Information about Swedish Match North America's Modified Risk Tobacco Product Applications

On June 10, 2014, Swedish Match North America, Inc. (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 tobacco products. SMNA is seeking certain product-specific modifications to the health warnings currently required under the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products. The Food and Drug Administration (FDA) is required by the FD&C Act to make MRTPAs (except for matters in the application that are trade secrets or otherwise confidential commercial information) available to the public for review and comment, and to refer the MRTPAs to the Tobacco Products Scientific Advisory Committee. To facilitate public review and comment, the availability of the redacted MRTPAs has been announced in the Federal Register and they are publicly available on both the Regulations.gov and the FDA.gov websites. Due to their size, the MRTPAs are included in Regulations.gov as approximately 800 supporting documents. The first supporting document includes a table of contents as well as other background information. The MRTPAs are posted in their entirety on Center for Tobacco Products' (CTP) website.

FDA has requested and was granted a waiver under Section 508 of the Rehabilitation Act of 1973. FDA will provide an accessible summary for each MRTPA and information on how to request an accommodation for those with disabilities who wish to access the content of any MRTPA that is posted on the website in a format that is usable for them. Persons with disabilities having problems accessing the above PDF file may call the CTP Call Center, 877.CTP.1373 for assistance.

Information about Redactions to SMNA's MRTPAs

SMNA's MRTPAs contain non-public information. Section 911(e) of the FD & C Act provides that FDA shall make the MRTPAs publically available "except matters in the application which are trade secrets or otherwise confidential, commercial information." 21 U.S.C. § 387k(e). FDA has redacted trade secrets and confidential information from the MRTPAs in accordance with federal law.

Questions and Answers

What are examples of trade secrets within SMNA's MRTPAs that FDA redacted?

Examples of trade secrets redacted by FDA include manufacturing processes, ingredient composition, and quality control procedures.

What are examples of confidential commercial information within SMNA's MRTPAs that FDA redacted?

Examples of confidential commercial information redacted by FDA include the identity and standard operating procedures of SMNA's business consultants and marketing research information.

How has FDA designated trade secret and confidential information within the MRTPAs?

The redaction code (b)(4) indicates the areas within the MRTPAs where FDA redacted trade secrets and confidential commercial information.

Has FDA redacted any other information within SMNA's MRTPAs?

Yes, FDA has also redacted privacy information such as the initials and dates of birth of clinical study participants. This information is not needed for people to comment on the submission and redacting it will protect study participants.

How has FDA designated privacy information within the MRTPAs?

The redaction code (b)(6) indicates the areas within the MRTPAs where FDA redacted privacy information.

How did FDA determine what information from the application could be released to the public and how much of the application to redact?

FDA cannot release information in an MRTPA that is trade secret or otherwise confidential commercial information without the applicant's consent. FDA, with input from SMNA, determined which information in its MRTPAs should be redacted. Additionally, in some areas, SMNA consented to release a significant amount of confidential commercial information that FDA would otherwise have had to redact.

Why do the hyperlinks within SMNA's MRTPAs not work?

FDA applied redactions to the MRTPAs with Adobe Acrobat software which removes hyperlinks during the application process.

Why are pages from the published literature in appendices 2a, 2b, 2c, 2d, 2e, 2f, 2g withheld?

FDA removed the pages from the published literature that SMNA submitted and that are subject to copyright. FDA has included the citations of the published literature in these appendices so that members of the public can reference these articles on their own if they choose to.

1. COVER LETTERS

1.1 General Loose (SKU 4852)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Loose**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Loose product (SKU 4852) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:
Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary

Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
(804) 225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Loose

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Loose (SKU 4852)	SE0000140	3/18/11 2/15/13	6/17/10 12/16/10 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the

basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of

the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.2 General Dry Mint Portion Original Mini (SKU 4800)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Dry Mint Portion Original Mini**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Dry Mint Portion Original Mini product (SKU 4800) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:
Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary

Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
(804) 225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Dry Mint Portion Original Mini

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Dry Mint Portion Original Mini (SKU 4800)	SE0000139	3/18/11 2/15/13	6/17/10 12/16/10 3/8/11 9/23/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

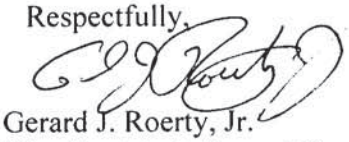
Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or

otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,



Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.3 General Portion Original Large (SKU 4880)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Portion Original Large**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Portion Original Large product (SKU 4880) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
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Richmond, VA 23219
(804) 787-5100 (phone)
(804) 225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Portion Original Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Portion Original Large (SKU 4880)	SE0000143	3/18/11 2/15/13	6/17/10 12/16/10 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

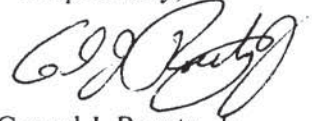
therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,



Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.4 General Classic Blend Portion White Large – 15 ct (SKU 4877)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Classic Blend Portion White Large – 15 ct**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Classic Blend Portion White Large product (SKU 4877) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
(804) 225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Classic Blend Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Classic Blend Portion White Large (SKU 4877)	SE0000138	3/18/11 2/15/13	11/12/10 3/8/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

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Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

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- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(c) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.5 General Classic Blend Portion White Large – 12 ct (SKU 4878)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Classic Blend Portion White Large – 12 ct**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Classic Blend Portion White Large product (SKU 4878) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
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Authorized Contacts:

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Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Classic Blend Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Classic Blend Portion White Large (SKU 4878)	SE0000138	3/18/11 2/15/13	11/12/10 3/8/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.6 General Mint Portion White Large (SKU 4352)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Mint Portion White Large**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Mint Portion White Large product (SKU 4352) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
(804) 225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Mint Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Mint Portion White Large (SKU 4352)	SE0000141	3/18/11 2/15/13	6/17/10 12/16/10 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.7 General Nordic Mint Portion White Large – 15 ct (SKU 4876)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Nordic Mint Portion White Large – 15 ct**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Nordic Mint Portion White Large product – 15 ct (SKU 4876) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
804-225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Nordic Mint Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Nordic Mint Portion White Large (SKU 4876)	SE0000142	3/18/11 2/15/13	11/12/10 3/8/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.8 General Nordic Mint Portion White Large – 12 ct (SKU 4875)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Nordic Mint Portion White Large – 12 ct**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Nordic Mint Portion White Large product – 12 ct (SKU 4875) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
804-225-7094 (fax)
Gerry.Roerty@SMNA.com

Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Nordic Mint Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Nordic Mint Portion White Large (SKU 4875)	SE0000142	3/18/11 2/15/13	11/12/10 3/8/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(e) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.9 General Portion White Large (SKU 4881)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Portion White Large**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Portion White Large product (SKU 4881) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
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Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Portion White Large (SKU 4881)	SE0000144	3/18/11 2/15/13	6/17/10 12/16/10 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into interstate commerce. Such an order is not required, however, if a manufacturer submits a report

under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

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Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according to the recommendations in FDA's Draft Guidance and containing all the information requested

therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(c) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein. Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

1.10 General Wintergreen Portion White Large (SKU 4882)

June 6, 2014

Center for Tobacco Products
Food and Drug Administration
Attn: Document Control Center
9200 Corporate Boulevard
Rockville, MD 20850

Re: **Modified Risk Tobacco Product Application for Swedish Match North America Snus Product, General Wintergreen Portion White Large**

Dear Sir or Madam:

Swedish Match North America ("Swedish Match" or the "Company") submits this application (the "Application") to the U.S. Food and Drug Administration ("FDA") seeking a modified risk tobacco product order under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act (the "Tobacco Control Act"), for its General Wintergreen Portion White Large product (SKU 4882) currently marketed in the United States (the "Snus Product").

The labeling and advertising for the Snus Product currently contain the warning statements mandated by Section 3(d) of the Comprehensive Smokeless Tobacco Health Education Act of 1986 ("CSTHEA"), as amended by Section 204 of the Tobacco Control Act. Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of snus with respect to risk reduction. Thus, this Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In accordance with FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications, Swedish Match hereby provides the following information in support of this Application:

Company Name and Address:
Swedish Match North America
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

Authorized Contacts:

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219
(804) 787-5100 (phone)
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Jim Solyst
Director, Federal Government Affairs
302 St. Ives Dr.
Severna Park, MD 21146
(410) 987-0299 (phone)
(410) 934-8942 (fax)
Jim.Solyst@SMNA.com

Brand name and, if applicable, subbrand name of proposed MRTPs:

General Wintergreen Portion White Large

Name of Manufacturer:

Swedish Match North America

Previous Regulatory Submissions:

Brand	FDA Submission Tracking Number (STN)	Date of Substantial Equivalence Report and Associated Amendments	Date of Ingredient Listing Submissions
General Wintergreen Portion White Large (SKU 4882)	SE0000145	3/18/11 2/15/13	6/17/10 12/16/10 3/8/11 1/20/12 7/25/12 4/5/13

Satisfaction of Premarket Review Requirements Under Section 910 of the Act:

As a general rule, a tobacco product manufacturer must obtain an order from FDA under Section 910(c)(1)(A)(i) of the Act before the manufacturer may introduce a new tobacco product into

interstate commerce. Such an order is not required, however, if a manufacturer submits a report under Section 905(j) and FDA issues an order finding that the tobacco product is substantially equivalent to a predicate product and is in compliance with the requirements of the Act.

On March 17, 2011, Swedish Match submitted a substantial equivalence report ("SE Report") to FDA for the Snus Product. The SE Report, along with its associated amendment, set forth the basis for Swedish Match's determination that the Snus Product is substantially equivalent, within the meaning of Section 910 of the Act, to a tobacco product commercially marketed in the United States as of February 15, 2007.

Because the SE Report was submitted prior to March 23, 2011, the Snus Product may continue to be legally marketed, pursuant to Section 910(a)(2)(B) of the Act, unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and the Snus Product is currently on the market in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for the Snus Product, as modified to include, among other things, certain proposed modified-risk claims in its label. In accordance with Section 911(l)(4) of the Act, Swedish Match hereby submits SE and MRTP information for the Snus Product in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

Dates of Prior Meetings with FDA:

Swedish Match and staff from FDA's Center for Tobacco Products met to discuss Swedish Match's plan to submit this Application on the following dates:

- June 27, 2012
- December 19, 2012
- May 8, 2013
- December 19, 2013
- January 9, 2014
- March 12, 2014

Type of Order Sought:

Swedish Match seeks a risk modification order under Section 911(g)(1) for the Snus Product described in this Application.

Trade Secrets or Confidential Commercial Information:

Enclosed please find a complete modified risk tobacco product application, organized according

to the recommendations in FDA's Draft Guidance and containing all the information requested therein. This Application is and contains non-public, trade secret, and confidential information that is protected under state and federal law from public disclosure.

Swedish Match understands that Section 911(c) of the Act requires FDA to make this Application publicly available, except matters in the Application which are trade secrets or otherwise confidential, commercial information. In order to facilitate FDA's publication of the disclosable portions only, Swedish Match herein submits both a complete, unredacted version of the Application and a second version with transparent highlights of the information that Swedish Match has identified as exempt from disclosure.

* * * *

Swedish Match appreciates FDA's careful consideration of this Application and looks forward to working with the Agency to secure an order under Section 911(g) for the proposed modified risk tobacco product discussed herein.

Please do not hesitate to contact the undersigned with any questions.

Respectfully,

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America

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2.4 Glossary

1-HOP	1-hydroxypyrene (urinary biomarker of exposure)
3-NT	3-nitrotyrosine
4NQO	4-nitroquinoline-1-oxide
AAAS	American Association for the Advancement of Science
AAHRPP	Association for the Accreditation of Human Research Protection Programs
ADI	Acceptable Daily Intake
ALS	Amyotrophic lateral sclerosis
AMI	Acute Myocardial Infarction
AP	Alternative Product
AUC	Area under the curve
B(a)P	Benzo(a)pyrene
Be	Beryllium
BMI	Body mass index
BOM	Bill of Material
Bq	Becquerel (SI derived unit of radioactivity)
CAN	Central Alliance for Alcohol and Drug Information
CAS	Chemical Abstract Services
CCP	Case-Control Study with Population Controls
CD	Crohn's disease
CDC	US Centers for Disease Control and Prevention
CDER	FDA Center for Drug Evaluation and Research
CHD	Coronary heart disease

CHO	Chinese Hamster Ovary
CI	Confidence interval
CO	Carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CPS-II	American Cancer Society's Cancer Prevention Study II
CRO	Contract Research Organization
CS	Cross-Sectional Study
CSTHEA	Comprehensive Smokeless Tobacco Health Education Act of 1986
CTP	FDA Center for Tobacco Products
CVAAS	Cold-Vapour Atomic Absorption Spectrometry
CVD	Cardiovascular disease
DG SANCO	Directorate-General for Health and Consumers
DMBA	Dimethylbenz(a)anthracene
DNA	Deoxyribonucleic acid
DPM	Dynamic Population Model
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EFSA	European Food Safety Authority
ENVIRON	ENVIRON International Corporation
ERP	Enterprise Resource Planning
ERR	Excess Relative Risk

ESTOC	European Smokeless Tobacco Council
EC	European Commission
EU	European Union
EWS	Early Warning Samples
FAPAS	Food Analysis Performance Assessment Scheme
FCTC	Framework Convention on Tobacco Control
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug and Cosmetic Act
FLD	Fluorescence detector
FTND	Fagerström Test for Nicotine Dependence
FTQ	Fagerström Tolerance Questionnaire
g	Gram
GAP	Good Agricultural Practice
GC/FPD	Gas Chromatography Analysis with Flame Photometric Detection
GC-ECD	Gas Chromatography Analysis with Electron Capture Detection
GC-FID	Gas Chromatographic Analysis with Flame Ionization Detection
GC-FPD	Gas chromatography with flame photometric detector (sulphur mode)
GC-MS	Gas Chromatographic Analysis with Mass Spectometric Detection
GC-MS/MS	Gas Chromatographic Analysis with tandem Mass Spectrometric Detection
GCP	Good Clinical Practice
GC-TCD	Gas Chromatography with a Thermo Conductivity Detector

GC-TEA	Gas Chromatography with a Thermal Energy Analyzer
GEMS	Global Environment Monitoring System
GH	Gestational Hypertension
GMO	Genetically modified organisms
GPC	Gel Permeation Chromatography
GRL	Guidance Residue Level
GRLs	Guidance Residue Limits
HAACP	Hazard Analysis and Critical Control Points
Hg	Mercury
HNO_3	Nitric Acid
HPB	4-hydroxy-1-(3-pyridyl)-1-butanone
HPHC	Harmful or Potentially Harmful Constituent
HPLC	High Performance Liquid Chromatography
HPV	Human papillomavirus
HR	Hazard ratio
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus-1
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IHD	Ischemic heart disease
ILO	International Labor Organization

