sectional, half included only adolescents and young adults, many were small in size (e.g., most had fewer than 50 snus users), and most did not control for all appropriate potential confounding factors. In addition, the applicant does not provide an argument as to why it is biologically plausible that effects of snus on gum disease and tooth loss would be significantly different from other smokeless tobacco products. Specifically, in 6.1.1.6 of the applications (page 427), SMNA states "The composition of snus was discussed in Chapter 2 of this report; properties of snus potentially related to effects on the oral cavity are presented in the discussion below." However, the applications did not include a discussion of how the SMNA snus products are significantly different from other smokeless tobacco products.

Despite these methodological limitations, several of the studies in youth populations found an association between snus use and dental caries (Hirsch et al., 1991), gingival recession (Monten et al., 2006) or gingival index (Modeer et al., 1980). One study found an association between snus and tooth wear in adults (Ekfeldt et al., 1990).

II. Epidemiological Evidence Related to SMNA Snus and Mouth Cancer

The applicant submitted published epidemiological studies of snus and oral cancer to support the request to remove “WARNING: This product can cause mouth cancer”. The application included six epidemiological studies, including three case-control and three prospective cohort studies. FDA conducted an independent systematic search for published epidemiologic studies of snus use and disease risk and did not identify any additional studies that pertained to snus and risk of oral cancer. The applicant reported that all but one of the six studies (Roosaar et al., 2008) did not find a significantly positive association between snus and oral cancer. The overall conclusion in Chapter 5 of the ENVIRON Snus Monograph was that “a large body of evidence finds that there is no consistent finding of an association between the use of snus and oral cancer” (page 139).

The underlying assumption of the MRTPAs, is that the snus products included in the studies are comparable to the snus products that are the subject of the MRTPAs. In support of this assumption, SMNA states in section 2 (page 90) of the main portion of the applications that during the period of study, SMNA products dominated the Scandinavian snus market: “There were no snus manufacturers other than Swedish Match North America, Inc. in Sweden until the 1990s. Since then, Swedish Match North America, Inc. has historically maintained a market share of more than 80-90%. In Norway, the Swedish Match North America, Inc. volume market share was above 90% until 2005, and ranged from 70-90% from 2006-2011” (page 90).

Here, we summarize the FDA’s preliminary findings regarding the studies, including design characteristics, results, and study quality, and potential threats to validity across studies.

Study Populations

In total, there were 6 identified studies that examined the association between snus and oral cancer, including three prospective cohort and three population-based case-control studies. Tables 2 and 3 summarize the design and main findings of each cohort study and Tables 4 and 5 summarize the design and main findings of each case-control study. Five of the 6 studies were conducted in Sweden, and 1 cohort study was conducted in Norway. All 3 cohorts began in the late 1960s or early 1970s and all have 20 to 30 years of follow up through linkages to national cancer and death registries. Boffetta et al., 2005 is based on a cohort of approximately 10,000 Norwegian males and assessed the association between snus use and risk of incident oral cavity and pharyngeal cancer, as well as esophageal, stomach, pancreatic, lung, kidney, and bladder cancer. In Luo et al., 2007, a subset of 126,000 never smoking males within the Swedish Construction Worker cohort (total 280,000 men), was analyzed for associations between snus and oral, pancreatic, and lung cancers. In Roosaar et al., 2008, a subset of 10,000 men within the Uppsala County cohort from central Sweden (total 20,000) was analyzed for associations between snus and incident oral, smoking-related cancer, and any cancer, as well as death due to all causes, cardiovascular disease, cancer, and respiratory disease. In Schildt et al., 1998, 354 cases were identified through the Regional Cancer Registry of Northern Sweden and were individually-matched to 354 controls identified in National Population Registry and National Registry for Causes of Death. In Lewin et al., 1998, 545 cases were primarily identified through weekly conferences among 6 different Ear, Nose and Throat (ENT) departments in southern Sweden, and 641 controls were identified through the population register in Stockholm and

southern region. In Rosenquist et al., 2005, 132 cases were identified from weekly meetings between 2 departments, and 320 controls matched to cases 3:1 were selected from the Swedish Population Register.

Exposure and Outcome Definitions

Definitions of the exposure varied among the studies. Among the cohort studies, exposure to snus was defined as “ever daily use at entry” in Roosaar et al., 2008, “regular current use” in Boffetta et al., 2005, and “current snuff use” in Luo et al., 2007. For all three cohort studies, exposure was assessed at baseline only. Among the case-control studies, active snuff use in Schildt et al., 1998 was defined as use within 1 year of the case’s diagnosis date; ever snuff use in Lewin et al., 1998 was defined as ever regular use of “1 package (50 grams) per week” and current users as using oral snuff use within “1 year prior to the time of the interview”; current snuff use in Rosenquist et al., 2005 was use within 6 months of the time of the interview.

Definitions of the outcome also varied among the studies. Among the cohort studies, all of which identified cases through registry-linkage, Roosaar et al., 2008 had the broadest definition of oral and pharyngeal cancer, while Boffetta et al., 2005 excluded lip cancers from their definition of oral cavity and pharyngeal cancer, and Luo et al., 2007 excluded salivary gland cancer and pharyngeal cancer from their definition of oral cancer. Among the case-control studies, Schildt et al., 1998 defined the outcome as squamous cell oral cancer cases, histopathologically verified, and reported to Regional Cancer Registry of Northern Sweden; Lewin et al., 1998 defined the outcome as head and neck cancer consisting of squamous cell carcinoma of the oral cavity, oro and hypopharynx, larynx, and esophagus (no ICD codes). While 90% of the cases were identified at weekly multidisciplinary conferences at all 6 ENT departments, the remaining 10% of cases were also identified from reports to regional cancer registry; Rosenquist et al., 2005 identified oral and oropharyngeal squamous cell carcinoma (OOSCC) at weekly meetings between two hospitals in the region. (See Tables 2 and 4)

Results of Cohort Studies

In the Norwegian cohort, based on Relative Risk (RR) estimates adjusted for age, smoking cigarettes, cigars and pipe, no elevated risk of oral cancer was observed for regular current snus use (RR=1.13, 95% CI=0.45-2.83), regular ever use (RR=1.1, 95% CI=0.5-2.41), and regular former use (RR=1.04, 95% CI=0.31-3.5) compared with never or occasional use (Table 3, Boffetta et al., 2005). In the Swedish Construction Worker cohort analysis restricted to never smokers and adjusting for age and BMI, no association was observed for oral cancer and current (RR=0.9, 95% CI=0.4-1.8), ever (RR=0.8, 95% CI=0.4-1.7), and former snus use (RR=0.7, 95% CI=0.1-5.0) compared to never tobacco use. Additionally, no clear dose-response relationship was observed for 1-9 grams per day and 10+ g/day compared with never use (p-trend=0.8) (Table 3, Luo et al., 2007). In the Uppsala County cohort, ever daily snus use was significantly associated with oral cancer (RR=3.1, 95% CI=1.5-6.6) after adjusting for calendar period, area of residence, alcohol consumption, smoking, and the interaction of age and smoking. When restricted to never smokers, the association was still elevated but no longer significant (RR=2.3, 95% CI=0.7-8.3) (Table 3, Roosaar et al., 2008) (See Table 3).

Results of Case-Control Studies

In Schildt et al., 1998, no association was observed for active and ever snus use (compared with never snus use) in analyses conditioned on age, sex, county (and date of death for deceased cases) (ORs 0.7 to 0.9) (Table 5). However, ex-snus use was associated with an elevated but non-significant risk of oral cancer in analyses that included ever smokers (OR=1.5, 95% CI=0.8-2.9) and those restricted to never smokers (OR=1.8, 95% CI=0.9-3.5). Among never smokers, a slight dose-response for lifetime snus consumption was suggestive (less than 156 kg, OR=0.8, 95% CI=0.4-1.6; greater than 156 kg, OR=1.3, 95% CI=0.6-2.6). In Lewin et al., 1998, current regular use of at least 1 package per week (compared to never tobacco use) was not associated with oral cancer after adjusting for age, region, alcohol, and smoking (OR=1.0, 95% CI=0.5-2.2) (Table 5). However, ever regular snus use (OR=1.4, 95% CI=0.8-2.4) and former snus use (OR=1.8, 95% CI=0.9-3.7) were associated with elevated but not statistically significant risks of oral cancer. Additionally, in the analysis restricted to never smokers, the risk of head and neck cancer (which includes oral cancer) was significantly associated with ever regular snus use (OR=4.7, 95% CI=1.6-13.8). Evaluated only for head and neck cancer, no strong dose-response was observed for duration and total consumption, but was suggestive for intensity of usage (≤ 50 grams per week, OR=0.8, 95% CI=0.5-1.3; >50 grams per week, OR=1.6, 95% CI=0.9-2.6). Rosenquist et al., 2005 did not observe any elevated risk of oral cancer associated with current (OR=1.1, 95% CI=0.5-2.5) and ever snus use (OR=0.7, 95% CI=0.3-1.3) as compared with never snuff use after adjusting for alcohol and smoking. Former snus use was associated with a significantly reduced risk of oral cancer (OR=0.3, 95% CI=0.1-0.9), in contrast with the previous 2 case-control studies. No strong dose-response was observed for duration or exposure time (hours per day), but a suggestive trend was observed for consumption (1 to 14 grams per day, OR=0.9, 95% CI= 0.3-2.5; >14 g/day, OR=1.7, 95% CI=0.5-5.7).

Select Methodological Issues

Precision (random error). Low precision due to small sample size hampers the ability to detect small effects of a particular exposure. Oral cancer is uncommon in Sweden. Thus, despite the large number of never-smoking snuff users in the Swedish Construction Workers Cohort (~35,000) and long follow-up period, there were only 60 oral cancer cases, nine of which were current snus users at baseline (Luo et al., 2007). The other studies had similarly small numbers of exposed cases due in part to the fact that they included more cancer sites, such as pharyngeal cancer as part of their case definitions. In summary, the modest numbers of exposed cases of the studies may have limited the ability to detect smaller effects of snus on the risk of oral cancer.