IOM	Institute of Medicine
IRB	Institutional Review Board
IRR	Incidence rate ratio
ISO	International Organization for Standardization
K	Potassium
KI	Karolinska Institutet
KP	Kaiser Permanente
LC-MS	Liquid Chromatography – Mass Spectrometry
LC-MS/MS	Liquid Chromatography-Triple Quadrupole Mass Spectrometry
LC-RID	Liquid Chromatography with a Refractive Index Detector
LOQ	Limit of Quantification
MASA-PCR	Mutant-allele-specific Amplification-polymerase Chain Reaction
MC	20-methylcholanthrene
mg	Milligram
MHRA	UK Medicines and Healthcare Products Agency
MI	Myocardial infarction
ML	Maximum Level
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MRL	Maximum Residue Level
MRTP	Modified Risk Tobacco Product
MS	Multiple sclerosis
Na	Sodium

NAB	N-nitrosoanabasine
NAT	N-nitrosoanatabine
NCC	Nested Case-Control Study
NDBA	N-nitroso-dibutylamine
NDEA	N-nitroso-diethylamine
NDELA	N-nitrosodiethanolamine
NDiPLA	N-nitrosodiisopropanolamin
NDMA	N-nitrosodimethylamine
NDPA	N-nitroso-N-propylamine
NEMA	N-nitroso-N-methylethylamine
NGO	Non-Governmental Organization
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Institute Survey
NIH	National Institutes of Health
NMOR	N-nitrosomorpholine
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone
NNN	N-nitrosonornicotine
NPIP	N-nitrosopiperidine
NPYR	N-nitrosopyrrolidine
NRT	Nicotine Replacement Therapy
NSAR	N-nitrososarcosine
NZHTA	New Zealand Health Tech Assessment
ONOO-	Peroxynitrite

OR	Odds ratio
OSCC	Oral Squamous Cell Carcinoma
OSTP	Oral Smokeless Tobacco Products
OTC	Over-the-Counter
PAH	Polycyclic aromatic hydrocarbon
PATH	Population Assessment of Tobacco and Health
PC	Prospective Cohort Study
POB	Pyridyloxobutylation (a type of DNA-adduct)
POII	Hamster cheek pouch cells
PP	Polypropylene
PREP	Potential reduced-exposure tobacco product
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QEMS	Quality and Environmental Management System
R&D	Research and development
RA	Rheumatoid Arthritis
RJR	R. J. Reynolds Tobacco Company
RR	Risk ratio
SALT	Swedish Screening Across the Lifespan Twin
SCB	Statistisk Sentralbyrå (Statistics Norway)
SCC	Squamous Cell Carcinomas
SCCP	Scientific Committee on Consumer Products
SCD	Sudden cardiac death
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks

SCHER	Scientific Committee on Health and Environmental Risks
SCL	Swedish Match Chemical Laboratory
Se	Selenium
SENCAR	Sensitive to Carcinogens
SES	Socioeconomic status
SFA	Segmented Flow Analysis
SGA	Small for Gestational Age
SIL	Snus Induced Lesion
SIMS	Swedish Match Ingredient Management System
SIRUS	Norwegian Institute for Alcohol and Drug Research
SKU	Stock-Keeping Unit
SNBH	Swedish National Board of Health and Welfare
SNIPH	Swedish National Institute of Public Health
SRNT	Society for Research on Nicotine and Tobacco
SSLC	Swedish Survey of Living Conditions
STN	Submission Tracking Number
STP	Smokeless tobacco product
SWEDAC	Swedish Board for Accreditation and Conformity Assessment
TCORS	Tobacco Centers of Regulatory Science
TL	Tolerance Limits
TN	Total Normal Nucleotides
TPA	12-O-tetradecanoylphorbol-13-acetate
TSNA	Tobacco-specific nitrosamine

TTB	Tobacco and Trade Bureau
UC	Ulcerative colitis
UHPLC	Ultra-High Performance Liquid Chromatography
UK	United Kingdom
ULF	Swedish Level of Living Survey
UPLC-MS/MS	Ultra Performance Liquid Chromatography – Triple Quadrupole Mass Spectrometry
US	United States
USDHHS	US Department of Health and Human Services
VAS	Visual Analogue Scale
VIP	Västerbotten Intervention Program
Vvmit	Mitochondrial Volume Density
WHO	World Health Organization

2.5 Summary

2.5.1. Tobacco Use and the Public Health

According to the World Health Organization ("WHO"), tobacco use continues to be the leading global cause of preventable death.[1] Premature deaths attributable to tobacco smoking are expected to rise to 6.4 million in 2015, and 8.3 million in 2030 (Gartner et al. 2007b). In the United States alone, more than 400,000 persons die each year from smoking-related diseases, and approximately 8,600,000 Americans have chronic illnesses related to smoking.[2]

Notwithstanding these alarming statistics, the risk of a man dying from a tobacco-related disease is less in Sweden than in any other European country, despite the fact that total tobacco consumption is comparable to that of other countries in Europe. Researchers refer to this paradox as "the Swedish Experience," a phenomenon which is most likely explained by the unique form of tobacco use among Swedish men, which largely takes the form of Swedish snus. Swedish men smoke substantially less than their counterparts in other countries with comparable rates of tobacco consumption, and the use of snus among Swedish men is more common than smoking. Moreover, although snus use has increased as smoking has declined, the overall rate of tobacco consumption in Sweden has also steadily declined.

The positive effect of this phenomenon is a very low frequency of tobacco-related illnesses among Swedish men and low smoking-related mortality rates. This unique situation is documented in a large number of epidemiological studies with findings such as the following:

- The incidence of lung cancer among Swedish men has declined over the past 20 years, which researchers link to the fact that Swedish men are smoking less and that many of them have switched to snus.

- There is no demonstrable correlation between the use of Swedish snus and oral cancer.

- Several studies have shown no increased risk of cardiovascular diseases among snus users.

Although the use of Swedish snus may have some negative health effects, research results have shown that health risks are substantially lower for the use of snus compared with smoking. In light of the medical consensus that Swedish snus is approximately 90-95% *less harmful* than smoking (Levy et al. 2004), it would be contrary to both sound science and sound regulatory policy to treat snus and cigarettes as *equally harmful*.

The overall effect from Swedish snus on public health comes down to the balance between its beneficial effect on smoking prevalence and its adverse effects on the overall prevalence of

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1 World Health Organization, http://www.who.int/tobacco/health_priority/en/.

2 Family Smoking Prevention and Tobacco Control Act of 2009, Pub. L. No. 111-31, § 2(13), 123 Stat. 1776 (2009) (hereinafter "Tobacco Control Act").

tobacco use (Lund 2013). Congress rightly recognized this balance when crafting the statutory standard governing the issuance of an order for the commercial marketing of an MRTP under the FDCA, as amended by the Tobacco Control Act. In accordance with Section 911(g) of the Act, FDA shall issue an MRTP order only if the product, as actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and also "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."

Swedish Match asserts that the scientific data and information presented in this Application fully satisfy the statutory standard under FDCA Section 911(g). These data demonstrate that the individual and population-level health risks associated with Swedish snus, as manufactured by Swedish Match, are signficantly lower than those of cigarettes. Consequently, Swedish Match believes that its Swedish snus products should be recognized as modified risk tobacco products under the Act. This science-based designation would recognize the important and constructive role that Swedish snus can play in reducing the adverse health consequences of tobacco use, and permit adult consumers to make informed decisions about the relative risks of Swedish snus as part of a pragmatic and effective harm reduction strategy.

2.5.2. MRTP Application Overview

The Tobacco Control Act was enacted to establish a regulatory framework to address the public health and societal problems attributable to tobacco. One of the statute's declared purposes is "to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote *less harmful* tobacco products."[3] In other words, the prospect of a less hazardous tobacco product is "not in and of itself problematic" but rather the "fundamental issue is that if a product is going to be marketed as being 'safer', then the claim must be true" (IOM 2012). Congress recognizes "the compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product"[4] and, thus, authorized FDA "to require that products . . . sold or distributed for risk reduction be reviewed in advance of marketing, and to require that the evidence relied on to support claims be fully verified."[5]

Swedish Match appreciates the detrimental public health impact that would ensue by permitting manufacturers to make unsubstantiated statements concerning MRTPs, whether express or implied.[6] This danger is particularly acute for those tobacco products that *do not in fact* reduce the risk of harm or tobacco-related disease associated with commercially marketed tobacco

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3 *Id.* § 3(4) (emphasis added).

4 *Id.* § 2(40).

5 *Id.* § 2(43).

6 *See id.* § 2(42) (emphasis added).

products.[7] However, where the scientific evidence establishes that a tobacco product *does in fact* reduce such risk of harm or disease, it is appropriate for the protection of the public health—and critical to FDA's fulfillment of its mission[8]—to "ensure that consumers are better informed . . . relating to the health . . . and safety of [the MRTP]."[9]

Swedish Match submits that Swedish snus, as manufactured by Swedish Match, is significantly less harmful than cigarettes, and that Congress has provided a mechanism under the Tobacco Control Act to inform adult consumers of snus's harm reduction potential. Accordingly, this MRTP Application provides a comprehensive analysis of the relevant scientific evidence relating to the health effects of Swedish snus and the public health impact of the product for users and non-users at both the individual and population levels. The scientific evidence presented in the Application is derived from a collection of rigorous, well-controlled studies conducted by various governments, academic institutions, and private companies. The Application presents two broad categories of scientific evidence, including (i) product-specific information which is derived from studies using Swedish Match's Swedish snus products and (ii) other relevant evidence from studies that examined products similar to the Company's products, including other forms of snus and other smokeless tobacco products. What follows is a brief overview of the categories of evidence presented herein, as well as an explanation of how that evidence applies to the recommendations set forth in FDA's Draft Guidance for Industry: Modified Risk Tobacco Product Applications (the "MRTP Guidance").[10]

2.5.2.1. Proposed Modified Risk Claim

This MRTP Application seeks CTP's approval to make modified-risk claims for ten (10) Swedish snus smokeless tobacco products[11] which are currently marketed in the United States

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7 *See id.* § 2(40) (emphasis added).

8 FDA Mission Statement, http://www.fda.gov/AboutFDA/WhatWeDo/.

9 *See* Tobacco Control Act at § 3(6).

10 FDA, Draft Guidance for Industry: Modified Risk Tobacco Product Applications, http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf.

11 This MRTP Application is being submitted for the following ten (10) Swedish snus products: General Loose (SKU 4852); General Dry Mint Portion Original Mini (SKU 4800); General Portion Original Large (SKU 4880); General Classic Blend Portion White Large – 15 ct (SKU 4877); General Classic Blend Portion White Large – 12 ct (SKU 4878); General Mint Portion White Large (SKU 4352); General Nordic Mint Portion White Large – 15 ct (SKU 4876); General Nordic Mint Portion White Large – 12 ct (SKU 4875); General Portion White Large (SKU 4881); and General Wintergreen Portion White Large (SKU 4882).

(collectively, the "Snus Products").[12] Specifically, Swedish Match seeks approval to modify the health warnings mandated for the Snus Products pursuant to Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, which requires all smokeless tobacco product labels to bear one of the following general statements:

1. WARNING: This product can cause mouth cancer.

2. WARNING: This product can cause gum disease and tooth loss.

3. WARNING: This product is not a safe alternative to cigarettes.

4. WARNING: Smokeless tobacco is addictive.

Although these warnings may be appropriate for certain customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the net individual and population-level public health risk-reduction benefit of snus. Thus, this Application seeks the following product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of Swedish snus as compared to other commercially marketed tobacco products:

- The revised labeling will not carry the mouth cancer warning.

- The revised labeling will not carry the gum disease and tooth loss warning.

- The revised labeling will change the "not a safe alternative to cigarettes" warning to "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

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[12] On March 17, 2011, Swedish Match submitted SE Reports to FDA for the Snus Products which are the subject of this MRTP Application. The SE Reports, along with their associated amendments, set forth the basis for Swedish Match's determination that the products are substantially equivalent, within the meaning of Section 910 of the Act, to tobacco products commercially marketed in the United States as of February 15, 2007. Because the SE Reports were submitted prior to March 23, 2011, each of the Snus Products may continue to be legally marketed unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and all ten (10) Snus Products may be lawfully marketed in the United States. Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Accordingly, this MRTP Application includes certain SE information for each of the Snus Products, as modified to include, among other things, certain proposed modified-risk claims in their respective labels.

- The revised labeling will keep the current addiction warning.

In other words, there would be two warning labels (and hence, two modified risk claims) subject to the MRTP order, and they would read as follows:

1. WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.

2. WARNING: This product is addictive.

2.5.2.2. Description of the Tobacco Product and Scientific Rationale for Its Potential Benefits

2.5.2.2.1. Description of the Snus Products

Each of the Snus Products which are the subject of this Application is a form of Swedish snus, a world-unique smokeless tobacco product which originated in the Nordic region of Europe nearly 200 years ago. According to the European Smokeless Tobacco Council ("ESTOC"), "snus" is defined as a smokeless tobacco product for oral use which is traditionally produced and used in Sweden and manufactured using a heat treatment process.[13] This definition distinguishes Swedish snus from all other types of smokeless tobacco, including some snus-like products recently introduced in the United States market which have distinctly different characteristics.

Swedish snus is made from selected, mainly air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. Put another way, Swedish snus contains only finely ground tobacco mixed with water, additives (e.g., cooking salt, sodium bicarbonate, etc.) and flavors. In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in premises that are hygienically suitable for food production.

Unlike nasal snuff, which is inhaled through the nasal cavity, Swedish snus is an oral smokeless tobacco product, and it is moist to facilitate use in the oral cavity. Thus, the Snus Products are moist (50-60% moisture) to semi-moist (30-45% moisture) oral tobacco products which are typically placed between the upper lip and the gum and do not require expectoration during use.[14]

The Snus Products are currently marketed in the United States with the statutorily mandated warnings required under Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act. However, this Application seeks to modify these warnings to better convey the product-specific scientific evidence demonstrating the individual and population-

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13 European Smokeless Tobacco Council, http://www.estoc.org/about-smokeless-tobacco.

14 By contrast, American moist snuff products are typically placed under the lower lip and require expectoration during use.

level public health risk reduction benefit of snus. This scientific evidence, including the rationale for the potential benefits of the Snus Products, is summarized below.

2.5.2.2.2. Scientific Rationale for the Potential Benefits of the Snus Products

2.5.2.2.2.1. Product-Specific Evidence

The most applicable evidence submitted in support of this MRTP Application is the result of research conducted using Swedish Match snus products. Typically, such product-specific evidence is only generated by the application sponsor. However, Swedish Match is fortunate to be able to submit an impressive body of product-specific evidence derived from third-party studies undertaken by, and with the support of, Swedish academic institutions and governmental authorities. This Swedish-based epidemiology evidence—also referred to herein as the "Swedish Experience"—has been widely cited by public health agencies and scientific institutions around the world, and it is fundamental to the FDA Center for Tobacco Products' ("CTP's") analysis of the modified risk claims presented in this Application.

The Swedish Experience evidence is supplemented by additional product-specific evidence collected by Swedish Match, including a series of clinical trials sponsored by the Company just prior to the passage of the Tobacco Control Act and additional research undertaken following the issuance of the MRTP Guidance. Of particular relevance to this MRTP Application is the evidence from two placebo-controlled, double-blind, randomized smoking cessation clinical trials which were conducted during 2008-2010. One of the studies was conducted at two sites in Serbia, and the other at five sites in the United States. Both studies tested whether *ad lib* provision of snus could affect subsequent smoking behavior among adult smokers motivated to quit (US and Serbia) or substantially reduce their smoking (Serbia). These clinical trials—which fulfill many of the key areas of investigation suggested in the MRTP Guidance—were initiated prior to the passage of the Act and are representative of Swedish Match's longstanding commitment to product stewardship and consumer protection. They are complemented by three Swedish Match trials comparing the nicotine pharmacokinetics and pharmacodynamics of various snus products compared to select nicotine replacement therapies ("NRTs"), which showed that snus is comparable to commercially available NRT products, and is associated with less abuse liability than cigarettes.