Confounding. Since smoking is such a strong risk factor for oral cancer, attempts to control for smoking in the analysis may still result in residual confounding if smoking is not measured accurately. Restriction of the analysis to never smokers ensures that the findings are not confounded by smoking, although such restrictions will reduce sample size and therefore precision of the findings. Both Luo et al., 2007 and Roosaar et al., 2008 raised the potential for negative confounding in smoking-adjusted estimates if individuals who both smoke and use snus are exposed to a lower smoking dose or are more likely to quit compared with exclusive smokers. For example, in the cohort study by Boffetta et al., 2005, a significantly inverse association was found between ever snus use and lung cancer based on the estimate restricted to current smokers, after adjusting for the amount of smoking (RR=0.68, 95% CI=0.51-0.90). In the same cohort, the

association between snus and lung cancer when restricted to never smokers was closer to null (RR=0.96, 95% CI=0.26-3.56).

Applying the same rationale to oral cancer, we assessed associations based on analyses restricted to never smokers only (Table 6). Out of four studies that reported these associations, Roosaar et al., 2008 still found an elevated risk but non-significant association between snus and oral cancer. Since precision is also decreased when restricting to never smokers, the loss of statistical significance in the Roosaar study could also reflect loss of precision rather than lack of association. Lewin et al., 1998 reported a significantly elevated risk of head and neck cancer among never smokers associated with ever snus use. However, in the cohort study by Luo et al., 2007 and case-control study by Schildt et al., 1998, the associations between snus and oral cancer among never smokers were null.

Information bias. Misclassification of either the exposure category or outcome category can result in information bias. All three cohorts relied solely on a baseline assessment of snus use, with 20-30 years of follow-up. If snus users quit over time, this would lead to an underestimate of an association between snus use and oral cancer. As mentioned above, a concern has also been raised about the potential for snus users who also smoke to be more likely to cut down or quit smoking compared with exclusive smokers which might contribute to negative confounding and lead to an underestimate of the association. In case-control studies, changes in behavior due to one's disease status may also occur. While the studies defined former snuff use as quitting at least 6 months or 1 year prior to the interview, change in behavior due to development of disease symptoms is still possible. We note that former snus use, but not current use was associated with a slightly elevated risk in two of the case-control studies.

Summary Discussion of Epidemiological Evidence on the Use of Snus and the Risk of Mouth Cancer

Based on the information provided, FDA seeks input from TPSAC on the strength of the body of evidence related to the association between the snus products included in the MRTPAs and oral cancer. FDA's preliminary assessment of the epidemiologic evidence identified issues that raise questions about the sufficiency of the evidence of no association between snus use and oral cancer. In summary, among the 6 studies, 1 cohort study by Roosaar et al., 2008 observed an elevated risk of oral cancer among ever daily snus users and 1 case-control study by Lewin et al., 1998 observed an elevated risk of head and neck cancer (which includes oral cancer) among ever regular snus users. In the same study by Lewin et al., 1998, there was a non-significant, but suggestive dose-response for intensity of usage.

In addition, the number of exposed cases tended to be small in most studies, thereby limiting their ability to detect smaller associations. Many of the observed associations were based on smoking-adjusted analyses which may be biased due to residual confounding by smoking. At the same time, analyses restricted to never smokers may minimize confounding, but precision is reduced. In total, four of the studies reported never smoker estimates: Roosaar et al., 2008 found a non-significant but elevated relative risk of snus and oral cancer, and Lewin et al., 1998 found a significantly positive association between snus and head and neck cancer (which includes oral cancer). Finally, because only baseline exposure was used in the cohort studies with no reassessment of the exposure, changes in behavior over time may lead to biased

estimates. Of particular concern is the potential for snus users to quit over time, leading to an underestimate of an association with oral cancer.

III. Epidemiological Evidence on the Use of Snus and the Overall Risks to Health

The applicant submitted published epidemiological studies of snus and overall health risks to support the request to revise “WARNING: This product is not a safe alternative to cigarettes” to “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” The applicant provides in Section 6.1.1 of the MRTPAs, “Health Risks Associated with the Use of Snus as Compared to Using Cigarettes”, a summary of a subset of available studies on the health effects of snus, and the 2013 ENVIRON Snus Monograph which, in Chapter 5 of the applications, is represented as a comprehensive review of the scientific literature on Swedish snus. FDA also conducted an independent systematic search for published epidemiologic studies of snus use and disease risk to identify any additional studies omitted from the application.

Here, we summarize the FDA’s preliminary findings regarding studies, including design characteristics, results, and study quality, and potential threats to validity across studies.

Summary of Applicant’s Approach

Section 6.1.1 of the applications summarize health risks of snus as compared with cigarettes in forest plots and bullet points for each disease endpoint. Disease endpoints selected for this comparison were based on some, but not all, endpoints with the highest number of deaths attributable to smoking based on the CDC 2008 estimates. The following endpoints selected based on this criterion were ordered from highest to lowest number of smoking-attributable deaths: lung cancer, cardio-vascular disease (CVD), stroke, respiratory disease and chronic obstructive pulmonary disease (COPD), esophageal cancer, pancreatic cancer, oral cancer, and stomach cancer accounting for 90% of all smoking-related deaths. The applicant also selected “several additional health outcomes” not based on the number smoking-attributable deaths: diabetes, metabolic syndrome, all-cause mortality, and non-cancer oral effects.

The applicant applied specific criteria for studies of snus and health effects for inclusion in the direct comparisons of health risks between snus use (also referred to as snuff use) and cigarette smoking. Studies must have reported both snus and smoking estimates using a common referent (usually non-users of tobacco). They also must have adjusted for other tobacco use in both snus and cigarette relative risk estimates. Results were summarized in bullet points accompanied by forest plots of relative risk estimates for visual comparisons of health risks between snus and cigarette smokers. More detailed information, such as sample size and point estimates with their respective 95% confidence intervals, was available through one hyperlink to the tables of Appendix VI of the ENVIRON Snus Monograph (Tables A VI-1 – 10). Only relative risk estimates stratified by or adjusting for current tobacco use were included in the forest plots. If multiple RR estimates were available from a given study, preference was given to RR estimates with common reference and exposure groups (e.g., ever smokers vs. ever snus users). Additionally, select RR estimates from meta-analyses (snus and smoking) and large cohorts (smoking only) were also presented, although the methodology used to identify and select these studies was not clearly described.

While section 6.1.1 of the application only focuses on a subset of the studies, Chapter 5 of the ENVIRON 2013 Snus Monograph (“ENVIRON Review of the Scientific Literature on Snus”) is

a what the applicant referred to as a “comprehensive” review of the scientific literature on Swedish snus’ through April 2013 covering a range of human health effects.

Summary of Applicant’s Findings

Table 7 summarizes the applicant’s conclusions of the evidence of health risk for selected outcomes. The applicant concludes (section 6.1.1.4 page 425): “The forest plots used to present relative risk estimates for outcomes from individual epidemiologic studies of snus users and smokers graphically summarize and compare disease risks from these two tobacco exposures. Additional risk estimates from meta-analyses and large cohort studies provide context for relative risks from individual studies. The results presented in this section demonstrate that the use of snus presents a much lower risk, if any risk at all, of the smoking-related diseases that result in the highest number of deaths among smokers, namely lung cancer, CVD, and stroke.”

In the conclusion of Chapter 5 of the ENVIRON 2013 Snus Monograph (pages 197-198) the applicant states: “This comprehensive review of the published scientific literature confirms the lack of serious adverse health effects associated with Swedish snus. The use of Swedish snus is clearly not associated with lung cancer, oral cancer, or incident ischemic heart disease (IHD) or myocardial infarction (MI), and stroke. The health risks known to be associated with chronic use of Swedish snus appear to be acute, reversible increases in heart rate and blood pressure likely due to nicotine, and a characteristic, reversible lesion in the mouth of snus users. There is no evidence that snus is associated with other mouth and gum diseases. Several adverse pregnancy outcomes are also clearly associated with use of snus during pregnancy. Overall, there is very little evidence that current use levels of snus in Sweden are associated with any significant long-term health effects, and ongoing research is hoped to provide additional information to resolve remaining areas of uncertainty. The areas of more important public health significance where the available evidence has not yet reached the level of “definitive” for a lack of association, and thus firm conclusions cannot yet be drawn, include the relationship between Swedish snus use and possible weight gain issues, metabolic syndrome and diabetes, hypertension, and fatal myocardial infarction.”

Select Methodological Issues

Qualitative comparison of relative risk estimates. The comparison of health risks between snus and cigarette smoking was based on a visual inspection (via forest plots) of the differences in relative risk estimates for the two products, rather than hypothesis testing. By doing this, no clear definition is given to specify what is meant by “substantially lower risks to health.” The apparent differences in magnitude of risk vary considerably by disease endpoint. For conditions such as diabetes, the relative risks appear comparable between snus and cigarettes based on the forest plot (page 422), though this was based on only a few studies with two of the studies arising from the same study population (Persson et al., 2000, Ostenson et al., 2012). Some endpoints, e.g., adverse pregnancy outcomes, were not included as forest plots in the comparison between snus and cigarettes. In section 6.1.4.2.3., the applicant stated that the SMNA product is contraindicated for pregnant women and even pointed out that risk of pre-eclampsia in pregnant snus users was elevated while significantly reduced in pregnant smokers (page 549): “The seemingly “protective” effect of cigarette smoking on pre-eclampsia has not been reported in users of Swedish snus (England et al., 2003; England et al., 2010), and these authors concluded

that snus use “was associated with increased risk of pre-term delivery and pre-eclampsia” (England et al., 2003). Pre-eclampsia was reduced in smokers (by about a third) but increased in snus users (by about 60%), compared to tobacco non-users.” FDA is concerned whether a qualitative comparison is sufficient for comparing risks between snus and cigarettes given the variation in differences across disease endpoints.

Selection of studies, risk estimates and disease endpoints or comparing the health risks of snus with that of cigarettes, the applicant’s process of selecting studies resulted in presenting only a subset of the data on the health risks of snus. For example, the forest plot for pancreatic cancer (page 417) only presents one study of snus by Luo et al., 2007 when in fact studies from the Norwegian cohort have also reported results for snus and pancreatic cancer (Boffetta et al., 2005 and Heuch et al., 1983). The results for these excluded studies were reported in the review in the ENVIRON 2013 Snus Monograph. The applicant’s main reason for excluding the Boffetta study was that an analysis of smokers adjusting for snus use was not conducted. However, it is conceivable that many studies on snus may not report estimates for smoking, since the health risks are much more established for smoking. At the same time, the applicant included additional studies such as large cohort studies of smoking as “indirect comparisons” but did not add the excluded snus studies to the same category. FDA is concerned that viewing only a partial (rather than full) set of the studies could lead to different conclusions regarding the health risks of snus.

As previously noted, since smoking is such a strong risk factor for smoking-related diseases, relative risk estimates restricted to never smokers are less biased than smoking-adjusted estimates, though often precision is lost. However, the applicant did not present those estimates unless the study also reported a comparable estimate for smoking (i.e., restricted to never snus users). For example, in the forest plot on pancreatic cancer (page 417) only the smoking-adjusted estimate (RR=0.9, 95% CI=0.7–1.2) for snus and pancreatic cancer was presented from the Luo 2007 study. Not presented was the association observed among never-smokers (RR=2.0, 95% CI=1.2-3.3) in the same study which could lead to different conclusions on pancreatic cancer. Boffetta et al., 2005 observed a significant association between ever snus and pancreatic cancer based on the smoking-adjusted estimate (RR=1.67, 95% CI=1.12–2.50). However, restricting the same association to never smokers lead to a loss of precision with only 3 exposed cases (RR=0.85, 95% CI=0.24–3.07). While there are tradeoffs between smoking-adjusted and never smoker estimates, it is beneficial to examine both sets of results when available before making a conclusion for any given endpoint.

Finally, the full range of health risks due to smoking was not presented in the snus vs. cigarette comparison. Adverse pregnancy outcomes may not have been assessed due a smaller smoking-attributable burden, but conditions such as aortic aneurysm, bladder cancer, kidney cancer, laryngeal cancer (listed as some of the top causes of smoking-attributable death in Table 6-1 on page 402) were not assessed by the applicant in this section. Aortic aneurysm might have been included as a CVD event, but was never assessed as a separate outcome. As noted in the ENVIRON report (page 150), only a limited number of studies have been done for cancers such as bladder, kidney and laryngeal cancer.

Limitations in the available evidence on the health risks of snus. As a whole, the body of evidence around the health risks of SMNA snus is considerably smaller than that for cigarettes. Using diabetes as an example (page 422), a meta-analysis that links smoking with diabetes based

on 25 prospective cohort studies has been published (Willi et al., 2007), while based on findings from only a few studies, an association between snus and diabetes is suggested, but much less definitively than for smoking. Thus, there is likely to be greater uncertainty around the health risks of snus. FDA identified a number of studies published since the last search of the literature by ENVIRON, including ones that observed positive associations between snus and post-stroke and MI mortality (Hansson et al., 2014; Arefalk et al., 2014) and between snus use in early pregnancy and risk of oral clefts (Gunnerbeck et al., 2014). As mentioned earlier, the fact that not all of the smoking-related endpoints were assessed by the applicant also in part reflects the lack of available studies of snus. In summary, assessing differences in the health risks of snus and cigarettes is challenging due to the limited availability of data on snus.

Summary Discussion of Epidemiological Evidence on the Use of Snus and the Overall Risks to Health

Based on the information provided, FDA seeks input from TPSAC on the strength of the body of evidence related to the association between the snus products included in the MRTPAs and the overall risks to health as compared to cigarettes. FDA also seeks the committee's input on how to compare disease risks between products; whether such comparisons should focus on the major smoking-related disease according to population burden or assess all relevant health outcomes; and whether the proposed warning statement adequately communicates that there are potential health risks associated with the use of SMNA snus.

There is no evidence of an association between snus and lung cancer and COPD. These diseases are primarily caused by smoking cigarettes and make up a large proportion of the public health burden due to cigarette smoking. However, FDA has concerns about the applicant's the proposed "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes." Particularly with respect to whether it adequately reflects the health risks of using snus

A number of epidemiologic studies have found associations between snus and various health endpoints such as pancreatic cancer, all-cause mortality, fatal MI and stroke, diabetes, and adverse pregnancy outcomes (including preterm delivery, stillbirth, pre-eclampsia, small for gestational age, and apnea). To illustrate, snus was found to increase the risk of dying from any cause by 23% to 40% among never-smokers in two prospective cohort studies (Roosaar et al., 2008; Bolinder et al., 1994). As mentioned above, FDA identified recently published research reporting significant positive associations between use of snus and adverse pregnancy outcomes, post-stroke mortality, and mortality following MI (Hansson et al., 2014; Arefalk et al., 2014; Gunnerbeck et al., 2014).

Regarding the Comparability of the SMNA Products with those Historically Produced by SMNA

Based on the information available to FDA regarding the chemical properties of the products from the MRTPAs, Substantial Equivalence (SE) reports, scientific literature and other sources, FDA identified that the 10 General brand snus products included in MR0000020-MR0000029 and other snus products manufactured by the applicant are similar in their basic ingredients (other than tobacco): Water, NaCl, Na₂CO₃, humectants, and flavorings; heat treatment

processes; product forms: loose and pouch; product standard: The GothiaTek® standard; and HPHC levels, which are discussed below.

Figures 3-22 to 3-27 of the MR0000020-MR0000029 (submitted in June 2014) presents historical HPHCs data on SMNA products tested during 2002 – 2011. These historical data (average and 95% CI) include levels in NNK, NNN, total TSNAs, B[a]P, nitrite, As, Pd, Cd, Ni, NDMA, and nicotine. (b) (4)

. In addition, Table 3-32 of the original MRTPA presents data (min, max, and arithmetic mean) on a wide range of HPHCs in (b) snus products tested in 2011. However, the applicant did not provide any information about the brand/sub-brand names of the products tested or whether these products were representative of those on the Swedish and Norwegian markets. The levels of the 9 HPHCs tested for the 10 new products appear to be within the ranges for other snus products reported in Figures 3-22 to 3-27. (b) (4)

However, the 10 snus products identified in the MRTPAs may have different tobacco blends than other Swedish Match North America, Inc. snus products. According to the applicant, each of the 10 new products contains 3 types of tobacco: sun-cured, dark air-cured, and bright tobacco. Historical snus products, according to SMNA scientists in a 2011 paper⁴, “...are a blend of air and/or sun-cured tobacco...” FDA finds that the 10 proposed modified-risk snus products have significantly different tobacco blends than previous SMNA snus products, and expect that these differences could result in different HPHC profiles.

FDA does not have information on the exact blends of all snus products marketed in Sweden. Therefore, we cannot say with certainty that the HPHC quantities in the 10 MRTPA products are comparable or lower than those of all snus products marketed in Sweden. It is possible, based on different tobacco blends in different snus products, that HPHC quantities could be higher in the 10 MRTPA products than other snus products marketed in Sweden. It is also possible that, in spite of different tobacco blends in different snus products, that HPHC quantities could be comparable or lower in the 10 MRTPA products than those of other snus products marketed in Sweden. In addition, 5 of the 10 new snus products under the General brand name are mint or wintergreen flavored.

FDA has not yet determined whether the products are similar enough to products historically used in Sweden in order to support the bridging of epidemiological data on older products to the proposed products.

⁴ Rutqvist LE, Curvall M, Hassler T, Ringberger T, Wahlberg I. 2011. Swedish snus and the GothiaTek(R) standard. *Harm Reduct J* 8 11.

IV. The Applicability of Evidence from the Swedish Experience with Snus to Infer Potential Impacts on Tobacco Use Behavior in the U.S. population

The applicant submitted an evidence summary derived from observational studies conducted primarily in Sweden, involving Swedish and other Scandinavian study participants, in order to assess possible impacts of modified risk tobacco product marketing on tobacco use behavior in the U.S., which could include, among current tobacco users:

- The likelihood that current tobacco product users will start using the product;
- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- The likelihood that consumers will use the product in conjunction with other tobacco products;
- The likelihood that users who may otherwise quit using tobacco products will instead use the product; and
- The likelihood that consumers will use the product as intended or designed.

Among non-users of tobacco:

- The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product;
- 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.

According to the applicant, between the mid-1980s and 2007, Sweden experienced a decreasing trend of daily smoking and an increase in snus use, especially among males. Among other conclusions, the applicant states that there is “conclusive evidence that Swedish smokers transition from cigarettes to snus, and that switching from cigarettes to snus is more common than switching from snus to cigarettes in Sweden”. SMNA also concludes that snus has been used as a smoking reduction and cessation aid in Sweden, that “males are more likely to use snus than nicotine replacement products to quit smoking, and that male snus users are more likely to quit smoking than smokers who do not use snus”.

Multiple factors contribute to the development of tobacco use behaviors among youth and young adults, and influence consumers’ tobacco product preferences, purchasing patterns, frequency of use and likelihood of cessation. On an individual level, genetics and physiological differences may impact the extent to which consumers develop nicotine addiction and tobacco-related adverse health outcomes, while external factors such as social influence, environment and culture can impact population-level patterns of tobacco use (DHHS, 2010). In Sweden, snus is a traditional tobacco product, which “for several generations has been an entrenched part of the culture” (Environ International, page 1), while in the US snus remains a relatively unused/unpopular tobacco product. In 2012-2013, snus was currently used by less than 1% of U.S. adults and among youth in 2013, 0.4% of middle school and 1.8% of high school students reported past 30 day snus use (Ambrose et al., 2014; Arrazola et al., 2014). In 2011, snus comprised 3.7% of the U.S. smokeless tobacco market (Delnevo et al., 2014). Chewing tobacco,

snuff and dip are more traditional forms of smokeless tobacco used in the U.S., and were used by 2.4% of the U.S. adult population in 2012-2013 (FDA Internal Analysis, 2015).

Similarities exist between current U.S. regulatory policies and those that have historically been in place in Sweden, most notably in health warnings displayed on smokeless product packages. Despite being exempted from the 2001 European Union (EU) ban on oral tobacco (including snus)⁵, Sweden follows warning label requirements as set forth by the EU's Tobacco Product Directive (TPD). Between 1989 and 2001, snus packaging in Sweden carried a warning that the product "can cause cancer". Beginning with the 2001 TPD, the cancer warning was removed and all smokeless tobacco (including snus) packages carried the warning "this tobacco product can damage your health and is addictive". Currently, as of 2014, smokeless tobacco packaging is required to display the text warning "this tobacco product damages your health and is addictive", and must cover 30% of the two largest surfaces of the unit packet and any outside packaging (EU TPD Article 12, 2014). Furthermore, the use of any packaging language that promotes or encourages consumption of the product is prohibited, including language suggesting that the product is less harmful than other tobacco products, or has healing, natural, organic or other implicit benefits. Additionally, smokeless tobacco package labeling cannot reference taste, smell or flavoring (EU TPD Article 13, 2014).