To complement the epidemiological evidence and to provide a preclinical, toxicological rationale for the essentially negative findings concerning cancer risks among snus users, Swedish Match also sponsored *in vitro* toxicological testing of extracts of Swedish snus. These tests included the Salmonella reverse mutation assay, mouse lymphoma assay, in vitro micronucleus assay, and tests of cytotoxicity. The results of these assays were broadly negative for Swedish snus. There were occasional positive responses, but these were effectively at the highest concentration only (i.e., concentrations well above those suggested by regulatory guidelines) and were often associated with significant cytotoxicity. These data contrast with data reported for combusted tobacco in the form of cigarettes, where strongly positive responses have been routinely reported for mutagenicity and cytotoxicity. These negative findings in a laboratory setting concur with

the large amount of epidemiological data from Sweden, data showing that Swedish snus is associated with considerably lower, if any, carcinogenic potential when compared with cigarettes.

Swedish Match has also conducted premarket consumer perception research designed to address several key areas of investigation set forth in the MRTP Guidance. The research assesses the effects of the proposed modified risk warning labels on Swedish snus packaging on both current users and non-users of tobacco products, and how exposure to the test and control warning labels impacts consumer behavior, understanding, and perception of the health risks associated with the product. The research study protocol was developed over a one-year period and in consultation with the Swedish Match MRTP Advisory Panel (the "MRTP Advisory Panel") and outside counsel experienced in FDA regulatory science. The protocol was considerably enhanced through a series of meetings with CTP staff, and it was refined by continual review conducted by the MRTP Advisory Panel.

Additional product-specific evidence derives from the results of secondary data analysis and modeling using the Dynamic Population Model ("DPM"). The DPM forecasts the public health impact of the proposed MRTPs by estimating changes in all-cause mortality for a hypothetical population of persons who have never used tobacco and who, as they age, may transition into and out of different tobacco exposure states, including current and former smoking or MRTP use. The DPM is a comprehensive and flexible model which provides a useful tool for the development of science-based regulatory policy related to tobacco harm reduction, as it helps to clarify assumptions underlying the arguments for or against the tobacco control policies being considered. Swedish Match financially supported the overall development of the DPM and provided the information to run the applications the results of which are presented herein.

Finally, another key component of the product-specific scientific evidence presented in the MRTP Application is GOTHIATEK®, the Company's proprietary quality standard which assures consumers that all Swedish Match products are subject to rigorous controls and maintain the highest quality throughout all the stages from tobacco plant to consumer. GOTHIATEK® requirements stipulate that the manufacturing process for Swedish snus must comply with Swedish law on food production and meet the requirements of quality standard ISO 9001:2000 and environmental standard 1401:1996. Swedish Match has also added its own objectives for quality and content beyond that which is required by law. For example, GOTHIATEK® sets the standards for raw material quality requirements, manufacturing process requirements, consumer product information requirements, and maximum permitted levels of undesirable substances in the finished, snus products.

2.5.2.2.2.2. Other Relevant Evidence

Although the most compelling evidence presented in the Application is clearly product-specific, there is a vast and ever increasing amount of applicable, non-product-specific studies published in scientific journals that further support the claims made herein. Some of this research is broader in scope and assess smokeless tobacco products in general, or novel products marketed as "snus."

Swedish Match recognized the importance of this information and prior to the passage of the Tobacco Control Act, contracted with ENVIRON International Corporation ("ENVIRON") to monitor the scientific literature and prepare a comprehensive compendium of the articles pertaining to snus. ENVIRON produced two reports that are particularly applicable to the Application:

1) Review of the Scientific Literature on Snus (Swedish Moist Snuff) (the "ENVIRON Snus Monograph 2013") and
2) Swedish Snus and US Smokeless Tobacco Use Behaviors (the "ENVIRON TUB Report 2013").

The former report presents a comprehensive review of the scientific literature on the potential health risks associated with the use of Swedish snus. The latter report presents a review of the scientific literature on snus and smokeless tobacco use in the United States and Scandinavia as it relates to tobacco use behaviors, including dual use, gateway issues, and smokeless tobacco as a smoking cessation aid. Both reports are submitted in their entirety for CTP's review as appendices to this Application (Appendices 6A and 6B, respectively).

In reviewing the scientific literature, it is important to note that snus is and always has been the dominant smokeless tobacco product on the Swedish market, comprising more than 99% of total annual smokeless sales. This means that all Swedish epidemiological studies that have assessed the effects of smokeless tobacco—irrespective of whether the word "snus" or "snuff" was used to qualify the studied product—almost certainly concerned Swedish snus. Swedish Match (including its predecessors in interest, Svenska Tobaksmonopolet, STM, or Svenska Tobaksaktiebolaget, STAB) has always dominated the Scandinavian snus market. There were no snus manufacturers other than Swedish Match in Sweden until the 1990s. Since then, Swedish Match has historically maintained a market share of more than 80-90%. In Norway, the Swedish Match volume market share was above 90% until 2005, and ranged from 70-90% from 2006-2011. As a practical matter, this means that all of the Swedish epidemiological studies have studied Swedish snus *as manufactured by Swedish Match*, regardless of whether this fact was specified in the published reports.

Figure 2-1. Swedish Match Product Volume Share in Sweden

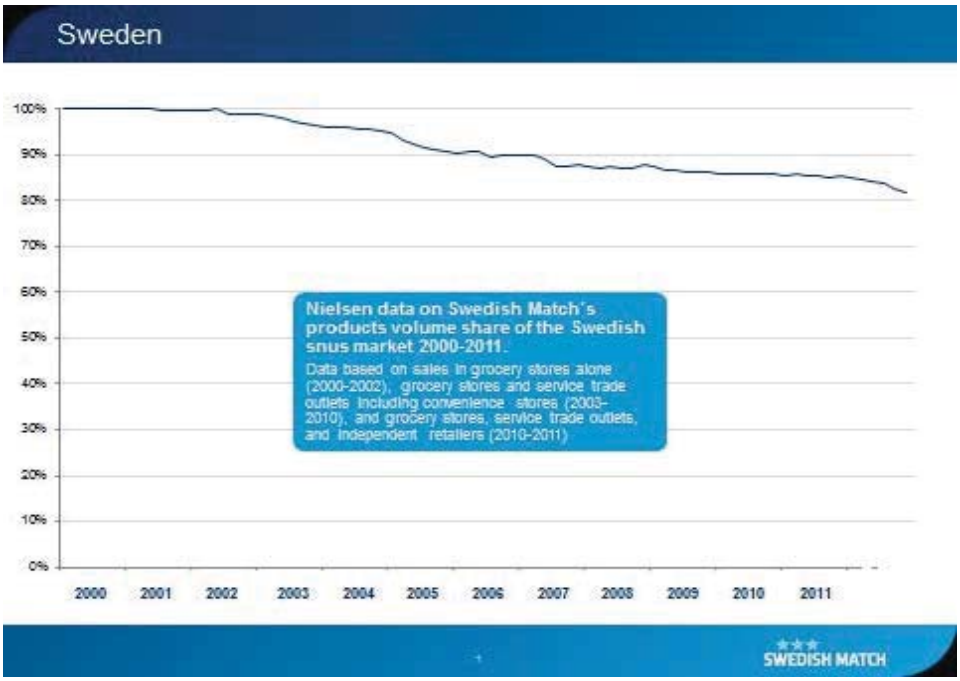
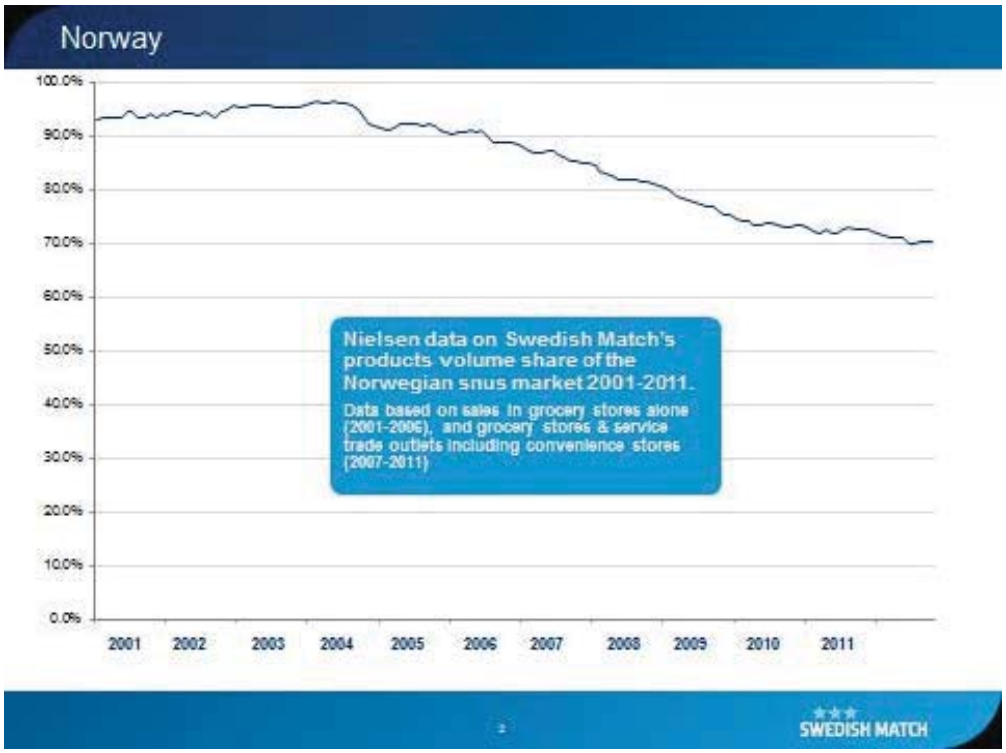


Figure 2-2. Swedish Match Product Volume Share in Norway



2.5.2.3. Summary of Information and Scientific Data Being Submitted

In its report titled *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM 2012), the Institute of Medicine of the National Academies Committee on Scientific Standards for Studies on Modified Risk Tobacco Products ("IOM") addressed the type of evidence and studies to be submitted to support modified-risk claims for existing commercially available tobacco products. In these cases, IOM recommended that epidemiologic evidence "weigh heavily in [CTP's] decision making" and be supported by evidence that "conclusively demonstrate[s] substantially reduced . . . biomarkers of risk." IOM explained that preclinical studies, though important, "play relatively minor roles (e.g., providing mechanistic context) in justifying a modified-risk claim for a product that is already on the market." IOM also suggested that "significant emphasis . . . be placed on extensive consumer and non-consumer testing" of the proposed packaging, advertising, and marketing materials in order to ensure the protection of the public health.

Swedish Match has marshalled all the available scientific evidence on Swedish snus in a manner consistent with IOM's recommendations. Based on the extensive epidemiology and toxicology data presented in this Application, Swedish Match proposes to remove the warnings that these products can cause mouth cancer and gum disease and tooth loss from the labeling for its Snus Products. Swedish Match further proposes to modify the third warning to state that, "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes." Finally, Swedish Match proposes to also include an addiction warning. The Company believes that the proposed changes are an important first step in the development of more appropriate, product-specific messages about Swedish snus which are rooted in sound science and tethered to the public health aims of the Tobacco Control Act.

2.5.2.3.1. Epidemiological Cohort Studies and Published Articles

IOM addressed extensively the evidence and studies needed to evaluate the effect of MRTPs on public health. With respect to the evidence and studies relating to the health effects of tobacco products, IOM stated that "[o]bservational epidemiologic studies play a critical and central role in the evaluation of MRTPs." According to IOM, "these methods form the basis for most evaluation studies of regulated products in the community. Long, intensive, and robust observational studies of actual health outcomes may be required to fully evaluate the net effects of MRTPs relative to conventional tobacco products." IOM further indicated that such studies should be enhanced by experimental designs, in particular, randomized controlled trials.

IOM's findings are reflected in the scientific evidence presented in this MRTP Application, which is derived largely from observational epidemiologic studies and enhanced by clinical trials. Swedish Match believes that there are three aspects of the Swedish Experience which are relevant to this Application, namely (i) the epidemiological studies and published articles that form the basis of the experience, including information on the governance of those trials, (ii) the use of the scientific evidence by public health agencies and scientific institutions globally, and

(iii) the applicability of the evidence to the United States market and the requirements for MRTPs more generally.

The scientific claims of the Swedish Experience are set forth in hundreds of published research articles, most of which derive from approximately 10-15 key epidemiological studies of Swedish and Scandinavian cohorts.[15] Like all cohort studies, these studies have their strengths and weaknesses, including varying cohort size, participation rates, and regional characteristics. Nevertheless, these studies are considered to be the most useful and authoritative sources of information globally for the study of Swedish snus, and researchers from academia, government, and industry have relied upon the data to conduct seminal research on this product type.

One of the most significant cohorts applicable to Swedish snus research is the Swedish Construction Industry's Organization for Working Environment, Safety and Health Cohort. This initiative started as a health service offered to construction workers and was not originally intended to form the basis for epidemiological research. However, after a few years the collected data were computerized and the information was made available to researchers at Swedish universities, including the Karolinska Institutet ("KI").[16] The epidemiology studies based on this cohort collected data on snus use over the 24-year period from 1969-1993. The primary strengths of the study were the large sample size (i.e., up to 340,000+ men depending on exclusion criteria), the high prevalence of snus use (i.e., 28%), and the large number of never-smoking snus users (i.e., 28%) (e.g., Luo et al. 2007). The primary limitation of these studies is the ambiguity in the coding of smoking status, most notably in the early years of data collection, and the lack of data on potential confounding factors, such as alcohol intake.

Another fundamental cohort study is the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease ("MONICA") Project that collected data over a 13-year period on, among other things, daily use of Swedish snus and other forms of smokeless tobacco among adults in the two most northern counties of Sweden. The strengths of the study include the accurate and consistent definitions of tobacco use, standardized data collection methods, and high percentage of participants receiving a follow-up examination. A limitation of the study, and in most cohort studies generally, is that a change in tobacco status could have occurred at any time during the study and follow-up period.

The Swedish Twin Registry cohort is the largest population-based twin registry in the world and has been the basis of several significant research studies, including a study by Hansson et al. (2009). The study cohort is representative of the general Swedish population, and controls for many important potential confounders of cardiovascular disease (e.g., age, smoking status,

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15 Appendix V of the ENVIRON Snus Monograph (2013) provides an annotated listing of the studies that are the foundation for the Swedish Experience.

16 Founded in 1810, KI is one of Europe's largest and most prestigious medical universities. It is Sweden's premier medical research institution, accounting for over 40% of the medical academic research conducted in Sweden and offering the country's broadest range of education in medicine and health sciences. See http://ki.se/en/about/startpage.

diabetes, high blood pressure, and high cholesterol).

A key element of the evidence of the Swedish Experience that addresses tobacco use behaviors in youths is the Children's Smoking and Environment in Stockholm County, or BROMS cohort. The BROMS study surveyed more than 3,000 fifth graders during the 1997-1998 school year and conducted annual follow-up surveys until 2005. The children were asked a series of questions relating to snuff (i.e., Swedish snus) use, including: whether they had ever tried oral snuff, age at initiation, symptoms at first use, progression to regular use, quit attempts, circumstances of tobacco use, and preferred brands. These data formed the basis of several significant publications, including those by Galanti et al. (2001b; 2001a) and (2008), Rosendahl et al. (2003), and Post et al. (2005).

Other key studies include the Malmö Diet and Cancer Cohort, two Uppsala County Cohorts, Swedish Annual Level-of-Living Survey and Swedish Survey of Living Conditions, Swedish Birth Registry, and the Northern Swedish Cohort.

Numerous scientific articles have been published based on the aforementioned and other Scandinavian cohorts. For example, for several years, researchers in the Department of Medical Epidemiology and Biostatistics at KI, Sweden's premier medical research institution, published numerous studies of the health risks related to snus use. These KI studies have profoundly influenced regulatory actions all over the world. Perhaps the best known are based on the aforementioned Swedish Construction Worker cohort which served as the basis for epidemiologic follow-up studies investigating associations between many risk factors and diseases.

One of the most convincing outcomes of the various Swedish Experience cohort studies is the replicability of findings across different data sets, strongly suggesting convergent validity. The credibility of these studies is further enhanced by a number of important factors, including Sweden's (i) widespread use of a unique personal identification number that permits computerized record linkages; (ii) population registers with high coverage that permit a highly reliable verification of vital status, immigration and emigration dates, and other information; (iii) national cancer registration since 1958 with a high coverage of detected cancer cases; (iv) national cause-of-death registration; and (v) availability of population-based registers for several disease outcomes such as cardiovascular diseases. Furthermore, the fact that these studies were funded by either governmental or non-profit organizations, and not by industry, likewise contributes to their relevance and application. All of the foregoing factors make the studies underlying the Swedish Experience (nearly all of which studied Swedish snus products manufactured by Swedish Match) credible and available to be applied in the consideration of this MRTP Application and in CTP's regulatory science decision-making framework more generally.

2.5.2.3.2. Institutional Reports citing the Swedish Experience

Tobacco harm reduction is a global public policy concern. Governmental and scientific authorities from several countries, including Sweden, Norway, New Zealand, and the United

Kingdom ("UK"), have undertaken studies resulting in published reports that address the key policy issues and recommendations. These scientific analyses have been conducted by a range of entities, including public health agencies, independent scientific advisory committees funded by governmental agencies, and a medical society. The reports have different goals and are intended for different audiences, but they all feature the Swedish Experience and its contribution to the tobacco harm reduction knowledge base and governmental policy and regulatory decisions.

The following seven (7) reports of international authorities are particularly relevant to CTP's consideration of the modified-risk claims set forth in this MRTP Application:

1. *Scientific Standards for Studies on Modified Risk Tobacco Products*, prepared by the Institute of Medicine Committee on Scientific Standards for Studies on Modified Risk Tobacco Products, 2012 (Appendix 2A);

2. *Health Effects of Smokeless Tobacco Products*, prepared by the European Commission (EC) Scientific Committee on Emerging and Newly Identified Health Risks, 2008 (Appendix 2B);

3. *A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective is Best for the Remaining Smokers in Scandinavia?*, a report by the Norwegian Institute for Alcohol and Drug Research, 2009 (Appendix 2C);

4. *Public Health Status Report: 2005*, a report of the Swedish National Board of Health and Welfare, 2006 (Appendix 2D);

5. *Systematic Review of the Health Effects of Modified Smokeless Tobacco Products*, Marita Broadstock, New Zealand Health Technology Assessment, 2007 (Appendix 2E);

6. *Harm Reduction in Nicotine Addiction: Helping People Who Can't Quit*, a report by the Tobacco Advisory Group of the UK Royal College of Physicians, 2007 (Appendix 2F); and

7. *Fifty Years Since Smoking and Health: Progress, Lessons and Priorities for a Smoke-Free UK*, Royal College of Physicians, 2012 (Appendix 2G).

Two of the studies—the 2012 IOM and 2008 SCENIHR reports—were undertaken at the request of regulatory science agencies and are particularly applicable to decision-making. The reports were initially used to provide scientific input to the regulatory process; however, the reports will undoubtedly also have a long-term impact and will serve as fundamental resources in ongoing policy and regulatory discussions.

The other reports examine public health policy and risk communication issues, and the quality of the evidence relating to tobacco harm reduction. The reports differ slightly in their intent and

application, but all address the complex and controversial issue of tobacco harm reduction, including how to characterize the risks posed by using Swedish snus and whether the product can serve as a smoking cessation aid.

All of the reports have made important contributions to national and regional tobacco control policy, and collectively, they provide a foundation for advancing tobacco harm reduction policy and science. Each report has advanced the current state of the scientific knowledge regarding tobacco use and, therefore, is highly relevant to CTP's consideration of this MRTP Application.[17] A more detailed overview of each report follows, and each report has also been included as an appendix to this Application, in Appendices 2A – 2G, respectively.

2.5.2.3.2.1. Institutional Reports

Scientific Standards for Studies on Modified Risk Tobacco Products, Institute of Medicine, 2012

At the request of the FDA, IOM formed a committee to identify the minimum standards for scientific studies that a sponsor should complete to obtain an order to market an MRTP from FDA. Due to FDA's familiarity with the content and recommendations of the IOM Report (2012), it is not necessary to either describe the report or assess how it has contributed to the development of tobacco policy and regulation. However, it is important to underscore IOM's statements about the importance of observational epidemiologic studies in the evaluation of MRTPs. IOM stated that "these methods form the basis for most evaluation studies of regulated products in the community. Long, intensive, and robust observational studies of actual health outcomes may be required to fully evaluate the net effects of MRTPs relative to conventional tobacco products." IOM also indicated that such studies should be enhanced by experimental designs, and in particular randomized controlled trials.

Scientific Opinion, Scientific Committee on Emerging and Newly Identified Health Risks ("SCENIHR"), 2008

In 2004, the EU's Directorate-General for Health and Consumers ("DG SANCO") requested that SCENIHR provide a "scientific opinion" on the health effects of smokeless tobacco products. The request cited the history and justification for the EU's ban on oral tobacco products, and addressed the validity of "claims that the use of smokeless tobacco could reduce harm related to other tobacco products." In response to the request, a SCENIHR working group was formed to evaluate the health effects of smokeless tobacco products ("STPs") with particular attention to

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[17] All of the reports address the health risks of MRTPs and, thus, are highly relevant to CTP's consideration of this Application. In particular, note that three of the reports were written by scientific committees—two of which were charged with addressing particular questions (i.e., IOM and SCENIHR), and a third which had more flexibility to determine the scope and focus of its report (i.e., the Royal College of Physicians' Tobacco Advisory Group).

tobacco for oral use, most notably Swedish snus.

The SCENIHR working group was charged with answering the following five questions regarding the health effects of STP:

1. What are the adverse health effects of smokeless tobacco products?

2. What is the addiction potential of smokeless tobacco products?

3. Do the available data support the claim that smokeless tobacco may constitute a smoking cessation aid comparable to pharmaceutical nicotine replacement products?

4. What is the impact of smokeless tobacco use on subsequent initiation of smoking?

5. Is it possible to extrapolate the information on the patterns of smokeless tobacco use, smoking cessation and initiation from countries where oral tobacco is available to EU countries where oral tobacco is not available?

Following a lengthy assessment and evaluation process, SCENIHR issued a final report and "opinion" on February 6, 2008 (SCENIHR 2008). The report includes an examination of groups of diseases for which cigarette smoking has an effect, and compared the health effects from smoking and from use of snus. A principal conclusion presented in the report is the following:

> Overall therefore, in relation to the risks of the above major smoking-related diseases, and with the exception of pregnancy, STPs are *clearly less hazardous*, and in relation to respiratory and cardiovascular disease *substantially less hazardous*, than cigarette smoking. The magnitude of the overall reduction in hazard is difficult to estimate, but as outlined above, for cardiovascular disease at least 50%, for oral and GI cancer and probably also at least 50%, and for respiratory disease close to 100%. (emphasis added)

A number of findings in the report support the characterization of Swedish snus as a potential harm reduction product, including the following:

1. Swedish snus has dramatically fewer adverse health effects than cigarettes. (pp. 113-114)

2. A smoker who switches to snus substantially reduces his or her risk for tobacco-related disease. (pp. 115-117)

3. The availability of snus as a substitute for cigarettes has had positive effects on Swedish public health. (pp. 116-117)

4. Swedish data contradict the hypothesis that snus is a gateway to smoking. (pp. 108, 116, 121)

There is general agreement among stakeholders that the SCENIHR report on smokeless tobacco products provides a useful addition to the scientific knowledge. However, the report has not yet resulted in a change in European Union tobacco harm reduction policy, including lifting of the ban on certain forms of oral tobacco.

A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective Is Best for the Remaining Smokers in Scandinavia? Norwegian Institute for Alcohol and Drug Research, 2009

This report was written by Dr. Karl Erik Lund, Norwegian Institute for Alcohol and Drug Research ("SIRUS") research director and author of several articles related to tobacco harm reduction. The report posits that tobacco harm reduction "should be an additional element in a future disease preventive strategy." The report provides an overview of current tobacco and harm reduction policies in Norway and other countries, and notes that "[d]espite the fact that measures to prevent smoking have been effective, and the proportion of smokers is decreasing in Scandinavia, the need for harm reduction measures has become greater." (Lund 2009).

Chapter five of the report examines whether Swedish snus should be considered to be a harm reduction product. More than simply acknowledging that "[r]eviews of the scientific literature show that snus is substantially less hazardous than cigarettes," the report reaches even bolder scientific conclusions, including that " . . . the pattern of use of snus in Sweden and Norway suggests that availability of snus must have a positive net effect on public health" and that "[t]here is little empirical data from Scandinavia to support the hypothesis that snus increases the risk of starting to smoke."

The report also includes a chapter addressing the reasons why harm reduction policy should be made "legitimate by the authorities." Recommendations include "informing people about snus… as an alternative to cigarettes in specific population groups" and suggest that "authorities could aim their message to the groups of smokers who cannot manage to quit smoking by any other means."

The report has generated considerable attention and discussion in Norway, both in the media and in the scientific community. Most significantly, it contributed to a "new attitude to use of snus as a harm-reducing product" by the Norwegian Directorate of Health. Indeed, the report itself includes a Prologue which quotes public health official Knut-Inge Klepp as to when medical professionals should recommend snus to "inveterate smokers." The Prologue section also contains the following statement from the Norwegian Directorate of Health website:

> We know that a large proportion of people who smoke have contact with a dentist or general practitioner, says Klepp. It is important that health care personnel take up the topic of smoking, recommend quitting, and help people who wish to quit. In the first instance they should try established methods such as nicotine chewing gum,

> nicotine patches or medicinal nicotine products available on prescription. If patients have tried these methods without being successful, the Norwegian Directorate of Health means that health care personnel in individual cases can consider that the patient should try snus instead.

Public Health Status Report: 2005, Swedish National Board of Health and Welfare, ("SNBH")

In 2003, the Swedish Parliament adopted a new public health policy that charges the Swedish National Board of Health and Welfare with preparing a public health policy report every five years. The first report was issued in 2006 and focuses on health determinants, or "the factors in the organization of society and people's living conditions and lifestyles that contribute to health or ill-health." The 2006 report presents a large number of determinants and clarifies their relationship to health.

The report (Swedish National Board of Health and Welfare 2006) contains a section titled *Continued Decline for Smoking as Snus Consumption Increases*. The report presents detailed information regarding use patterns, and notes, for example, that snus is used by slightly more than 23% of men and less than 3% of women in Sweden. Furthermore, the percentage of the population aged 16-84 years among whom snus is used on a daily basis rose from 10.3 to 13.0% between 1996/97 and 2004. The report also presents detailed socioeconomic data. For example, snus use is far more common for people born in Sweden, men ages 25-44 years, unskilled workers, and single men with children.

The report also addresses health implications and the ongoing debate about whether snus is a smoking cessation aid or instead a gateway to smoking. It notes that there is general consensus that the health hazards of snus are minor compared with those of smoking. The report also cites contemporary studies showing that snus does not increase the risk of myocardial infarction morbidity. Conversely, the report also cites the scientific literature from the Karolinska Institute indicating that snus may increase the risk of pancreatic cancer and may cause injury to unborn and newborn babies. The report states that the scientific source material for the latter conclusions is not always strong, but the assumption should always remain that snus is not harmless.

The tobacco section of the report also addresses the role of snus in smoking cessation. It poses, but leaves unanswered, the question of whether public health officials should suggest to smokers they switch to snus. The report cites data from the Sweden's Living Condition Surveys which indicate that, for every person who progressed from snus to smoking, there were four who switched from smoking to snus. It concludes that, apparently, many people have used snus as a means to give up smoking, and that the risk that young adults will progress from snus to smoking is far smaller than the risk that a non-smoker will take up smoking.

Importantly, the report's tobacco section is part of a broader state of public health report intended for a mass audience. Thus, it provides a risk communication service and addresses a critical health issue—tobacco harm reduction—in a manner which is seldom (if ever) presented to the general public.

Systematic Review of the Health Effects of Modified Smokeless Tobacco Products, Marita Broadstock, New Zealand Health Technology Assessment ("NZHTA"), 2007

The NZHTA report focuses on the quality of the international evidence for the health effects of using modified smokeless tobacco products. The report sets forth several conclusions regarding the strengths and limitations of the evidence, including the range of products evaluated, range of health outcomes considered, exposure measurement, confounders and risk modifiers, statistical power and study designs.

The report is primarily snus-oriented. A systematic review of the literature determined that 18 papers were eligible for inclusion in the review, including 16 primary studies which were conducted in Sweden. The report's Background chapter includes a section titled "Snus as Potential Reduced-Exposure Products" which presents a thorough description of the Swedish experience and addresses the transferability of the experience to New Zealand and elsewhere.

In a section assessing the limitations of current research, the report identifies industry funding as a potential liability. Although funding source is a potential concern that should be considered when examining the evidence, the report notes that research findings and interpretations found in industry-funded studies typically are similar to those in non-industry-funded studies. Furthermore, the report condemns the polarizing positions and statements that often characterize the debate in this arena, as "[n]either stance is an accurate or helpful representation of the complexities of this debate." (Broadstock 2007).

A principal conclusion stated in the report is that the evidence indicates that ". . . snus use, compared with smoking, has much lower health risks associated with a range of head, neck and gastro-intestinal cancers. Indeed, compared with non tobacco use, snus did not lead to an increased risk for those cancers, although larger studies are required to increase the precision of these risk estimates."

Harm Reduction on Nicotine Addiction: Helping People Who Can't Quit, Tobacco Advisory Group of the Royal College of Physicians (the "Royal College"), 2007

The Royal College has a long history of addressing tobacco and public health concerns in the UK, including issues related to tobacco harm reduction. Several of the recommendations made by the Royal College have become established international practice. However, the recommendations did not address the problem of the smoker who cannot quit. Thus, in 2007, the Royal College embarked on a project which resulted in the report *Harm Reduction on Nicotine Addiction: Helping People Who Can't Quit* and makes the "case for harm reduction strategies to protect smokers."