Summary Discussion of evidence from the Swedish experience with snus to infer potential impacts on tobacco use behavior in the U.S. population

Based on the information provided, FDA seeks input from TPSAC on the applicability of the evidence on the Swedish experience with snus to infer impacts on the U.S. population. Specifically, FDA seeks input on whether the epidemiological data concerning snus patterns in Sweden is relevant to assessing the likelihood that current tobacco users and non-users in the U.S., will switch to or initiate use of snus.

FDA's preliminary assessment of the Swedish experience with snus raises questions about the applicability of the evidence to infer potential impacts on the U.S. population of tobacco users and non-users. The current warning required of snus packaging in the US are comparable to those displayed in Sweden during the period of greatest population shift away from cigarette smoking to snus use. In addition, Sweden prohibits modified risk messaging on snus packaging. Despite these similarities, the adoption of snus has been dramatically different in the US compared to Sweden.

A marketing order as proposed by SMNA would result in marketing conditions for their snus products that differ markedly from that in Sweden. There are also cultural differences with respect to the use of snus which differ markedly between the two cultures. Historically, snus has not been explicitly promoted as a less risky alternative to cigarettes in Sweden (Nordgren and Ramstrom, 1990). It is not entirely clear, from the evidence submitted by SMNA nor independent literature reviews performed by FDA, what factors have served as the leading

⁵ Snus is available for purchase in Sweden, Denmark and Norway, and is legal for personal use in Finland, but has been banned throughout European Union (EU) member states since 2001. Sweden negotiated exemption to the snus ban as a condition of joining the EU.

drivers for Sweden's population shift towards snus use. The EU's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2008) has deliberated on the transferability of Swedish evidence to inform potential future impact on tobacco use behaviors and has concluded that "...the association between patterns of smokeless tobacco use and smoking cessation differs between populations and is likely to be affected by cultural, societal and other factors...it is not possible to extrapolate future patterns of tobacco use across countries" (SCENIHR 2008, page12).

V. Comprehension of the Modified Risk Information in the Context of Total Health

The applicant submitted a study with consumers to assess comprehension and perception of the proposed changes to the warnings on snus products. Section 911(h)(1) of the FD&C Act requires that “any advertising or labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the disease and health-related conditions associated with the use of tobacco products.”

Here, we provide an overview of the study design and summarize select methodological issues.

Study Overview

SMNA conducted a premarket “Consumer Perception Study” (CPS) which was an online experimental study conducted with U.S. adults ages 18 years and older (N = 13,203) recruited from an internet consumer panel administered by Insight Express. The total study sample was split into two categories: current tobacco users (n = 6,593), defined as those who identified as daily users of any tobacco product (or NRT); and non-users (n = 6,610), which included both former regular users and never tobacco users. Participants were randomly assigned to view one of six warning labels, resulting in six experimental conditions. These conditions were: the 4 current warnings, 1 proposed modified risk warning (“a substantially lower risk”⁶), and 1 alternate version of that modified risk warning that omitted the word “substantially”. We summarize the design accordingly: 2 (Tobacco use: Current vs. Non-User) x 6 (Claim type: 4 current claims, 2 alternate MR claims) between-subjects experimental design.

Participants were exposed to a color image of 3 products displaying the respective warning label. Following exposure to the product image/warning label, participants completed a questionnaire that included items assessing: subjective understanding of the warning label; perceptions of warning label clarity and believability; perceptions of harm of snus; and perceptions of comparative harm of snus relative to other tobacco products, to cessation, and to NRT. In addition, to address questions about potential impact on tobacco use behavior, there were items assessing behavioral intentions, including: perceived likelihood of using the product and likelihood of purchasing the product.

Select Methodological Issues

Our evaluation of the CPS identified limitations that must be considered when attempting to draw conclusions from the study. Below, we describe some of these challenges.

Measures of Relative and Absolute Risk Perception. The study is predicated on the assertion that the U.S. public currently overestimates the health risks associated with using snus. In turn, the applicant proposes to modify warnings to improve the accuracy of those risk perceptions—

⁶ Note, this wording is a variation on the modified warning requested in the application, in that the latter uses the plural, “risks”.

namely, by reducing perceived risk. To demonstrate that people overestimate the health risks associated with snus, the applicant cites prior research suggesting that many consumers in the U.S., Sweden, and other countries rate snus as presenting health risks that are equal to or greater than those of cigarettes. The applicant also argues that data from the CPS show similar overestimation of the risks of snus relative to those of cigarettes, and that the proposed warning modifications “promote a better understanding of the actual health risks of snus as compared to cigarettes” (page 124). However, it is important to note that such results concerning the relative risks of snus compared to cigarettes are only part of the picture that must be considered when evaluating the potential effects of modified risk information. Equally important are public perceptions of the absolute (i.e., non-comparative) health risks of snus use, which may be accurate (or too low), even if people overestimate the risks of snus relative to cigarettes. Importantly, the accuracy of absolute perceptions of risk cannot necessarily be determined based solely on the types of measures included in the CPS. For example, whether everyday use of snus presents “Moderate risk,” “Extremely harmful risk,” or something in between may have no objective benchmark with which to compare in order to evaluate the accuracy of perceptions. Understanding the appropriateness of the absolute level of risk perception, although highly challenging, is crucial to evaluating whether consumers have an appropriate understanding of the modified risk information.

Lack of Statistical Analysis Plan. The applicant did not provide a statistical analysis plan, formulated *a priori*, that identifies criteria for evaluating the study’s results. Lack of pre-specified criteria for the “success” of a study allows for biases in the interpretation of findings (Ioannidis and Lau, 2003, page 117). For example, the CPS included survey questions about the ease of understanding, clarity, and believability of warning labels. For all three items, the applicant’s analyses revealed that the proportion of respondents giving ratings at the upper end of each scale (Very easy; Very clear; Extremely believable) was significantly smaller for the proposed modified warning compared to all four current warnings. Correspondingly, the proportion of respondents giving ratings at the lower end of each scale (Very difficult; Very vague; Not at all believable) tended to be significantly greater for the proposed modified warning compared to the current warnings. These findings suggest that the proposed modified warning is more difficult to understand than the current warnings. However, because the applicant did not pre-specify its criteria for evaluating the study results, it is unclear how these results were used, if at all, by the applicant in reaching its conclusion that, “Study results demonstrate subjects’ comprehension and understanding of the proposed warning labels...” (page 704). Indeed, in the absence of criteria that would indicate otherwise, the results actually suggest the opposite conclusion – that compared to the current warnings, consumers find the proposed modified warning less understandable.

Weaknesses in the design of its survey questions. In general, the quality of information that can be obtained from a study of consumer perception depends on the construct validity of the survey items – that is, the extent to which the items assess the constructs they are intended to measure. For illustrative purposes, we describe three examples of construct validity issues that have arisen in evaluating the CPS. First, measures of consumer comprehension were subjective, meaning that respondents rated their own level of understanding. The use of subjective measures may overestimate the extent to which consumers understand the warnings. Psychological research has found that people tend to be over-confident in their self-assessments of comprehension and may “think they have understood a piece of text when they have not”

(Dunning et al., 2004, page 87). Importantly, we are not suggesting that consumer perception research should avoid all self-assessments, but rather that the interpretation of results should acknowledge the likelihood of inflated ratings across all study conditions. Moreover, in light of these limitations, self-assessment questions might be most useful when complemented by more objective measures of understanding or comprehension.

A second construct validity issue in the CPS concerns the measures of risk perceptions and likelihood of using snus. Rather than directly asking respondents to report their risk perceptions and intentions, the CPS asked respondents questions of the type: “How does the information you saw on the warning label directly influence your ...” For example, the item designed to assess perceptions of the absolute health risk of using snus asked, “How does the information you saw on the warning label directly influence your perception of the risk that using snus every day would pose to your health?” Response options ranged from “1 – No risk” to “7 – Extremely harmful risk” and “8 – Label had no impact.” We note that, rather than assessing perceptions of risk or likelihood of using snus, these items appear to assess whether and how respondents believe that the warning label influenced these outcomes. Notably, asking respondents to identify the influence of a stimulus on their thought processes or responses is not a valid psychological methodology because people may not be aware of how particular stimuli have influenced their thoughts and behaviors (Nisbett and Wilson, 1977). To help ensure that response items assess the constructs or outcomes they are meant to assess, FDA recommends the use of items that are similar to or identical to ones that have been previously validated or published in peer-reviewed literature, when possible.

Lack of an assessment on the impacts on behavior. The CPS purports to provide information about the potential influence of modified warnings on behavior, such as initiation of snus use by non-users of tobacco and by current smokers interested in quitting. In its Study Overview (page 689), the applicant stated that the CPS assessed the effects of warning labels on behaviors including “Tobacco use behavior among current tobacco users” and “Tobacco use initiation behavior among non-users.” However, it is important to note that the CPS did not assess effects of warnings on behavior. Rather, the study assessed effects on behavioral intentions, such as self-reported likelihood of using or purchasing snus. Although behavioral intentions are important and considered proximal predictors of behavior in many domains, measures of intentions should not be conflated with measures of actual behavior. Precise terminology and interpretation of measures facilitates FDA’s evaluation of the available evidence regarding the potential impact of proposed modified risk information on the tobacco use behavior of U.S. consumers.

Summary Discussion of the Comprehension of the Modified Risk Information in the Context of Total Health

Based on the information provided, FDA will review the CPS findings with caution to identify what conclusions can be drawn about consumer reactions to the proposed warning modifications. These limitations notwithstanding, this study was not designed to address the implications of conveying modified risk information in the context of a warning label. Thus, FDA seeks input from TPSAC on the possible implications for consumer comprehension of the modified risk information, and perceptions of the product, of conveying modified risk information in the context of the warning label and possible implications the proposed revision to the warning may have on how consumers regard government-mandated warnings on other tobacco products.

Swedish Match North America, Inc. proposes to remove two warnings currently mandated for smokeless tobacco, to maintain one warning, and to modify one warning. In particular, they propose to alter the current “No tobacco product is safe” warning to include a modified risk claim: “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” Thus, modified risk information about these snus products would be conveyed to consumers in two ways: (1) passively, by the removal of warnings (i.e., mouth cancer and gum disease) from product labels, labeling, and advertising; and (2) actively, through a warning label amended to include a statement about a potential benefit of product use (i.e., reduced risk) relative to another class of products (cigarettes). This active communication of modified risk information in the context of a government-mandated warning label raises additional questions about consumer understanding of that modified risk information. Moreover, this change raises questions regarding the implications for consumer regard of government-mandated warnings on other regulated tobacco products.

The CPS was not designed to assess the impact of the context of modified risk information on consumer understanding, which could be done, for example, through a comparison of the impact of including modified risk information in the warning label (as SMNA proposes) with including it elsewhere on the product label, separate from and in addition to the warning label. A related question was addressed in a study conducted by Capella and colleagues (2012), and is noted in the CPS protocol (Appendix 6E, page 3). In particular, this experimental study examined the effect of presenting modified risk information in combination with a warning label. Results that are presented in the paper suggest the effect of the warning label on risk perceptions was affected by the inclusion of modified risk information among nonsmokers.

The presence of language that conveys a benefit of product use (relative to another product class) included in a place where consumers expect to see information about potential risks could cause confusion. The CPS study findings (discussed previously) point to a pattern wherein participants in the modified risk warning label condition reported the warning was more difficult to understand, less clear, and also less believable, compared to those who viewed the current warnings. In the absence of further investigation (e.g., qualitative data), however, it may be difficult to unpack and interpret these patterns and how these outcomes are related to each other. Nevertheless, these results highlight gaps in information surrounding what exactly consumers are taking away from a warning label that conveys modified risk information.

Finally, given that the amended warning includes the communication of (relative) benefits of use (compared to use of another product class)—information that is atypical for inclusion in a product warning (Wogalter, 2006)—it is unclear if consumers still perceive this statement as a warning at all. Without studies specifically designed to test this question, we cannot infer how consumers will perceive and comprehend this type of modified risk information conveyed within the context of a warning label that is authorized by FDA, as a regulatory agency.

VI. The Appropriate Postmarket Studies and Surveillance to be Conducted Should the Products be Marketed as Modified Risk Tobacco Products

The applicant describes a general plan for a postmarket surveillance and study program should FDA issue a marketing authorization order for this application. The applicant also provides a draft, preliminary outline of a postmarket survey protocol, while stating that the protocol will continue to be refined during the Agency MRTPA review.

The applicant describes the objectives of this program as follows:

- (1) “to evaluate the benefit to the population as a whole of the labeling changes proposed in this MRTP Application.” and
- (2) “to monitor and collect information regarding unanticipated and undesired events related to the Snus Products once they are introduced to the market, and to contribute to the establishment of an adverse event reporting mechanism.” (page 751)

(b) (4)

(see page 751). For aim 2, the applicant states a commitment to work with FDA on the building and testing of an adverse event reporting mechanism.

The applicant states that postmarket surveys will build upon the information obtained from the company’s premarket consumer perception survey (described in Section 6.4 of the application). The survey instrument will include questions from this premarket research, as well as “questions to assess consumer perception about different types of tobacco products and their effects on individuals’ health, and to generate data for use in the Dynamic Population Model (DPM) discussed in Section 6.5 of this Application.” (page 751) The applicant notes that the Population Assessment of Tobacco Health study will support and inform development of the postmarket surveys, as well.

The applicant notes a set of tools, including the “(b) (4) (b) (4) and many others—to provide information relating to consumer behavior and perception in Sweden and the United States.” (page 752) (b) (4)

(b) (4)



Summary Discussion on the Appropriate Postmarket Studies and Surveillance to be Conducted, Should the Products be Marketed as Modified Risk Tobacco Products

Based on the information provided, FDA seeks input from TPSAC on postmarket surveillance and studies should an MRTP order be issued for the SMNA snus products included in the MRTPAs. Furthermore, FDA seeks recommendations on the design features of a postmarket surveillance and studies program in order to monitor product use transitions for specific brands which may have a low market penetration and may vary across population type and over time and methods for assessing the impact of a specific MRTP order on youth perceptions and behavior in a postmarket setting.

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Appendix

Table 1. Summary of the studies designs and main findings for snus and gum disease/tooth loss

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Hirsch et al. 1990	“The aim of this study was to screen the tobacco habits of individuals 14 to 19 years of age in the City of Göteborg, Sweden, and to analyze the caries epidemiological data with regard to possible association with tobacco use.”	<ul style="list-style-type: none"> ● Cross-sectional ● Sweden, 1986 ● 2,145 males and females age 14-19 ● Participation Rate: 2145/2167=98.9% 	<ul style="list-style-type: none"> ● 197 used snuff/snuff dipping (Yes/no) 	<u>Unadjusted analyses comparing snus users to non-users</u> <ul style="list-style-type: none"> ● Decayed Missing and Filled Teeth (DMFT) ● Decayed proximal surfaces (DSp) ● Initially decayed proximal surface (DIp) ● Decayed filled proximal surface (DFSp) 	<u>Unadjusted analyses comparing snus users to non-users</u> <p>“For DMFT, DFSp and DIp all values were significantly higher p <0.001 in all groups for tobacco users, smokers and snuff dippers compared to those not using tobacco in any form.”</p>

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Hugoson et al. 2012	<p>“The present investigation should be regarded as a further evaluation of some intra-oral caries-associated variables and the effect of smoking and snus use on dental caries. The hypothesis was that smoking or the use of snus will not significantly increase the risk of dental caries compared to non-tobacco users.”</p>	<ul style="list-style-type: none"> ● Cross-sectional (3 stratified random samples) ● Jönköping, Sweden ● 1983, 1993 and 2003 ● 1983: 539 males and females from age groups 20's-70's ● 1993: 543 males and females from age groups 20's-70's ● 2003: 509 males and females from age groups 20's-70's ● Participation Rate 1983: 550/780=70.5% ● Participation Rate 1993: 552/780=70.8% ● Participation Rate 2003: 523/780=67.1% ● Same population as Hugoson and Rolandsson 2011 	<ul style="list-style-type: none"> ● 1983: 22 daily snus users ● 1993: 38 daily snus users ● 2003: 44 daily snus users 	<p><u>Analyses adjusted for age, gender, SES</u></p> <ul style="list-style-type: none"> ● odds of decayed and filled tooth surfaces (classified as low/high according to median %) <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● # of teeth ● Visible plaque index ● secretion rate ● buffer capacity ● mutans strept ● lactobacilli 	<p><u>Analyses adjusted for age, gender, SES</u></p> <ul style="list-style-type: none"> ● no association between snus and decayed or filled surfaces any year, adjusted for age, gender SES (ORs not given) <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● In unadjusted analyses, in 1983, snus users had significantly more teeth and fewer mean decayed or filled surfaces than non-users ● In unadjusted analyses, in 1993, snus users had significantly less decayed and filled surfaces than non-users, ● No differences between snus users and non-users in 2003

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Ekfeldt et al. 1990	“The aim of this study was to introduce and individual tooth wear index with the potential to rank persons with regard to incisal and occlusal wear and to use this index to study factors related to such wear in an adult Swedish population.”	<ul style="list-style-type: none"> ● Cross-sectional ● Jönköping, Sweden 1983 ● 585 males and females age 20+ ● participation rate not stated ● may be same population as 1983 cross-section of Hugoson 2012 and Hugoson and Rolandsson 2011, however with a total n of 585 instead of 550 	<ul style="list-style-type: none"> ● snus use yes/no ● number of snus users not stated 	<p><u>Analyses adjusted for number of teeth, sex, bruxism, age, buffer capacity</u></p> <ul style="list-style-type: none"> ● size of correlation between predictive factors and individual tooth wear index (incisal and occlusal wear) 	<p><u>Analyses adjusted for number of teeth, sex, bruxism, age, buffer capacity</u></p> <ul style="list-style-type: none"> ● snus explained 1.2% of the variance in the final adjusted model predicting individual tooth wear index

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Rolandsson et al. 2005	“The purpose of this comparative study was to investigate effects of snuff on oral health status of adolescent males.”	<ul style="list-style-type: none"> ● Cross-sectional study ● Värmland, Sweden – year not provided ● 80 males age 16-25 (ice hockey players and students) ● Users and non-users were matched by age ● Participation Rate: 80/170=47.1% 	<ul style="list-style-type: none"> ● Used snuff every day or almost every day ● 40 snus users 	<p><u>Analyses adjusted for hours used per day and type of snus used (study restricted to males)</u></p> <ul style="list-style-type: none"> ● Risk factors for degree of oral mucosal lesions in snus users only <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● Oral health problems and oral health care (not represented statistically) ● Number of teeth ● Restorations/filled teeth ● Probing pocket depth ● Gingival recessions ● Plaque ● Gingivitis 	<p><u>Analyses adjusted for hours used per day and type of snus used (study restricted to males)</u></p> <ul style="list-style-type: none"> ● Among snus users, degree 1 snus lesions were associated with number of hours a day OR 4.11 (CI 1.09-15.55) of snus use and degree 2 snus lesions were associated with number of hours a day and type of snus used (portioned compared to loose) <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● In unadjusted analyses, no significant differences in restorations/fillings, plaque, gingivitis between groups (p-value for t-tests >0.05). ● No deepened periodontal pockets found in either group. ● “Recessions between 1-5 mm were measured in seven snuff users and these were situated in connection with a mucosal lesion.” No mention in paper of recessions in non-users. No statistical analyses conducted. ● no significance tests reported for number of teeth

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Bergström et al. 2006	“The aim of the present study, therefore was to investigate the possible association between the use of moist snuff and periodontal bone loss in subjects with moderate to long-term duration of use.”	<ul style="list-style-type: none"> ● Cross-sectional ● Karlskrona, Sweden Nov. 2002-Dec. 2003 ● 84 males age 26-54 ● Participation Rate Not given, simply state “84 participants volunteered to participate” 	<ul style="list-style-type: none"> ● 25 current snus users ● 21 former snus users ● 28 never snus users <p>“Users were categorized according to duration of snuff use into 2 exposure groups: light exposure users including participants with duration of less than 15 years and heavy exposure users including participants with duration of 15 years or more.”</p> <p>10 current users and 8 former users were former smokers. All never users were never smokers.</p>	<p><u>Analyses adjusted for age</u></p> <ul style="list-style-type: none"> ● association between snus and periodontal bone height (radiographical distance from the cement–enamel junction (CEJ) to the periodontal bone crest (PBC) -- arithmetical mean of all CEJ-PBC determinations served as a measure of the periodontal bone height in the individual (case-mean).) <p><u>Unadjusted analyses comparing snus users to all other groups</u></p> <ul style="list-style-type: none"> ● # of teeth ● deepened periodontal pockets ● gingival bleeding ● plaque 	<p><u>Analyses adjusted for age</u></p> <ul style="list-style-type: none"> ● “controlling for age, the association between snus use and bone height was not statistically significant.” <p><u>Unadjusted analyses comparing snus users to all other groups</u></p> <ul style="list-style-type: none"> ● unadjusted no significant differences in number of teeth, periodontal pockets, gingival bleeding or plaque