The report was prepared by the Royal College's Tobacco Advisory Group, chaired by Dr. John Britton. In the report preface Dr. Britton states, "We demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives would be saved." (RCP 2007). The report is intended to contribute to the national and

global policy debate, and in the preface Dr. Britton laments that "the regulatory systems that currently govern nicotine products in most countries, including the UK, actively discourage the development, marketing and promotion of significantly safer nicotine products to smokers."

The report provides a comprehensive presentation of the key issues relating to tobacco and nicotine addiction and includes a long list of references, thereby serving as a significant contribution to the scientific literature. However, what sets the report apart from others is the inclusion of clearly stated tobacco control conclusions and recommendations. Many of the conclusions and recommendations are specific to Swedish snus, including the following:

1. "On toxicological and epidemiological grounds, some of the Swedish smokeless (snus) products appear to be associated with the lowest potential for harm to health."

2. "Some of the smokeless tobacco products also increase the risk of oral cancer, but, if true of Swedish smokeless tobacco, the magnitude of this effect is small."

3. In Sweden, the available low-harm smokeless products have been shown to be an acceptable substitute for cigarettes to many smokers, while 'gateway' progression from smokeless to smoking is relatively uncommon."

The final recommendation concerns the establishment of a "nicotine regulatory authority to take control of all aspects of regulation of all nicotine products." Such an approach is consistent with the Royal College's conclusions that the "regulation of nicotine products, whether medicinal or tobacco-based, thus needs radical reform to ensure that the market forces of affordability, promotion and availability act in a strong and directly inverse relation to the hazard of the nicotine product, and that the marketing and use of nicotine products are carefully monitored to maximize public health benefit."

Fifty Years Since Smoking and Health: Progress, Lessons and Priorities for a Smoke-Free UK, Royal College of Physicians, 2012

In March 2012 the Royal College issued a report titled *Fifty years since Smoking and health: Progress, lessons and priorities for a smoke-free UK*. The report consists of papers from a conference that marked the 50th anniversary of its seminal 1962 report *Smoking and health*.

One of the articles—*Reducing harm from nicotine use* by Dr. Ann McNeill—focuses on harm reduction and calls for a "radical change in policy from government and regulators, that will encourage innovation in alternative nicotine products . . . ." The article cites the Swedish experience with snus as "proof" of the concept of tobacco harm reduction. Dr. McNeill cites key statistics from the Swedish experience and concludes that snus "has been proven a viable harm-reduction product because it delivers high doses of nicotine and is as freely available as cigarettes, but also less expensive, as well as being generally socially acceptable. Snus is not a safe product, but its health risks are minimal compared with those of regular smoking." (RCP 2012).

The article concludes with a series of policy recommendations, many of which relate directly to the provisions governing MRTPs under the Tobacco Control Act and to the Swedish Match quality standard GOTHIATEK®. For example, Dr. McNeill suggests that harm reduction products should be regulated "to guarantee purity and acceptable safety standards"— which are primary goals of GOTHIATEK®. Dr. McNeill also calls for more improved risk communication and recommends a program to "inform health professionals and the public about this new strategy; and monitor performance and effectiveness when in place"—an approach which is consistent with the premarket review and postmarket surveillance requirements of the Tobacco Control Act.

2.5.2.3.2.2. Types of Institutions

Several different types of institutions have played key roles in the ongoing initiatives relating to tobacco harm reduction. Two institutions—IOM and SCENIHR—are scientific organizations that established independent technical committees to examine a specific tobacco regulatory issue for a given timeframe. Two other institutions—SNBH and SIRUS—are national public health agencies, whose responsibilities include understanding the lifestyles and habits of the population they serve and effectively characterizing and communicating the associated risks. The third type of institution (namely, the Royal College) is a medical society, whose mission includes taking part in national debates on medical, clinical and public health issues.

Independent Scientific Advisory Committees

Independent scientific advisory bodies (such as the IOM and SCENIHR) have become increasingly instrumental in the United States and European Commission ("EC" or the "Commission") regulatory science process. These bodies are often essential when a governmental agency must make difficult and complex decisions relating to a controversial subject or product. As CTP is familiar with the IOM committees formed to address tobacco harm reduction-related issues, we therefore focus here on the EC's SCENIHR process.

In 2004, the Commission established three independent, non-food Scientific Committees, namely (i) the Scientific Committee on Consumer Products (SCCP), (ii) the Scientific Committee on Health and Environmental Risks (SCHER), and (iii) the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The mission of the committees is to provide the Commission, and through the Commission, other European institutions, with scientific advice in the fields of consumer safety, public health and the environment. The committees are managed by DG SANCO and follow comprehensive rules of procedure. The rules are intended to ensure the committees "perform their tasks in compliance with the principles of excellence, independence, transparency and confidentiality as well as with the principles and standards for scientific advice on risk assessment."[18] The principle of excellence refers to the performance and

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[18] Scientific Comms. on Consumer Safety, Health & Envtl. Risks, and Emerging & Newly Identified Health Risks, European Comm'n, Rules of Procedure 5 (Apr. 2013), available at http://ec.europa.eu/health/scientific_committees/docs/rules_procedure_2013_en.pdf.

outcome of the entire process. The principle of independence refers to the organization and results of the process, including in particular the independence criteria and the conditions for the participation of members, advisors and experts.

The EC committees provide advice, but they do not determine policy. According to DG SANCO, "[t]he opinions of the Scientific Committee present the views of the independent scientists who are members of the committees" and "do not necessarily reflect the views of the European Commission."[19] The term "opinion" refers to the findings and analysis of the committee, not the opinion of an individual member of the committee.

National Public Health Agencies

Public health agencies, including those in Sweden, Norway, and New Zealand, must understand the lifestyles and habits of the population they serve and effectively characterize and communicate their associated risks. With respect to tobacco, the fundamental message communicated by most public health agencies can be summarized as follows: tobacco products are extremely harmful, consumers should not use the products, and if they do, they should seek help to stop using the products. Although these are appropriate messages for any public health agency to communicate, a truly comprehensive harm reduction strategy requires that an agency communicate a more nuanced message than simply "don't use tobacco products."

The Public Health Agencies of Sweden (SNBH and the National Public Health Authority, formerly, the Swedish National Institute of Public Health ("SNIPH")) and the Norwegian Directorate of Health have confronted the issue of tobacco harm reduction, including how best to characterize the risks posed by using Swedish snus and whether the product should be characterized as a smoking cessation aid. The agencies were compelled to do so, in part, because snus is a widely used in both countries. Further, the public health agencies were obligated to fully consider the increasing body of evidence regarding the health risks of snus. The fact that much of the evidence related to Swedish snus use is based on cohort studies in Sweden and Norway motivated those agencies to fully address if and how the evidence should impact national public health initiatives.

Public Health Agencies of Sweden

SNBH and SNIPH are state agencies under the Swedish Ministry of Health and Social Affairs. Both agencies work to promote health and prevent ill health and injury, especially for population groups most vulnerable to health risks. A principal task of SNIPH is to monitor and coordinate the implementation of the national public health policy. SNIPH also serves as the national expert agency for the development and dissemination of methods and strategies based on scientific evidence in the field of public health.

In Sweden, SNIPH works closely with other governmental units, academia, and non-governmental organization (NGOs) in determining tobacco usage patterns, and assessing and

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19 *Id.*

communicating the associated health risks. A key fellow national agency is Statistics Sweden, whose main task is to supply customers with statistics for decision- making, debate and research. Statistics Sweden ovesees the Living Conditions Surveys which have been instrumental in determining tobacco usage patterns.

SNBH produces the *Public Health Policy Report* every 5 years. The reports present an evaluation of disease outcomes and offers recommendations for priorities that can improve attainment of the overarching goal of the national public health policy.

Norwegian Institute for Alcohol and Drug Research ("SIRUS")

SIRUS is an independent administrative government body under the Ministry of Health and Care Services.[20] SIRUS conducts social scientific research, compiles documentation, and provides information on substance use and abuse. SIRUS's work is divided into three areas, each of which is staffed by a dedicated research team. These areas include alcohol research, drug research, and tobacco research. In recent years SIRUS funding has resulted in a number of scientific articles authored by SIRUS research director Dr. Karl Lund. Much of Lund's research has focused on the association between use of snus and quit rates for smoking.

The New Zealand Health Technology Assessment ("NZHTA")

NZHTA was a research unit of the University of Otago that provided analytical services to the New Zealand Ministry of Health. NZHTA is no longer active, but its publications are still relevant and accessible.

The New Zealand Ministry of Health

The New Zealand Ministry of Health has traditionally been the key agency for policy development in the tobacco control area and is involved in a large number of policy, service development and operational aspects of tobacco control. The Ministry is currently working on a number of initiatives in its continual efforts to fight the tobacco epidemic. These include the introduction of pictorial warnings on tobacco packages, increased access to NRT, and a review of tobacco displays in New Zealand. In 2006 the Ministry requested NZHTA to undertake a systematic review of the international evidence for health effects of using modified smokeless tobacco in order to inform the Ministry's policy considerations "regarding harm minimization."

Medical Societies

Medical societies exist in many countries to support and represent physicians and to further public health goals. In the UK, the Royal College has been in existence for nearly 500 years, supporting physicians during every stage of their careers and seeking to improve the quality of

[20] Although part of the Ministry, SIRUS is an independent research institution with a scientific council. Other agencies within the Ministry include the Norwegian Directorate of Health.

patient care. The Royal College sets and monitors standards of medical training, establishes evidence-based clinical guidelines, and offers education programs that provide physicians with the knowledge and skills they need for high performance. It is also involved in public health more generally, including campaigning for change, advising government and Parliament, and taking part in national debates on medical, clinical and public health issues.

The Royal College has been a leader in addressing tobacco harm reduction, and its committees prepare reports on tobacco use and other pressing public health issues. These reports have significant impact in the UK and globally, and are comparable in stature to reports issued by the US Surgeon General. The Royal College first addressed tobacco policy in its 1962 report *Smoking and Health* and has remained at the forefront tobacco policy ever since. This seminal report and several of the Royal College's recommended policies have become established international practice.

The Royal College issued the report *Harm reduction in nicotine addiction: Helping people who can't quit* in 2007. In March 2012, it issued a report consisting of papers from a conference that marked the 50th anniversary of the 1962 report. One of the articles, *Reducing harm from nicotine use* by Dr. Ann McNeill, focused on harm reduction and—citing the Swedish Experience with snus—called for a "radical change in policy from government and regulators, that will encourage innovation in alternative nicotine products."

2.5.2.3.3. Transferability of the Swedish and Norwegian Experience to the United States

2.5.2.3.3.1. Overview

The previous subsections describe the Swedish epidemiological evidence and how it has been considered by institutional authorities in Sweden, Norway, the UK, New Zealand and the EU. In examining the evidence, researchers from these countries have typically concluded that the use of snus rather than cigarettes significantly reduces individual risk; and the Norway SIRUS articles imply a population benefit. However, researchers have expressed uncertainty regarding the transferability of the Swedish Experience. (Gartner et al. 2007a).

Comparisons between the effects of snus and cigarettes in the Swedish studies have concerned the type of cigarettes and smoking patterns that have been prevalent in Sweden over the years. Thus, it could theoretically be argued that, since the cigarette brands and smoking patterns that are prevalent in the United States may be different from those in Sweden, the Swedish studies may not be relevant for the US market. However, this is not the case. Appendix VI to Chapter 5 of the ENVIRON Snus Monograph (2013), compares health outcomes among Swedish smokers to results from several large US cohorts. Notwithstanding the methodological issues associated with comparing different types of studies (which is a point extensively discussed in the review), the results nonetheless illustrate a considerable concordance between the US and Swedish studies in terms of health outcomes (i.e., lung cancer and various other forms of cancer, cardiovascular diseases ("CVD"), stroke, diabetes, and all-cause mortality among smokers). These observations

support the applicability of the Swedish epidemiological data to the US context, and further substantiate Swedish Match's claim that Swedish snus, as manufactured by Swedish Match, is substantially less hazardous than cigarettes.

Notwithstanding the above, assessing the likelihood of the transferability of the Swedish and Norwegian experiences with snus to the United States also requires careful consideration of the conditions in the Scandinavian countries that account for the switch and an examination of the context in which the shift occurred. What occurred in Sweden and Norway is well documented—cigarette smokers wanting to quit smoking tried NRTs and various other alternatives, but many preferred Swedish snus and were able to use the product to successfully transition from cigarettes (Lund and McNeill 2013). The movement began as, and remains to this day, a grassroots phenomenon. In other words, the shift from cigarettes to snus throughout Scandinavia was not the product of a nationally coordinated initiative originating from the centers of political activity, but rather was a trend which started with common citizens at a local level. Indeed, both the Swedish and Norwegian experiences occurred in the complete absence of a national coordinated advertising campaign, and with very little support from the countries' public health and medical communities. Although there was limited advertising in Sweden in the 1970s, for the past few decades there has been no advertising in either country. Thus, Norwegian researcher Karl Erik Lund has noted that "the market shift has happened in a 'dark market' where any active promotion of snus has been banned for decades." (Lund 2013)

In Sweden, the grassroots movement was likely in reaction to the mounting evidence of the negative health impacts of smoking. The switch from smoking to snus began to occur in the late 1960s to early 1970s. Thereafter cigarette sales declined while snus sales rose and, by 1990, sales of the two products were equal. Since 1990, however, snus sales have continued to increase while cigarette sales have significantly declined. During this same time period, smokers increasingly acknowledged the negative health effects of smoking and began considering alternatives. Most smokers were not aware of the risk reduction offered by Swedish snus, rather they were seeking an alternative to cigarettes and tried snus, a traditional Swedish product (Lund and Scheffels 2012; Overland et al. 2008).

The Swedish grassroots movement eventually migrated to Norway, where snus is also a traditional product (though not to the same extent as in Sweden) and can be easily purchased (i.e., Norway is a not a member of the EU which bans the sale of snus except in Sweden). The transition from cigarettes to snus has occurred with a concomitant decrease in total consumption of tobacco. In Norway there has been a 15% reduction since 1985 (Lund and McNeill 2013).

2.5.2.3.3.2. Comparing the Swedish and Norway Experiences with Snus

The first condition that contributed to the Swedish and Norwegian Experiences—or any tobacco harm reduction transition—is the existence of a population of smokers that is willing to try alternative products in an attempt to quit. Historically, the percentage of current smokers

attempting to quit—which is approximately 40-50%—has been similar in Sweden and Norway and the United States. (Lund 2013)

A second condition relates to smokers' knowledge of the various nicotine delivery products available. Smokers in all three countries are aware of NRTs and understand the risk reduction opportunities they offer. However, there are differences regarding smokers' knowledge and perception of Swedish snus. In Sweden and Norway, snus is the overwhelmingly dominant smokeless product. In the United States, the most popular form of smokeless tobacco are spit products, although snus is growing in popularity (e.g., in 2012, sales of Swedish Match snus products were expected to have doubled from the previous year). In all three countries, the majority of smokers overstate the health risk from snus compared to cigarettes (Lund and Scheffels 2013; Overland et al. 2008).

A third condition is that the alternative product must be able to satisfy smokers' needs. In his 2013 article, Lund identifies several reasons why snus is preferred over medicinal nicotine products, including that (i) the snus nicotine dose is almost the same as for cigarettes and (ii) snus products, in contrast to nicotine chewing gum and nicotine patches, offer "functions that are identical to those offered by cigarettes" and, like cigarettes, "taste of tobacco and thus ha[ve] a sensory effect that medicinal nicotine products perhaps lack." (Lund 2013).

A fourth condition necessary for a wholesale switch from cigarettes to snus is the existence of an initiative among smokers that results in a word-of-mouth movement toward a less risky product. Typically, such a movement grows exponentially once a critical mass has been reached. In Sweden that tipping point likely occurred around 1990 when the sales of cigarettes and snus were roughly equal. In Norway, by contrast, the tipping point seems to have occurred during the 2005-2008 timeframe during which SIRUS was conducting research. A grassroots market for snus has yet to fully develop in the United States, but sales are steadily increasing and there is an ever-growing group of bloggers, journalists with tobacco periodicals, and other vocal snus users.

The significance of a word-of-mouth movement cannot be underestimated because governmental authorities are not currently communicating tobacco harm reduction and continuum of risk concepts to the public. None of the public health agencies in Sweden, Norway, or the United States provide science-based advice regarding the risk reduction potential of alternative tobacco products; rather the primary message in these three countries is to stop using tobacco products. Consequently, a smoker who turns to a public health agency website for advice is not going to receive any encouragement to try any alternative products to cigarettes other than NRTs. That said, there are subtle differences regarding how the public health and medical establishments refer to snus. For example, in Sweden, physicians and other public health professionals are more likely to acknowledge that snus use is preferable to smoking. They also are more likely to believe that it is acceptable to inform smokers—and particularly smokers who have been unsuccessful in quitting—to try snus as a means to stop smoking. This willingness is due in part to the grassroots tipping point that has already occurred, and health professionals' difficulty in discounting the significance of the Swedish Experience.

Swedish medical professionals are also undoubtedly influenced by the message of some influential reports, including for example, the "Continued Decline for Smoking as Snus Consumption Increases" section of the *2005 Swedish Public Health Report*. This report addresses whether snus is a smoking cessation aid or, alternatively, a gateway to smoking. It recognizes the general consensus that the health hazards of snus are minor as compared to those of smoking, and cites contemporary studies showing that snus does not increase the risk of myocardial infarction morbidity. Conversely, it also cites the scientific literature indicating snus may increase the risk of pancreatic cancer and cause injury to unborn and newborn babies, before concluding that, while the scientific source material is not always strong, the assumption should always be that snus is not harmless.

In Norway, the SIRUS Report and Lund articles provide similar support for health care professionals to acknowledge the harm reduction potential of snus.

2.5.2.3.3.3. Contrasting the Swedish and Norwegian Experiences with Snus

The Swedish and Norwegian experiences with snus have many key parallels. For example, in both countries the shift away from smoking to snus use began with men, but in recent years the percentage of women snus users has increased. Further, in both countries, snus is reported by ever-smokers to be the most preferred method for quitting (Lund 2013), and in both countries Swedish Match snus products are widely used to do so.

Nothwithstanding these similarities, one fundamental difference between the two countries' experiences concerns when, and over what period of time, the respective switch from cigarettes to snus occurred. In Sweden, the switch occurred over three decades and allowed for the collection of epidemiological information on health outcomes which resulted in the publication of numerous scientific articles demonstrating the reduction in individual risk. In Norway, the transition has been much more recent and rapid, which does not allow for epidemiological findings, but nonetheless has focused research attention on the smoking cessation potential of Swedish snus. This public health policy focus in Norway is due to acceptance of the Swedish evidence, the timing of the Norwegian research, and the role of the SIRUS. SIRUS was instructed to evaluate public measures that were initiated in Norway during the period from 2003-2008 to prevent the use of tobacco (Aaro et al. 2009). This coincided with the momentum that the concepts of tobacco harm reduction and continuum of risk (which also happen to be integral elements of the Tobacco Control Act in the United States) were gaining globally. In 2009, SIRUS issued the report *A Tobacco-Free Society or Tobacco Harm Reduction? Which Objective Is Best for the Remaining Smokers in Scandinavia?* The report described the growing Norwegian experience with snus and examined the role of snus as a harm-reducing alternative to smoking.

The report's principal author and SIRUS director, Dr. Karl Erik Lund, has written follow-up articles (funded by the Norwegian Directorate of Health and by the Norwegian Research Council) that further address the public health benefit of the switch to snus and whether the

Norwegian experience is transferable to other counties. In a 2011 article , Lund and co-authors (Lund et al. 2011) include a section on *The Consequences for Public Health* and state: "The extent and nature of the impact on public health will depend upon the relative risk hazard of snus and smoking, and the relative uptake and use by smokers and nonsmokers." The authors also note that identifying the net effect of snus use from a public health perspective is a "complicated task" but that "the conditions for carrying out this task are best in countries such as Norway and Sweden, using our observational data on the transition between cigarettes and snus."

In a 2012 article, *Association Between Willingness to Use Snus to Quit Smoking and Perception of Relative Risk Between Snus and Cigarettes*, Lund suggests that devising methods to inform smokers about the risk continuum of tobacco products could be an important research priority in countries where snus is allowed to compete with cigarettes for market share (Lund 2012). Lund's subsequent 2013 publication, *Tobacco harm reduction in the real world: has the availability of snus in Norway increased smoking cessation*, found that snus is reported by ever-smokers in Norway to be the most preferred method for quitting smoking, and that former smokers make up the largest segment of Norwegian snus users (Lund 2013).

2.5.2.3.3.4. Summary and Future Prospects for Snus in the United States

There will always be differences among the experiences with snus in Sweden, Norway, and United States given these countries' differing tobacco regulatory environments. Tobacco regulation in Sweden is governed by an EU Directive which does not allow for modified risk claims. By contrast, Norway is not a member of the EU, and does not have a comprehensive tobacco control law. However, current government-funded research focuses on the use of snus as a cessation device. Finally, in the United States, the Tobacco Control Act establishes an MRTP review and approval process, but does not permit tobacco products to make smoking cessation claims. Notwithstanding these obvious differences, nearly all of the conditions that contributed to the Swedish and Norwegian experiences presently exist in the United States. Indeed, Swedish Match believes that the most fundamental difference between the US and Scandinavian experiences stems from snus's status as a traditional Swedish and Norwegian product. This product history greatly contributed to the grassroots movement which not only led to an exponential increase in smokers switching to snus, but also prompted the public health community to conduct critical research and provide more nuanced information to smokers regarding the potential benefits of switching to snus.

Even though the Scandinavian tradition of snus use cannot be transferred to the United States, many other US developments can help to create conditions that will contribute to the beneficial impact of snus products as a leading alternative to smoking. Unlike Sweden and Norway, the United States has a comprehensive tobacco control law that includes a science-based process for determining whether a product can be marketed with modified risk claims. Implementation of the Tobacco Control Act has resulted in a significant increase in the attention paid to cigarette alternatives. If FDA were to issue MRTP orders for the Snus Products, public awareness and knowledge of this particular type of cigarette alternative is likely to increase substantially,

possibly leading to the type of grassroots movement that has occurred in Sweden and Norway. This grassroots phenomenon is particularly important given that the proposed modified risk claims for the Snus Products do not include a significant change in the advertising and marketing campaigns for the products. This means that the growth in US market volume for the Snus Products will depend to a large extent on word-of-mouth sales and smokers' response to external influences. Word-of-mouth sales have already contributed to the steady increase in snus sales in the United States, which are expected to continue to rise among current smokers if the Snus Products are permitted to be marketed as MRTPs.

Another factor contributing to the growing awareness of alternatives to smoking in the United States is the increasing amount of tobacco research and resulting scientific articles on the subject. Of particular note are (i) the ongoing FDA/NIH sponsored Population Assessment of Tobacco and Health study ("the PATH Study") that includes, among other things, a thorough and comprehensive examination of knowledge, attitudes, and beliefs toward snus and other smokeless products and (ii) FDA and NIH's joint establishment of fourteen (14) Tobacco Centers of Regulatory Science (TCORS) for tobacco-related research, designed to generate research on reducing toxicity and carcinogenicity, adverse health consequences, marketing and tobacco product risk messaging, and other topics that will inform the regulation of tobacco products. These areas of groundbreaking research will undoubtedly receive considerable media attention, thereby increasing public understanding of the concepts of tobacco harm reduction and continuum of risk for various tobacco products, including Swedish snus.

In short, whether the Swedish and Norwegian experiences are, in whole or in part, transferable to the United States cannot be fully known until MRTP orders are granted for the Snus Products and postmarket surveillance is conducted. In the meantime, however, Sweden and Norway provide a "natural laboratory" (Lund 2013) for the study of how snus typically competes for market share with cigarettes and contributes to a growing recognition among smokers of the beneficial harm reduction potential of snus at both the individual and population levels. For that reason, Swedish Match believes that the Swedish and Norwegian Experiences remain highly relevant to CTP's consideration of this Application and the potential public health benefit of the Snus Products discussed herein.

2.5.2.3.4. Swedish Match Clinical Trials and Clinical Studies

Observational data from Sweden illustrate that, during the past three to four decades, many smokers have switched from cigarettes to Swedish snus. The data also show that, among snus users with a previous history of smoking, daily dual use of both cigarettes and snus is infrequent. These observations confirm that many Swedish smokers have quit smoking cigarettes completely by switching to snus. This transition from cigarettes to snus (which started in the late 1960s-early 1970s and is a fundamental part of the Swedish Experience) has contributed to the internationally record low rates of smoking among Swedish males and their comparatively low rate of smoking-related disease.

Due to methodological issues in cross-sectional survey data on smoking behavior it has been

suggested that—despite the compelling population data noted above—the absence of experimental evidence from randomized clinical trials makes it difficult to draw reliable conclusions as to the effectiveness of snus as an aid to clinical smoking cessation. To address this concern, Swedish Match has since sponsored a number of clinical trials to investigate this and other issues.

2.5.2.3.4.1. Smoking Cessation Studies

Between 2008 and 2010, Swedish Match sponsored two placebo-controlled, double-blind, randomized clinical trials to investigate the effectiveness of snus as an aid to clinical smoking cessation to support the compelling population data from the Swedish Experience (Fagerstrom et al. 2012; Joksic et al. 2011; Rutqvist et al. 2013). One of the studies was conducted at two sites in Serbia, and the other at five sites in the United States. Both studies tested whether *ad lib* provision of snus could affect subsequent smoking behavior among adult smokers motivated to quit (United States and Serbia) or substantially reduce their smoking (Serbia). The trials compared Swedish snus manufactured according to the GOTHIATEK® standard with almost identical placebo products with no tobacco or nicotine. The trials included end-points related to biochemically-verified, complete smoking cessation. Measurements of abstinence, biochemical verification, and statistical analyses were conducted according to recommendations by the Society for Research on Nicotine and Tobacco (SRNT).

In the absence of any previous controlled trials of snus, Swedish Match believed it was reasonable to use a placebo-comparator because this design would generate direct information about the efficacy of snus. Moreover, because a double-blind, placebo-controlled approach is considered to be the gold standard for evaluating clinical interventions, and indeed is typically the first step to establish efficacy, Swedish Match likewise adopted this approach in the conduct of its studies. This design necessarily precluded the inclusion of a second, orally administered comparator (e.g., nicotine gum or lozenges), as use of snus products would interfere with a subject's ability to use gum or other oral products, and vice versa. Theoretically, it might have been possible to include a nicotine patch as an additional comparator, although a placebo-controlled, double-blind study design including snus, placebo snus, nicotine patch, and a placebo patch would have implied significant challenges in terms of study product logistics and may have decreased participant compliance with their allocated treatment.

None of the participating sites in Serbia or the United States had previous experience with smoking cessation interventions. Moreover, with the exception of one site in Serbia, none of the sites had previously been involved in clinical interventions that included use of Swedish snus. Study participants were recruited by word-of-mouth and by advertisements in various local media, not by referrals from other centers. In the United States, potential participants were also identified in a database of healthy volunteers interested in participating in phase 1-4 clinical trials, typically of pharmaceutical products.

Since use of NRTs is quite prevalent among US smokers who want to quit, it was expected that a substantial proportion of the participants in the US study would have a history of previous unsuccessful quitting attempts with NRTs. It would then be possible to assess the relative

efficacy of snus among those with a previous history of NRT exposure versus those without such a history. Information on possible cross resistance between snus and NRT (e.g., "Does snus work among smokers who have failed on NRT?") might be considered as clinically more relevant than a direct comparison of efficacy with an NRT (e.g., "Is snus more or less efficacious than NRT?"). In the Serbian trial, on the other hand, it was expected that few participants would have tried NRT or other pharmaceutical cessation aids because the cost of such products typically is prohibitive for most Serbian smokers.

The design of the US trial entailed a relatively short period (16 weeks) of active treatment during which participants were issued study products. Thereafter, subjects were instructed to refrain from nicotine-containing products, unless there was an imminent danger of smoking relapse among those who had managed to quit. This design mimics that typically used in many previous randomized trials of NRT products where the objective is not only to promote smoking cessation but also to treat the participants' dependence to nicotine (Silagy et al. 2007).

In the Serbian trial the primary outcome variable during the first 6 months was smoking reduction. It was hypothesized that recruitment to a smoking cessation program may be more successful if the proposed goal is to reduce smoking rather than total cessation. Smokers who have made previous unsuccessful quit attempts might abstain from participating in a program if the requirement is immediate, total abstention. Initial smoking reduction may facilitate complete cessation later on (Asfar et al. 2011). Only those participants who were found to have substantially reduced their smoking at the week 24 visit were actively followed up to 48 weeks. During weeks 24-48, the main objective was complete cessation. Study products were distributed throughout the study period with no prescribed tapering after a specified time point. The aims of the trial thus focused on smoking cessation but did not include treating the participants' nicotine dependence. The Serbian design can be described as being naturalistic because clinical experience from Scandinavia indicates that smokers who use snus as a smoking cessation aid typically do not switch abruptly from cigarettes to snus. The transition period of dual daily use can last from weeks to many months. Many successful quitters continue to use snus long term (Gilljam and Galanti 2003).

The minimal differences in the designs of the Serbian and US trials in part reflected differences between the two countries' social environments. In the United States, numerous smokeless tobacco products and prescription-free smoking cessation aids are readily available to most smokers at a cost comparable to cigarettes. By contrast, Serbian society tends to be much less supportive of smokers who are trying to quit. For example, smoking bans in public places and workplaces are uncommon in Serbia. Smokers there have little access to cessation support programs, and pharmaceutical cessation aids are more expensive than cigarettes. Consequently, the Serbian public is generally less informed than their American counterparts about the health hazards associated with smoking.