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Hugoson and Rolandsson 2011	“The aim of the present study was to examine how deleterious the current smoking and use of Swedish snus is for periodontal health compared with non-users.”	<ul style="list-style-type: none"> ● Cross-sectional (3 stratified random samples) ● Jönköping, Sweden ● 1983, 1993 and 2003 ● 1983: 539 males and females from age groups 20's-70's ● 1993: 543 males and females from age groups 20's-70's ● 2003: 509 males and females from age groups 20's-70's ● Participation Rate 1983: 550/780=70.5% ● Participation Rate 1993: 552/780=70.8% ● Participation Rate 2003: 523/780=67.1% ● dual users excluded ● Same population as Hugoson et al. 2012 	<ul style="list-style-type: none"> ● 1983: 22 daily snus users ● 1993: 38 daily snus users ● 2003: 44 daily snus users 	<p><u>Analyses adjusted for age, gender, education, employment, marital status</u></p> <ul style="list-style-type: none"> ● odds of periodontal disease severity groups 1, 2, 3 vs groups 4, 5 (groups 4 and 5 include alveolar bone loss 1/3+, groups 1,2,3 include healthy adults, adults with gingivitis and alveolar bone loss up to 1/3) ● probing pocket depth ● gingival index ● bone level index <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● subgingival calculus and supragingival calculus ● visible plaque index ● number of teeth ● gingival recessions ● gingival inflammation (Bleeding on probing) ● bone level index ● probing pocket depth 	<p><u>Analyses adjusted for age, gender, education, employment, marital status</u></p> <ul style="list-style-type: none"> ● 1993 adjusted for age, gender, SES and subgingival calculus and smoking OR for snus use in group 4 and 5 compared to group 1, 2, 3 0.75 (0.14-4.11) ● bone level index and gingival index showed no association any year after controlling for age, gender, SES ● probing pocket depth associated with snus use in 1983 OR=3.98 after adjusting for age, gender SES, not verified in 1993, 2003 <p><u>Unadjusted analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● in unadjusted analyses number of teeth higher in snus users than non-users 1983 ● in unadjusted analyses bone loss index higher in snus users than non-users in 1983 ● in unadjusted analyses gingival recessions (percentage of sites) lower in 1993 in snus users compared to non-users ● no association between snus and plaque index, gingival index, probing pocket depth, subgingival calculus or supragingival calculus in unadjusted analyses in any year

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Montén et al. 2006	“The purpose of the present study was therefore to evaluate the potential influence of the use of smokeless tobacco (moist snuff) on the periodontal conditions in adolescents.”	<ul style="list-style-type: none"> ● Cross-sectional ● Sweden, year not given ● 103 males age 19 ● all participants were never smokers ● Participation Rate not stated 	<ul style="list-style-type: none"> ● 33 current snus use <p>yes/no</p>	<p><u>Analyses adjusted for plaque, gingivitis and toothbrushing (entire study restricted by age and gender)</u></p> <ul style="list-style-type: none"> ● odds of one or more teeth with gingival recession in snus users compared to non-users (in full mouth and anterior tooth region) <p><u>Unadjusted Analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● visible plaque score ● # of teeth ● gingivitis ● gingival recession ● alveolar bone loss (ABL) ● clinical attachment loss (CAL) ● mean probing pocket depth (PPD) 	<p><u>Analyses adjusted for plaque, gingivitis and toothbrushing (entire study restricted by age and gender)</u></p> <ul style="list-style-type: none"> ● odds ratios for gingival recession in snus users compared to non-users were 3.72 (1.4-9.9) for all teeth and 5.099 (1.7-15.5) in the anterior maxillary tooth region after adjusting <p><u>Unadjusted Analyses comparing snus users to non-users</u></p> <ul style="list-style-type: none"> ● unadjusted analyses no significant differences in mean # of teeth, plaque or gingivitis ● ABL, CAL and PPD in unadjusted analyses, however mean values within 0.1mm between groups (p>0.05)

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Wickholm et al. 2004	“The aim of this epidemiological investigation was to compare the prevalence of periodontal disease in tobacco users who consume either cigarettes or snuff, and those who use both products.”	<ul style="list-style-type: none"> ● Cross-sectional ● Sweden before 1985 (based on statement of participant’s ages and birth year) ● Males and females age 31-40 ● n=1674 ● Participation Rate: 1674/3273=51.1% 	153 snus users (122 current snus users, 31 former users) (54 Ever snus, 99 mixed snus/cigarettes)	<p><u>Analyses adjusted for age, gender, education, plaque and smoking</u></p> <ul style="list-style-type: none"> ● odds of Periodontal disease (defined as 3 teeth with pocket depth \geq 5mm) <p><u>Unadjusted analyses comparing snus users to all other groups (never user, ever or mixed)</u></p> <ul style="list-style-type: none"> ● Plaque Index ● Gingival Index ● Calculus Index ● Gingival recessions ● pocket depth (3 or more teeth \geq 5mm) 	<p><u>Analyses adjusted for age, gender, education, plaque and smoking</u></p> <ul style="list-style-type: none"> ● adjusted analyses current snus use not associated with periodontal disease OR 0.71 (0.32-1.41) ● adjusted analyses former snus use not associated with periodontal disease OR 2.25 (0.71-5.95) <p>indication of association with former compared to never users</p> <p><u>Unadjusted analyses comparing snus users to all other groups (never user, ever or mixed)</u></p> <ul style="list-style-type: none"> ● gingival index, calculus index, recessions and pocket depth greater in snus users than never users but no pairwise comparisons ● no significant differences in plaque

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Mod�er et al. 1980	“The present investigation was designed to study the relation between the use of tobacco and oral health in schoolchildren.”	<ul style="list-style-type: none"> •Cross-sectional •Huddinge, Sweden (pre-1980) •232 males and females ages 13-14 •Participation Rate not stated 	<ul style="list-style-type: none"> •13 took snuff regularly (11% of boys took snuff, n=119 boys, no females used snuff) 	<u>Analyses adjusted for or oral health (study restricted by age)</u> <ul style="list-style-type: none"> • associations between cigarettes and plaque, decayed surfaces and filled teeth •associations between snus and gingival index 	<u>Analyses adjusted for oral health (study restricted by age)</u> <ul style="list-style-type: none"> •snus was significantly correlated (p<0.001) with gingival index (all teeth) after controlling for plaque and gingival index (upper front jaw) plaque an brushing habits • in unadjusted analyses, gingival index was 1.1 in snus users and 0.89 in non-users • “comparing snuff takers and non the only variable which differed significantly at P <.001 was gingival index on all surfaces and upper front jaw”
Andersson and Ax�ll 1989	“The aim of this study was to register and compare clinical oral mucosal lesions and gingival recessions associated with the use of two different smokeless tobacco products, loose snuff and portion-bag packed snuff.”	<ul style="list-style-type: none"> •Cross-sectional •Sweden, 1986-1987 •male adults •n=252 •75% participation in construction workers , not stated for shipyard workers or those referred to study 	252 self-reported loose snuff vs portioned snuff use. Inclusion criteria: no other tobacco habit than snuff and reported daily snuff consumption for at least 3 months	<u>Adjusted for placement of snus, years of snus use, age, grams of snus</u> <ul style="list-style-type: none"> • “gingival recessions registered as snuff related if the borderline of the vestibular snuff dipper’s lesion was in contact with the retracted gingival margin” •snuff dippers lesion 	<u>Adjusted for placement of snus, years of snus use, age, grams of snus</u> <ul style="list-style-type: none"> •relative risk snuff dippers lesion in loose compared to portioned snuff users 3.39 (p=0.01) •relative risk gingival recessions loose vs portioned use 8.71 (p=0.009)

Author Publication year	Aim/Outcome	Population	Exposure	Outcome	Results
Juliñ et al. 2008	“The primary aim of the present study, on a subject-based level, was to investigate risk factors and risk indicators associated with the occurrence of incipient alveolarbone loss in Swedish 19-year-olds, with special reference to immigrant background. A secondary aim was to determine the occurrence of risk indicators and risk factors in relation to subgingival calculus.”	<ul style="list-style-type: none"> •Cross-sectional •Sweden, 2001 •686 males and females 19 years old • 87% attended appointment, 686 / 800 (85.8%) final population 	83 current daily snus users (frequency was measured as never, sometimes or daily, but in statistical analyses the categories “never” and “sometimes” were combined)	<u>Adjusted for education level and occupation status of parents (study restricted by age)</u> <ul style="list-style-type: none"> •odds of incipient alveolar bone loss 	<u>Adjusted for education level and occupation status of parents (study restricted by age)</u> <ul style="list-style-type: none"> •odds ratio of incipient alveolar bone loss in snus users compared to non-users 1.15 *0.7-1.89) P=0.59
Källestål and Uhlin 1992	“The aim of the present investigation was to study the association between buccal attachment loss and various factors, earlier suggested as etiological for gingival recession.”	<ul style="list-style-type: none"> •Case-control •Sweden, 1987-1989 •137 Gender not specified, likely both •ages 18-22 •Participation Rate Not provided but final n=137/195 (70% of original cross-sectional) 	<ul style="list-style-type: none"> •Use of smokeless tobacco yes/no •number of snus users not stated 	<ul style="list-style-type: none"> •Buccal attachment loss (similar to gingival recession according to authors) present if attachment situated ≥ 1 mm from CEJ (cement enamel junction) 	<ul style="list-style-type: none"> •“No differences in the use of smokeless tobacco between the referent and the case group were detected in the present study” (This sentence from the discussion is the only sentence discussing results related to snus in the paper’s methods, results or discussion section)