Swedish Match also sponsored a systematic review and meta-analysis of randomized trials of Swedish snus or snus-type products that include long-term smoking cessation as a clinical end-point. The review and meta-analysis were conducted according to the internationally accepted

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ("PRISMA") guidelines,[21] and the US and Serbian trials were the only studies meeting the defined criteria. Thus, the two clinical trials conducted by Swedish Match are the only randomized trials to date that have evaluated the role of Swedish snus or snus-type products for long-term smoking cessation.

Meta-analyses are frequently conducted for observational epidemiological studies in which there may be variation in study design (e.g., case-control or cohort), type of exposure, and extent of adjustment for potential confounding variables. Meta-analysis is also appropriate of relatively similar randomized controlled trials with the same active and placebo treatments. Thus, despite the differences between the two smoking cessation studies sponsored by Swedish Match, there are enough similarities to make it worthwhile to combine the evidence from the studies to allow a more powerful test of whether use of snus versus placebo affects the rate of quitting smoking. Both studies were relatively small (United States: 125 in each group; Serbia: 158 snus and 161 placebo), and a meta-analysis of appropriately defined endpoints allowed improved insight into the main hypotheses of interest, namely those related to biologically-verified, complete smoking cessation.

A governance structure for the trials was established before the studies were initiated. In the absence of an internationally accepted governance structure for clinical studies of tobacco products or industry-sponsored trials, Swedish Match decided prior to study initiation that the governance and conduct of the two trials should be as similar as possible to the accepted procedures for controlled clinical trials of pharmaceutical products. Thus, the governance structure implemented by Swedish Match included all the following elements:

- Protocols were developed in collaboration between the individual research teams and the sponsor according to internationally accepted guidelines.

- Studies were performed in accordance with International Conference on Harmonisation ("ICH") guidelines, Declaration of Helsinki guidelines, and all applicable national, state, and local laws.

- Written, full informed consent was obtained from all study participants.

- Conduct of the study was approved by an appropriately constituted institutional review board ("IRB") or independent ethics committee ("IEC").

- Trials were conducted according to full Good Clinical Practice ("ICH-GCP")

- Management of all clinical and other study-related information, including monitoring, conducted by internationally well-reputed Contract Research Organizations ("CROs") with extensive experience of controlled clinical trials of pharmaceutical products (*Serbian study*: i3 Research, *US study*: Covance).

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[21] *See* PRISMA guidelines, http://www.prisma-statement.org.

- All data handling and statistical analyses were conducted by external contractors according to pre-specified statistical analysis plans (*Serbian study*: i3 Statprobe, *US study*: Covance).

- Prospective registration of the trials was made at www.clinicaltrials.gov.

- Sponsor committed to publishing results irrespective of trial outcomes.

- Publication in peer-reviewed scientific journals was sought according to the Consolidated Standards of Reporting Trials ("CONSORT") guidelines.[22]

- Sponsor committed to making individual study data available for systematic reviews and/or meta-analyses conducted according to internationally accepted PRISMA guidelines.

The first results of the individual trials were published in 2011 and 2012 (Fagerstrom et al. 2012; Joksic et al. 2011). The systematic review and meta-analysis were conducted in 2012, and a full report summarizing the main findings was published in 2013 (Rutqvist et al. 2013). As explained below, trial results showed that participants allocated to snus were 2-3 times more likely to quit smoking completely compared to those allocated to placebo:

1. Based on the defined primary outcome in the meta-analysis (i.e., biologically-verified complete cessation during 23-24 weeks), the success rate was higher in the group allocated to snus in both Serbia (5.7% vs 1.9%), and the United States (4.0% vs 1.6%). The meta-analysis estimated the relative success rate at 2.83 (95% confidence interval: 1.03-7.75, exact p: 0.06, chi-squared p: 0.03).

2. For all defined biologically confirmed secondary outcomes in the meta-analysis (including continued abstinence rates during shorter time periods, and 1-week point prevalence abstinence rates), success rates were about twice as high in the group allocated to snus, and statistically significant ($p<0.05$).

3. For smoking cessation in the last four weeks of each study, the overall rates were 12.4% for snus and 6.6% for placebo (relative success rate 1.86, 95% confidence interval: 1.09-3.18), indicating that snus offers a real advantage to smokers who seek to quit smoking.

4. There was no statistically significant evidence that the relative success rate with snus in terms of the defined primary outcome in the meta-analysis differed according to gender, age at entry, age at smoking initiation, Fagerström score, history of previous quit attempts, or history of previous exposure to NRT. However, the study's small sample size may have limited its power to detect statistically significant heterogeneity.

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[22] *See* CONSORT guidelines, http://www.consort-statement.org.

5. An indirect comparison with results of a recent Cochrane overview (Silagy et al. 2007) in terms of relative success rate versus a placebo comparator suggests that the effect of snus is comparable to that achieved with NRT products. Indeed the hypothesis that snus may be even more efficacious is supported by population data from Sweden and Norway and is consistent with results from clinical studies on nicotine uptake from Swedish snus compared with nicotine chewing gum which show that the uptake from snus is comparable to but generally faster than from gum.

6. The relatively low overall continuous quit rates observed in both studies may be attributable to a variety of factors, including (i) the fact that none of the participating centers has previous experience with smoking cessation interventions, (ii) the negative cultural connotations of using smokeless tobacco products in the United States, (iii) a social environment in Serbia which is not supportive of quit attempts among smokers, and (iv) the methods used for recruiting participants which differed from those typically used for trials of pharmaceutical smoking cessation interventions.

7. Snus was safe and generally well tolerated in both the US and Serbian studies. Some treatment-related adverse events occurred more often in the snus groups but they were generally classified as mild. These adverse events reflected the classical symptoms related to nicotine exposure, including nausea, salivation, vomiting, and hiccups. No serious adverse events associated with use of snus were reported.

In sum, the experimental data on Swedish snus substantiate the observational population data from Scandinavia and support the conclusion that Swedish snus can increase complete smoking cessation among smokers motivated to quit or substantially reduce their smoking. Importantly, the observed effects of snus were clearly not limited to a Scandinavian social setting, as the US and Serbian trials showed comparable results. (All study documents, including raw data and relevant reports, are included in Appendix 2H to this MRTP Application.)

Cessation studies including participants motivated to quit report 6-month continuous abstinence rates that typically are higher than those observed in the US and Serbian trials (Silagy et al. 2007). Current results on complete cessation are more comparable to those typically seen in smoking reduction trials including smokers with no immediate wish to stop smoking completely. It is also possible that the aforementioned negative cultural connotations of smokeless tobacco in the US contributed to the observed overall success rates. In Serbia there is no traditional use of any form of oral tobacco products, so there are no negative cultural connotations associated with such products. However, the social environment in Serbia with a high smoking prevalence, few smoking restrictions, and a generally low public awareness of the dangers of smoking, is not supportive of quit attempts among smokers who want to stop smoking. Higher cessation rates with snus are reported in real-life surveys of Swedish and Norwegian smokers (Lund et al. 2010; Lund et al. 2011; Ramström and Foulds 2006). This may be due to self-selection of subjects and perhaps due to phasing in STP use over a much longer period. In the current trials use of study products was relatively limited, although in the Serbian study it tended to increase over time. This suggests that it may take some time before smokers become accustomed to using snus

products instead of cigarettes. In the US trial study products were not available to participants after week 16.

In sum, the evidence derived from Swedish Match's smoking cessation clinical trials is applicable to several sections of the MRTP submission as presented in the MRTP Guidance.[23] The clinical trials complement the Swedish Experience research, and together they provide evidence needed to address the five key areas of investigation listed under Summary of All Research Findings. In particular, the questions that the MRTP Guidance poses with respect to the health risks of the proposed MRTPs are primarily addressed by the Swedish epidemiological evidence, with supporting evidence from the clinical trials. The clinical trials also provide much of the relevant evidence for the MRTP Application's discussion of tobacco use behavior.

2.5.2.3.4.2. Nicotine Uptake Studies

It is widely accepted that nicotine is the main dependence-producing constituent in tobacco and that rate of delivery from a tobacco product is closely related to its abuse potential. In addition, the pharmacological effects of nicotine on the brain's "reward system" are also central to a smoker's liking of nicotine-delivering alternatives to cigarettes, and putatively an important determinant of a product's efficacy for smoking cessation purposes. Orally administered nicotine cannot produce the rapid, high peaks of nicotine in arterial blood to the brain that is typically associated with smoking. Even so, nicotine supplementation in the form of NRT is clearly associated with a modest increase of cessation rates among smokers motivated to quit. It has been hypothesized that the relatively low level of efficacy observed for NRTs in controlled clinical trials and in population studies is related to the nicotine delivery profile of currently available NRT products, which may insufficiently reduce craving and urges to smoke. In Scandinavia, snus is the most commonly reported quitting aid among males, and appears to be associated with a higher success rate than NRT or counseling among both males and females. These circumstances make it reasonable to study the nicotine pharmacokinetics and subjective effects of snus, particularly in relation to commonly used NRT products.

Swedish Match has sponsored three clinical trials (the SM WS 02, SM WS 06, and SM WS 12 studies) of the nicotine pharmacokinetics and subjective effects of different brands of Swedish snus (Lunell 2003; Lunell and Curvall 2011; Lunell and Lunell 2005) using nicotine gum (2 or 4 mg) or nicotine lozenges (6mg) as comparators. (All study documents, including raw data and relevant reports, are included in Appendices 2I, 2J, and 2K, respectively, to this Application.) The governance and conduct of the trials was the same as for clinical trials of pharmaceutical products or medical devices. The trials were conducted by an external contractor with extensive experience in nicotine pharmacokinetics. The main methodological strength of these studies was their use of randomized, cross-over designs, highly standardized administration of study products, and state-of-the-art methods for the chemical and pharmacokinetic analyses. Results of the first two studies have been published in international, peer-reviewed scientific journals, and publication of the third study is underway.

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[23] MRTP Guidance at 35.

These nicotine uptake trials used pouched snus products with different characteristics relevant to nicotine uptake (e.g., pouch size, nicotine content, pH, and moisture) and covered the range of products currently marketed by Swedish Match in Scandinavia. The SM WS 12 study also tested the simultaneous use of two pouches as this consumer behavior is not infrequent (Digard et al. 2009).

The products covered by this MRTP Application are substantially similar to the products tested in the nicotine uptake trials. Although the tested snus products are not identical to the Snus Products included in this Application, the tested products covered the range of relevant product characteristics (e.g., pouch size, humidity, pH, etc.) of all the Snus Products in the Application. In particular:

- General Classic Blend Portion Large (SKU 4877 and SKU 4878) is substantially similar to the Catch White Licorice 1.0 g products tested in the SM WS 02 study, the General White Product tested in SM WS 06 study, and the General PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

- General Dry Mint Portion Original Mini (SKU 4800) is substantially similar to the Catch Licorice Dry Mini product tested in the SM WS 02 study.

- General Mint Portion White Large (SKU 4352) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the General PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

- General Nordic Mint Portion White Large (SKU 4876 and SKU 4875) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the Genereal PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

- General Portion Original Large (SKU 4880) is substantially similar to the General Large product tested in SM WS 02 study.

- General Portion White Large (SKU 4881) is substantially similar to the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

- General Wintergreen Portion White Large (SKU 4882) is substantially similar to the General Large product and the Catch White Licorice product tested in SM WS 02 study, the General White 1.0 g product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

- Although the trials did not test any loose snus products, product form (i.e., pouch versus loose) has not been found to be a determinant of nicotine uptake from snus-like products

(Digard et al. 2012). Therefore, it is reasonable to conclude that General Loose (SKU 4852) is substantially similar in terms of nicotine uptake to the General Large 1.0 g and Catch White Licorice 1.0 g products tested in the SM WS 02 study, the General White Product tested in SM WS 06 study, and the PSWL 1.0 g product with a nicotine content of 0.8% tested in the SM WS 12 study.

Results from the three nicotine uptake trials illustrate that Swedish snus is generally associated with a somewhat faster absorption of nicotine than from pharmaceutical gum and lozenges, and a corresponding faster onset of subjective symptoms (e.g., head rush). In contrast, the estimated mean extracted amount of nicotine as well as AUC_{inf} was higher from a 4 mg gum compared to a 1.0 g snus pouch despite a lower C_{max}. There was high inter-individual variation in nicotine extraction and uptake from snus which was not linear with pouch size, suggesting that surface area, saliva penetration, and diffusion factors may be equally or even more important determinants of nicotine absorption from snus than pouch weight. Also, the more rapid nicotine delivery from snus compared to the selected NRT comparators may help to explain why many smokers have quit cigarettes completely by switching to snus, why snus is the most frequently reported cessation aid among male smokers in both Sweden and Norway, and why Scandinavian population surveys of the success rate with different quitting aids suggest that snus is superior to NRT.

These trials provide a basis for considerations related to the abuse liability of Swedish snus products. Results show that the nicotine pharmacokinetics and pharmacodynamics of snus (and, relatedly, the Snus Products) are comparable to some commercially available NRT products, although time to C_{max} was consistently shorter with snus. This suggests that the abuse liability of snus is somewhat higher than with NRTs, but clearly significantly lower than for cigarettes. Such a finding comports with a clinical trial by (Fagerstrom et al. 2010) which showed a much higher tobacco cessation rate (33.5%) among placebo-allocated snus users included in a randomized trial of varenicline, than is typically seen in tobacco cessation trials among placebo-allocated cigarette smokers. Relatedly, the expression "continuum of dependence" was coined in a paper by Fagerström and Eissenberg (2012) in which they suggested that abuse potential was lowest among NRT users, intermediate among STP users, and highest among smokers.

2.5.2.3.5. Biomarkers

Biomarkers, interpreted carefully and in the context of additional data from clinical and/or epidemiological studies, may be used to assess the actual internal dose of a tobacco component to which a tobacco user might be exposed. While there are certain limitations to the available biomarkers, they can be used to supplement information from product analyses as they reflect total exposure, bypassing differences in routes of exposure and product use behavior. In addition, biomarker levels on a population basis may provide an indication of general trends in internal exposure to certain components of a well characterized product.

A panel of biomarkers to components in tobacco products has been recently proposed for the use in product regulations. Although many biomarkers are less relevant for non-combusted tobacco products such as snus, the panel does include the potentially relevant biomarkers of nicotine,

tobacco-specific nitrosamines ("TSNAs"), polycyclic aromatic hydrocarbons ("PAHs"), aldehydes, cadmium, and acrylamide. To date, published studies (Andersson et al. 1994; Andersson et al. 1995; Bolinder et al. 1997b; Bolinder 1997; Bolinder et al. 1997a; Bolinder and de Faire 1998; Eliasson et al. 1991; Eliasson et al. 1995; Ellingsen et al. 2009; Heling et al. 2008; Holm et al. 1992; Richter et al. 2009b, as cited in Nilsson 2011; Österdahl and Slorach 1988; Post et al. 2005; Wennberg et al. 2006) are available that have investigated the biomarkers of nicotine, TSNAs, cadmium, and selenium in regular users of traditional Swedish snus.

Commonly measured biomarkers of nicotine include cotinine in plasma or serum. However, their levels may be impacted by the route of exposure, as first pass metabolism of nicotine to cotinine via the oral route may result in higher blood concentrations of cotinine that do not necessarily reflect increased exposure to the parent compound, nicotine. This metabolic pathway does not occur following exposure to nicotine via the inhalation route. Thus, total nicotine equivalents in urine are considered to better represent the total nicotine dose absorbed. (Benowitz et al. 2009; Benowitz 2009; Ebbert et al. 2004; Hecht et al. 2010).