Table 2. Study characteristics of cohort studies of snus and oral cancer

Main Author	Publication year	Country	Cohort name	Study Period	Study Population	Exposure	Outcome	Sample size	Funding source
Roosaar	2008	Sweden	Uppsala County	1973-4 to 2002	From population-based survey on oral lesions, all residents of Enkoping or Habo age 15 and older, central Sweden, total 20,333, 68% participation, analysis restricted to 9,976 men	Exposure assessed by self-administered questionnaire at baseline (1973-4); subcohort of 252 men also reassessed in 1993-5; "Exposure to snus was categorized as never or ever daily use at entry into the cohort in 1973-74."	Incident cancer: oral and pharyngeal cancer (ICD7 140-148 all oral cavity and pharyngeal), record-linkage to registers of cancer; 99.4% follow-up	9860 total, 1548 ever daily use of snus, 34 oral/pharyngeal (11 ever daily use)	Swedish Cancer Society, Swedish Medical Research Council, Swedish Dental Society
Boffetta	2005	Norway		1966 to 2001	Sample of general adult population from 1960 census AND relatives of Norwegian migrants to the US; total 12,431 men alive in 1966; participation rate above 75%	Exposure assessed by questionnaire at baseline (1964 and 1967); snus use classified as regular current, regular former or never or occasional use	Incident cancer: oral cavity and pharyngeal cancer (ICD7 141-148 all except lip), linkage with nationwide residence, mortality and cancer incidence registries; 15 or 0.15% lost to follow-up (or 99.9% follow-up rate)	10,136 total; regular current use 1,999; regular former use 1,216; 34 oral and pharyngeal cancers	US National Cancer Institute with the Cancer Registry of Norway
Luo	2007	Sweden	Swedish construction worker cohort	1978-1992 to 2004	Workers in Swedish building industry; analysis restricted to men; participation 98%	Exposure assessed by nurse interview during at least one visit between 1978-92; snus use status based on first visit (never, previous, or current)	Incident cancer; ICD7 140, 141, 143, 144 (not saliva, pharynx); linkage to population and health registers; 98% follow up	279,897 total male; 125,576 never smokers; 34,818 current snus; 37,755 ever snus; 60 oral cancers	Swedish Cancer Society

Table 3. Results of cohort studies of snus and oral cancer

Main Author	Year	Snus exposure	Number of exposed cases	Inclusion of smokers	Outcome	RR	95% CI	Adjustment Factors	Referent
Roosaar	2008	ever daily	5	No	Oral and pharyngeal cancer (ICD7 140-148)	2.3	(0.7, 8.3)	calendar period, area of residence, alcohol consumption	never daily use of snus
Roosaar	2008	ever daily	11	Yes	Oral and pharyngeal cancer (ICD7 140-148)	3.1	(1.5, 6.6)	calendar period, area of residence, alcohol consumption, smoking, age x smoking	never daily use of snus
Boffetta	2005	regular current	6	Yes	Oral and pharyngeal cancer (ICD7 141-148 all except lip)	1.1	(0.5, 2.8)	age, smoking cigarettes, cigars and pipe	never or occasional snuff
Boffetta	2005	regular ever	9	Yes	Oral and pharyngeal cancer (ICD7 141-148 all except lip)	1.1	(0.5, 2.4)	age, smoking cigarettes, cigars and pipe	never or occasional snuff
Boffetta	2005	regular former	3	Yes	Oral and pharyngeal cancer (ICD7 141-148 all except lip)	1	(0.3, 3.5)	age, smoking cigarettes, cigars and pipe	never or occasional snuff
Luo	2007	current	9	No	Oral cancer (ICD7 140, 141, 143, 144)	0.9	(0.4, 1.8)	age and BMI	never tobacco
Luo	2007	ever	10	No	Oral cancer (ICD7 140, 141, 143, 144)	0.8	(0.4, 1.7)	age and BMI	never tobacco
Luo	2007	former	1	No	Oral cancer (ICD7 140, 141, 143, 144)	0.7	(0.1, 5.0)	age and BMI	never tobacco

Main Author	Year	Snus exposure	Number of exposed cases	Inclusion of smokers	Outcome	RR	95% CI	Adjustment Factors	Referent
Luo	2007	1-9 g/day	2	No	Oral cancer (ICD7 140, 141, 143, 144)	0.7	(0.2, 2.8)	age and BMI	never tobacco
Luo	2007	10+ g/day	8	No	Oral cancer (ICD7 140, 141, 143, 144)	0.9	(0.4, 2.0)	age and BMI	never tobacco

* Sex: All studies included only men

** Measure: HR (Cox)

Table 4. Study characteristics of case-control studies of snus and oral cancer

Main Author	Publication year	Country	Cases	Controls	Exposure	Sample Size	Funding source
Schildt	1998	Sweden	Squamous cell oral cancer cases (ICD7 140,141,143-5), histopathologically verified, diagnosed 1980-9, reported to Regional Cancer Registry of Northern Sweden, 4 northern counties, 96% response rate	For each of 175 living cases, 1 living control from National Population Registry matched by closest in age, same sex, same county; for each of 235 deceased cases, 1 deceased control from National Registry for Causes of Death (matched on age, sex, county, yr of death); 91% response rate	Mailed questionnaire to living or next-of-kin of deceased, classified as active, never or ex-snuff use (a person who had quit the habit at least 1 year before the diagnosis year of case)	354 cases; 354 matched controls	Research Foundation of the Department of Oncology, Umea University, Swedish Tobacco Research Council, Mrs. Berta Kamprad Foundation and Orebro County Council Research Committee
Lewin	1998	Sweden	Incident squamous cell carcinoma of the oral cavity, oro and hypopharynx, larynx, and esophagus (no ICD), study base all men born in Sweden between 40-79 living in Stockholm county or southern Sweden Jan 1988 to Jan 1991; cases identified at weekly multidiscipline conferences at all 6 ENT departments; 10% cases also identified from reports to regional cancer registry; 90% response rate	Selected from stratified random sampling every 6 months during the study period from computerized population register in each region; stratification by region (Stockholm and southern region) and age (40-54, 55-64, 65-79); 85% response rate	Interview based on structured questionnaire conducted by nurse; oral snuff use classified as ever use (ever regularly used 1 package (50 grams) per week), current use (used oral snuff 1 year prior to the time of the interview), and never used	545 cases; 641 controls	Cancer Society of Stockholm, the Swedish Cancer Fund, and the research fund of the Swedish Tobacco Company

Main Author	Publication year	Country	Cases	Controls	Exposure	Sample Size	Funding source
Rosenquist	2005	Sweden	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141 tongue, 143 floor of the mouth, 144 oral cavity not otherwise spec, 145 oropharynx); born in Sweden and without a previous cancer diagnosis; identified at weekly meetings between 2 hospitals in region; total 132 patients, 91 males and 41 females; 80% response rate	3 controls to 1 case selected from Swedish Population Register based on stratified random sampling; matched on age ± 3 y, sex and county; born in Sweden with no previous cancer diagnosis and lived in Southern Healthcare Region of Sweden; 81% response rate	Interview and exam for all cases and controls; classified as never users, current users and ex-users (had stopped taking snuff at least 6 months before the interview)	132 cases; 320 controls	This work was supported by the Cancer Foundation of Malmo University Hospital, the Gunnar Nilsson Cancer Foundation, the Berta Kamprad Foundation, the Swedish Dental Society, the Faculty of Odontology, Malmo University, the Alfred Osterlund Foundation, the Swedish Cancer Society and the King Gustaf V Jubilee fund.

Table 5. Results of case-control studies of snus and oral cancer

Main Author	Year	Sex	Exposure	Number of exposed cases	Inclusion of smokers	Outcome	OR	95% CI	Adjustment Factors	Referent
Schildt	1998	Men/women	Active	39	Yes	squamous cell oral cancer (140,141,143-145)	0.8	(0.5, 1.3)	conditioned on matching factors, also smoking, light beer, beer, wine, liquor	never snuff
Schildt	1998	Men/women	Active	39	Yes	squamous cell oral cancer (140,141,143-145)	0.7	(0.4, 1.1)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	ex-user	28	Yes	squamous cell oral cancer (140,141,143-145)	1.5	(0.8, 2.9)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	Ever	67	Yes	squamous cell oral cancer (140,141,143-145)	0.9	(0.6, 1.4)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	Active	19	No	squamous cell oral cancer (140,141,143-145)	0.7	(0.4, 1.2)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	ex-user	9	No	squamous cell oral cancer (140,141,143-145)	1.8	(0.9, 3.5)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	Low lifetime consumption (<=156 kg)	4	No	squamous cell oral cancer (140,141,143-145)	0.8	(0.4, 1.6)	conditioned on matching factors	never snuff
Schildt	1998	Men/women	High lifetime consumption (>156 kg)	13	No	squamous cell oral cancer (140,141,143-145)	1.3	(0.6, 2.6)	conditioned on matching factors	never snuff

Main Author	Year	Sex	Exposure	Number of exposed cases	Inclusion of smokers	Outcome	OR	95% CI	Adjustment Factors	Referent
Lewin	1998	Men	ever regular use (1 package per week)	25	Yes	oral	1.4	(0.8, 2.4)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	current regular use (1 package per week) (1 year prior)	10	Yes	oral	1	(0.5, 2.2)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	former regular use (1 package per week)	15	Yes	oral	1.8	(0.9, 3.7)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	>50 grams/week		Yes	oral	1.7	(0.8, 3.9)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	ever regular use (1 package per week)	83	Yes	head and neck	1.1	(0.7, 1.5)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	current regular use (1 package per week) (1 year prior)	43	Yes	head and neck	1	(0.6, 1.6)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	former regular use (1 package per week)	40	Yes	head and neck	1.2	(0.7, 1.9)	age, region, alcohol, smoking	never tobacco users
Lewin	1998	Men	ever regular use (1 package per week)	9	No	head and neck	4.7	(1.6, 13.8)	age, region, alcohol	never tobacco users
Lewin	1998	Men	current regular use (1 package per week) (1 year prior)		No	head and neck	3.3	(0.8, 12.0)	age, region, alcohol	never tobacco users
Lewin	1998	Men	former regular use (1 package per week)		No	head and neck	11	(1.4, 117.8)	age, region, alcohol	never tobacco users

Main Author	Year	Sex	Exposure	Number of exposed cases	Inclusion of smokers	Outcome	OR	95% CI	Adjustment Factors	Referent
Rosenquist	2005	Men/women	current	13	Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	1.1	(0.5, 2.5)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Ever	20	Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.7	(0.3, 1.3)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Former	7	Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.3	(0.1, 0.9)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Fermented	16	Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.7	(0.3, 1.4)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	non-fermented	4	Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.6	(0.2, 1.9)	alcohol, smoking	never used snuff

Main Author	Year	Sex	Exposure	Number of exposed cases	Inclusion of smokers	Outcome	OR	95% CI	Adjustment Factors	Referent
Rosenquist	2005	Men/women	Duration <30 years		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.6	(0.3, 1.3)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Duration >=30 years		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.8	(0.2, 2.8)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Exposure time (h/day) <=10		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.9	(0.3, 1.5)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	Exposure time (h/day) >10		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.5	(0.2, 1.6)	alcohol, smoking	never used snuff
Rosenquist	2005	Men/women	1 to 14g/day		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	0.9	(0.3, 2.5)	alcohol, smoking	never used snuff

Main Author	Year	Sex	Exposure	Number of exposed cases	Inclusion of smokers	Outcome	OR	95% CI	Adjustment Factors	Referent
Rosenquist	2005	Men/women	>14g/day		Yes	Oral and oropharyngeal squamous cell carcinoma (OOSCC) (ICD7 141, 143, 144, 145)	1.7	(0.5, 5.7)	alcohol, smoking	never used snuff

Table 6. Results of associations of snus and oral cancer restricted to never smokers

Main Author	Year	Time of exposure	Exposed cases	Effect Estimate	(95% CI)	Adjustment Factors	Measure	ICD	Referent
Lewin	1998	ever regular use (1 package per week)	9	4.7	(1.6, 13.8)	age, region, alcohol	OR	oral, pharyngeal, larynx, esophagus	never tobacco users
Schildt	2001	Active	19	0.7	(0.4, 1.2)	conditioned on matching factors	OR	ICD7 140,141,143-148	never snuff
Luo	2007	Current	9	0.9	(0.4, 1.8)	age and BMI	RR (Cox)	ICD7 140,141,143,144	never tobacco
Roosaar	2008	ever daily	5	2.3	(0.7, 8.3)	calendar period, residence, alcohol	RR (Cox)	ICD7 140-148	never daily use of snus

Table 7. Summary of applicant’s conclusions for selected health endpoints

	Snus vs. cigarettes	Snus health risks
Lung cancer	“The results indicate that Swedish snus users are at no greater risk of developing lung cancer than non- or never-users of tobacco, while smokers are 7 to 30 times more likely to develop lung cancer based on two studies of the large Swedish Construction Worker cohort (Bolinder et al., 1994; Luo et al., 2007).” (p 406 section 6.1.1.3 of the Application)	"Well controlled epidemiological evidence indicates that Swedish snus is not associated with lung cancer." (p 149 section 5.3.7 of the ENVIRON Snus Monograph)
Cardiovascular disease	“The results indicate that, consistent with what is known about smoking and overall CVD risk, the observed increased risk in smokers is generally 1.5 to 3 times that observed among nontobacco users. However, overall CVD risk was not increased among snus users.” (p 407 section 6.1.1.3 of the Application)	"Though there are known acute effects of nicotine on the cardiovascular system, no increased risk of cardiovascular disease has been detected epidemiologically, with the possible exception of a moderate increased risk of death due to a CV event. This increased risk of mortality due to a CV event among snus users has only been observed in the Construction Workers Cohort in Sweden..." (p 166 section 5.4.4 of the ENVIRON Snus Monograph)
Stroke	“Overall, the stroke risk among Swedish snus users appears to be no different than that of non-users of tobacco, while the risk is consistently at least 40% greater among smokers compared to non-users of tobacco.” (p 410 section 6.1.1.3 of the Application)	"None found an increased risk of all stroke types combined among current or former snus users...In one study that examined ischemic stroke, an increased risk of ischemic stroke was observed among snus users, however, in this study, no dose-response relationship with ischemic stroke was observed...The two recent reviews of stroke studies published through 2008, both reported no increased risk of stroke incidence. One of the recent reviews suggested an increased risk from fatal stroke based on one study in which a significant increased risk of fatal ischemic stroke was observed, but when results of studies of fatal stroke were combined by Boffetta and Straif, the risk of fatal stroke was not significantly elevated." (p 169 section 5.5.3 of the ENVIRON Snus Monograph)
Respiratory disease	“There is no known mechanism by which snus could cause nonmalignant respiratory disease....Thus, based on mechanistic considerations; Swedish snus is widely accepted not to be associated with chronic lung disease, even in the absence of epidemiological confirmation.” (p 412 section 6.1.1.3 of the Application)	"Among these studies, statistically significant positive associations with snus use and subsequent...respiratory death...were observed in single studies, thus no strong conclusions about associations between snus use and these health outcomes can be drawn based only on single studies." (p 190 section 5.11.14 of the ENVIRON Snus Monograph)

	Snus vs. cigarettes	Snus health risks
COPD	“In sum, it is widely accepted that COPD results from long term exposure from airborne irritants such as tobacco smoke and air pollution... Thus, based on these observations and considerations, Swedish snus is widely accepted not to be associated with COPD or any other acute or chronic non-malignant lung disease, even in the absence of supportive epidemiological evidence.” (pp 413-414 section 6.1.1.3 of the Application)	
Esophageal cancer	“Even if the summary relative risk estimate among snus users of 1.6 reported by Boffetta et al., (2008) is accurate, as compared to the risk of esophageal cancer among smokers, the increased risk among snus users is at least several fold lower compared to that among current smokers.” (p 415 section 6.1.1.3 of the Application)	"Overall, the epidemiology studies suggest no association between snus use and esophageal cancer, but limitations in the available studies, and inconsistent results of the meta-analyses indicate a need for additional study of this outcome." (p 149 section 5.3.7 of the ENVIRON Snus Monograph)
Pancreatic cancer	“Although uncertainties and inconsistencies exist as to whether the risk of pancreatic cancer among snus users is increased, pancreatic cancer is consistently increased among smokers, as reported in multiple studies and meta-analyses...” (p 416 section 6.1.1.3 of the Application)	"Two cohort studies suggest that use of Scandinavian smokeless tobacco could be associated with increased risk of pancreatic cancer among some subgroups of the population. However, there are troubling inconsistencies between the two studies with respect to the specific subgroups at risk (only individuals who were also current smokers in one study vs. only never-smokers of tobacco in the second study)...the available evidence suggests that snus and other smokeless tobacco forms are not associated with pancreatic cancer." (p 150 section 5.3.7 of the ENVIRON Snus Monograph)
Oral cancer	“Overall, relative risks for snus users do not suggest a relationship between snus and oral cancer and further indicate that snus users are at no greater risk of developing oral cancer than non- or never-users of tobacco.... the risk of oral cancer morbidity and mortality is consistently increased among the smokers, with risk estimates ranging from 1.7 to 27...” (p 418 section 6.1.1.3 of the Application)	"The available evidence suggests that use of Swedish snus is not associated with an increased risk of oral cancer." (p 149 section 5.3.7 of the ENVIRON Snus Monograph)
Stomach cancer	“Overall, the risk of stomach cancer among smokers was clearly increased, while the evidence consistently suggests that the risk of stomach cancer among snus users appears to be no different than non-users of tobacco...” (p 419 section 6.1.1.3 of the Application)	"For stomach cancer, no studies found that use of snus was associated with any significant increase in risk of overall or cardia stomach cancer (cardia is the upper portion of the stomach), but one study found an elevated risk for the noncardia subtype of stomach cancer. These data suggest no association between snus use and stomach cancer overall, but additional research will help confirm whether the finding for the noncardia subtype is real." (p 150 section 5.3.7 of the ENVIRON Snus Monograph)

	Snus vs. cigarettes	Snus health risks
Diabetes	“Overall, it is unclear whether the risk of diabetes among snus users is different from those who do not use tobacco... A clear association between diabetes and smoking was also observed in a meta-analysis by Willi et al., (2007).” (page 421 section 6.1.1.3 of the Application)	"One prospective study (a cohort study that generated both prevalence and incidence data) found that use of snus was not associated with increased risk of type 2 diabetes. Another prospective study with several limitations reported that the use of snus (adjusted for smoking) was associated with type 2 diabetes, while a significant association was not observed among never-smoking snus users. Of the other three epidemiological studies, one study observed a significant increase in the prevalence of type 2 diabetes among snus users, while the other two studies did not." (p 174 section 5.6.3 of the ENVIRON Snus Monograph)
All cause mortality	"The results for all-cause mortality from the two available studies (Bolinder et al., 1994; Roosaar et al., 2008) are inconsistent... The significant excess risk of all-cause mortality among snus users reported by Roosaar et al., (2008) may be due to confounding by other factors, such as smoking or exposure misclassification... Regarding all-cause mortality, Lee (2011) stated, “more evidence is clearly needed.” (page 424 section 6.1.1.3 of the Application)	"Two studies observed small increases in risk of all-cause mortality among snus users, however, the potential for residual confounding from or misclassification of smoking in these studies remains a concern before strong conclusions from these studies can be drawn." (p 190 section 5.11.14 of the ENVIRON Snus Monograph)
Pregnancy outcomes		"Daily use of snus during pregnancy is associated with a modest reduction in average birth weight (though less than smoking), small-for-gestational-age birth, and increased risk of preterm delivery, stillbirth, and neonatal apnea... Daily use of snus during pregnancy is not associated with risk of, preeclampsia, gestational hypertension, or antenatal bleeding." (p 185 section 5.10.4 of the ENVIRON Snus Monograph)
Dental effects and periodontal disease		"No effects of snus use were on gingivitis, gingival recessions, and other dental conditions were consistently identified among studies that controlled for important confounders such as socioeconomic status (SES) and oral hygiene habits... The use of snus is not associated with periodontal disease or any individual indicators of periodontal disease based on the results of seven studies, five of which accounted for the potential confounding effects of SES or oral hygiene habits." (p 442 section 6.1.1.7 of the Application)
Snuff dipper’s lesion		"Swedish snus may cause a characteristic type of oral mucosal lesion that regress following cessation of snus use. There is no evidence that they progress to cancer, even with long-term use." (p 442 section 6.1.1.7 of the Application)

	Snus vs. cigarettes	Snus health risks
Leukoplakia and Dysplasia		"While snus does exert an effect on the oral mucosa, the available epidemiologic data fails to support that snus is associated with dysplastic lesions or with precarcinogenic effects on the oral cavity. Furthermore, there is no clinical evidence to suggest that when dysplastic lesions occur in snus users, they transform into malignancies." (page 442 section 6.1.1.7 of the Application)