Information from nicotine pharmacokinetic parameters is relevant for nicotine delivery, total dose, and abuse liability assessments. The time to maximum plasma nicotine concentrations in snus users appears to be dependent on the usage time, but to a lesser extent on nicotine content or portion size. On the other hand, maximum nicotine concentration ("C_{max}") and areas under the curve ("AUC") appear mostly dependent on total nicotine content (per pouch or portion size). Whether the tested snus-like product was loose or pouched had no influence on these parameters. (Digard et al. 2012; Holm et al. 1992; Lunell and Curvall 2011; Lunell and Lunell 2005).

A number of studies in regular snus users (Andersson et al. 1994; Andersson et al. 1995; Bolinder et al. 1997b; Bolinder 1997; Bolinder et al. 1997a; Bolinder and de Faire 1998; Eliasson et al. 1991; Eliasson et al. 1995; Ellingsen et al. 2009; Holm et al. 1992; Post et al. 2005) show that mean or median cotinine levels in plasma or serum range from 137 to 399 ng/mL depending on the amount of snus consumed (average 11-32 g/day). In the saliva, average levels ranged from 80 to 343 ng/mL. Urinary biomarkers of nicotine measured in regular users of snus were as follows: for nicotine itself, 29 µg/mmol creatinine; for cotinine, approximately 1000–1210 µg/L; for total cotinine, 5926 µg/L; and for nicotine equivalents, 14.3-35.6 mg/24 hrs.

In addition, TSNAs and their metabolites have been measured in various human bodily fluids, including saliva, blood, and urine, as well as in toenails. Urinary NNAL is the most commonly-measured biomarker of TSNA exposure, and is considered to reflect 12-17% of the NNK dose. Four studies of TSNA biomarkers in users of Swedish snus have been identified. Of those, one publication (Österdahl and Slorach 1988) measured TSNA levels in saliva during snus use. Snus in the 1980s contained higher TSNA concentrations than contemporary snus products. More recently, urinary total NNAL was measured in users of conventional US STPs that were switched to Swedish snus. Of the two clinical studies available (Gray et al. 2008; Hatsukami et al. 2004), only one (Hatsukami et al. 2004) appears to have been of sufficient duration to examine for and detect differences in levels before and after the switch. In this study, total NNAL levels decreased significantly (to half the concentration measured at baseline) by week 4.

Importantly, urinary total cotinine levels in this study did not change significantly, indicating the decreased toxicant exposure could not be explained by a decrease in tobacco intake and mean product use was similar to that reported for regular snus users. No studies measuring biomarkers of NNN in snus users were identified. POB-DNA adducts were significantly increased in oral mucosa of Swedish snus based on information provided in a study abstract (Heling et al. 2008; Richter et al. 2009b, as cited in Nilsson 2011); however, the importance of these adducts in oral cancer development has been questioned.

In the available studies of biomarkers of metals/metalloids, levels of both cadmium and selenium biomarkers in regular users of traditional Swedish snus were similar to those detected in non-tobacco users, indicating that exposure to these constituents from snus use does not result in a significant contribution over background intake from other sources. (Ellingsen et al. 2009; Wennberg et al. 2006).

2.5.2.3.6. Non-Clinical Toxicology Studies

Although epidemiologic evidence, supported by biomarker data, must weigh most heavily in CTP's assessment of a proposed MRTP, non-clinical studies can still play a role in justifying a modified-risk claim. Non-clinical studies with STPs (including Swedish snus) in laboratory animals were reviewed elsewhere (Grasso and Mann 1998). In these *in vivo* studies, test material was administered mixed in the diet, placed in hamster cheek pouches, or inserted into surgical lip canals in rats. No tumors were reported in any of these studies. A lifetime feeding study in rats, with STPs constituting 20% of the diet, was conducted by Homburger (Homburger et al., 1976). No cancer or other systemic effects were observed.

The studies of individual chemicals and STP extracts used include (Kim et al. 2002; Rivenson et al. 1988; Schwartz et al. 2010; Summerlin et al. 1992). In these studies, the test material was administered via hamster cheek pouches, surgical lip canals, swabbing of the oral cavity, and additions to the drinking water. No tumors resulted from treatment with STP extracts, unless the extracts used to swab the oral cavity were enriched by the addition of NNN and NNK. In these cases, small numbers (3) of oral papillomas were reported. Oral tumors were also observed in significant increases over controls with "neat" NNN and NNK, and with use of the positive control, 4-nitroquinoline oxide.

Swedish Match has sponsored *in vitro* toxicological testing of extracts of Swedish snus (Coggins et al. 2012), and all study documents are included in Appendix 2M to this Application. These tests included the *Salmonella* reverse mutation assay, mouse lymphoma assay, in vitro micronucleus assay, and tests of cytotoxicity. The results of these assays were broadly negative for Swedish snus. There were occasional positive responses, but these were effectively at the highest concentration only (i.e., concentrations well above those suggested by regulatory guidelines) and were often associated with significant cytotoxicity. These data contrast with data reported for combusted tobacco in the form of cigarettes where strongly positive responses have been routinely reported for mutagenicity and cytotoxicity.

Based on these studies, Swedish snus has minimal activity in state-of-the-art *in vitro* and *in vivo*

toxicology assays. Importantly, these results concur with those from repeated epidemiological studies on Swedish snus use in Sweden and elsewhere, lending further support for the harm reduction potential of the Snus Products which are the subject of this Application, compared to combusted tobacco, most notably cigarettes.

2.5.2.3.7. Premarket Consumer Perception Research

In support of this Application, Swedish Match conducted a Premarket Consumer Perception Research Study ("the Consumer Perception Study") to assess the effect and comprehension of the company's proposed MRTP labels[24] on the public in accordance with Sections 911(g)(1)(B), 911(g)(4)(B) and (C), and 911(h)(1) of the Act.

The Consumer Perception Study is a quantitative randomized, controlled study of 13,200 subjects comprised of 6,600 smokers and 6,600 non-tobacco users. Study subjects ranged in age from 18 to 64 years, with gender, age, income, ethnicity and geographic subgroups within each group. The study was conducted by InsightExpress, a full service research provider specializing in online data acquisition, using an online questionnaire.

Study subjects were split into six cells, each with a smoker and a non-tobacco user arm of 1,100 subjects each. Four control cells (comprised of four 1,100 subject smoker arms and four 1,100 subject non-tobacco user arms) were shown color images of a General Snus product container bearing one of the four warnings currently required for smokeless tobacco products pursuant to Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act. Two test cells (comprised of two 1,100 subject smoker and two 1,100 subject non-user arm) tested the proposed modified risk warning statements for the Snus Products which are the subject of this Application. One of the test cells tested the statement "Warning: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes." The other tested the statement "Warning: No tobacco product is safe but this product presents lower risk to health than cigarettes."

In preparing the research protocol and conducting the study, Swedish Match benefitted greatly from input and recommendations from both FDA and the MRTP Advisory Panel. Swedish Match participated in a series of pre-submission meetings with CTP to discuss and refine the study research concept and protocol. Each meeting provided Swedish Match with a clearer understanding as to how the research should be conducted to ensure the protection of the participants surveyed and enhance the usefulness of the data to the MRTP process. The MRTP Advisory Panel also provided comprehensive reviews of the study protocol, were kept apprised of the discussions with CTP, and reviewed the final version of the protocol.

Pursuant to discussions with CTP, Swedish Match sought the involvement of an IRB to ensure

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[24] Swedish Match proposes only to modify the mandatory warnings featured on the *labels* pursuant to the MRTP order granted; it does not intend to change the *advertising* for the Snus Products.

the protection of human subjects in the study. Accordingly, Swedish Match contracted with (b) (4) a leading provider of independent IRB services for major pharmaceutical companies, universities, individual researchers, academic medical centers, and community hospitals since 1993. (b) (4) was instrumental in reviewing various aspects of the study protocol and helping ensure that the study was conducted in a manner which provided proper protections for the rights and welfare of the research subjects who participated.

The results from the Consumer Perception Study address four of the five key areas of investigation required to support an MRTP order, namely: the effect on tobacco use behaviors among current users; the effect on tobacco use initiation among non-users; the effect of marketing on consumer understanding and perceptions; and the effect on the population as a whole. The results of this research are specific to the Snus Products which are the subject of this Application, and further supplement the extensive preclinical, toxicology and epidemiology data related to the effects and use of Swedish snus as compared to traditional cigarettes. Study results are discussed extensively in Section 6.4 of this Application and are summarized below:

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Behavior Among Current Tobacco Users:* The modified risk claims resulted in a modest increase in the likelihood that current tobacco users would use or purchase snus, and a minimal increase in the likelihood that they would engage in dual use of both cigarettes and snus. The modified risk claims also increased the likelihood that imminent quitters and reducers would be more likely to use, more motivate to buy, and less likely to be discouraged from using snus. A quarter (25%) of the imminent quitters who were likely to use snus reported that they were likely to be dual users of snus and cigarettes, and most of those reported that they would use snus to reduce or quit cigarettes.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Initiation Behavior Among Non- users:* The modified risk claims were no more likely than the current claims to encourage non-users of tobacco to use or buy snus. Although the current claims were more likely than the proposed modified risk claims to deter snus use among non-users of tobacco, more of those exposed to the modified risk claims reported that the claims were not likely to impact their decision to buy snus. None of the claims were likely to influence former tobacco users to use or motivate them to purchase snus. As with the other non-users of tobacco, the modified risk claims were less likely to deter former users from using or purchasing snus, however significantly more reported that the claims would not impact their decision.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Consumer Understanding and Perceptions of the Product:* While most of the total respondents, current users and current non-users of tobacco found the modified risk claims to be understandable and clear, these results were significantly lower than those reported for the current warnings. This may be due to the greater concreteness of the current claims and

consumers' greater familiarity with the currently mandated warning labels. Fewer than half of the total respondents, current users and current non-users considered the modified risk claims to be believable, while those rating the current claims as believable exceeded 60%. Following exposure to the modified risk claims total respondents, tobacco users and non-users of tobacco were more likely to rate snus as posing a moderate risk and less likely to report that it was harmful or extremely harmful than they were prior to exposure to any of the claims. This contrasted with those exposed to the current claims, more of whom reported that snus was harmful or very harmful and fewer of whom reported that snus posed a moderate risk. A similar pattern was demonstrated in the results of the comparisons of snus to cigarettes. Significantly more of those exposed to the modified risk claim rated snus as somewhat less harmful than cigarettes compared to those exposed to the current claims significantly more of whom reported that cigarettes and snus are equally harmful. These data suggest that the modified risk claims were successful in educating consumers about the actual and comparative risks of snus and cigarettes. The results are more consistent with the message conveyed regarding the actual risk as reflected in the clinical and epidemiology studies described in this Application.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Minorities:* The results for minority users and non-users of tobacco are similar to those for the total user and non-user populations and do not appear to raise unique issues or concerns for the minority populations. Most of the minority users and non-users found the modified risk claims to be understandable and clear. As with the total population and smokers and non-smokers generally, these results were significantly lower than what was reported for the current claims. Following exposure to the claims the risk perception patterns for minority respondents followed a pattern similar to that reported for total respondents, users and non-users. Again, those exposed to the modified risk claims more likely to report that snus posed a moderate risk and less likely to report that it posed an extremely harmful risk than those exposed to the current claims. The results further suggest that that modified risk claims are unlikely to motivate minority non-users to use or buy snus.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Low Income:* The perception of clarity, understanding and credibility reported by low income users and non-users of tobacco are similar to what was reported by the total user and non-user populations. Following exposure to the claims the risk perception patterns for low income respondents followed a pattern similar to, but less dramatic than, that reported for total respondents, users and non-users, with those exposed to the modified risk claims more likely to regard snus as a moderate risk and somewhat less harmful than cigarettes. The modified risk claims were also unlikely to cause or motivate low income non-users of tobacco to use or by snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for the low income population.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups-Youth:* The Consumer Perception Study did not raise concerns that

the modified risk claims would have an adverse effect on youth ages 18 to 24 years. In general, this population found the claims to be clear and understandable. Their perception of the risk following exposure to the claims was similar to, but not as dramatic as, that reported by the total, user and non-user populations. Youth exposed to the modified risk claims were more likely to report that snus posed a moderate risk and a somewhat lower risk than cigarettes. The modified risk claims were also unlikely to cause or motivate non-users ages 18 to 24 to use or buy snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for youth ages 18 to 24.

- *The Effect of Marketing Swedish Snus with a Modified Warning Label on the Population as a Whole:* The Consumer Perception Study assessed the effects of the modified risk warnings on the total population, including total users of tobacco products, total non-users of tobacco products, and minority, low income and youth users and non-users of tobacco. It also assessed tobacco users who reported being imminent quitters or reducers; dual users of snus and other tobacco products and current non-users who reported being former users of tobacco. The study did not reveal an adverse impact of the modified risk warnings on the population as a whole or on any of the aforementioned subpopulations.

The overall results of the Consumer Perception Study demonstrate that the proposed warning labels for the Snus Products are unlikely to produce unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study results demonstrate subjects' comprehension and understanding of the proposed warning labels and support the conclusion that the modified risk claims are not misleading, but rather promote a better understanding of the actual health risks of snus as compared to cigarettes. While the proposed modified warning labels changed consumers' perception of the harmfulness of snus, additional measures are needed to more substantially alter consumer risk perception in order to make it more consistent with the scientific evidence.

In sum, the Consumer Perception Study provides several key insights related to intended use of the Snus Products by current users and non-users of tobacco products, and the results of this research supplement the extensive preclinical, toxicology and epidemiology data presented in this Application regarding the effects and use of snus as compared to cigarettes. Survey results significantly contributed to the decision to include the term "substantially" in the proposed label change, that is "No tobacco product is safe, but this product presents *substantially* lower risks to health than cigarettes." The survey results were consistent with the scientific literature on relative risk perception of snus (Lund 2012) and the term "substantially" is supported by the voluminous product-specific scientific evidence from Sweden.

2.5.2.3.8. Dynamic Population Model ("DPM")

Because of the difficulties inherent in making premarket assessments of the effect of an MRTP's introduction on the population as a whole and the public health, FDA encourages the development and application of innovative analytical methods which estimate the potential health effects expected to result from changes in the distribution and use of different tobacco

products in a given population.[25]

Accordingly, Swedish Match has supported the development and application of a DPM designed to estimate changes in all-cause mortality due to modified risk tobacco products. The DPM estimates all-cause mortality for a hypothetical population of persons who have never used tobacco and who, as they age, may transition into and out of different tobacco exposure states, including current and former smoking or MRTP use. The DPM is discussed more fully in Section 6.5 of this Application.

The DPM compares the number of survivors in a base case comprised of current, former and never smokers followed as they age with the number of survivors in a counterfactual exposure scenario that includes current, former and never users of the MRTP as well as current and former users of cigarettes. The analyses specifically evaluate effects due to use of the MRTP by those who, in the absence of the MRTP, would have remained tobacco-free (i.e., non-smokers) and those who would have quit smoking. The DPM can also estimate the effects of the MRTP being more attractive than cigarettes to youth who are at risk of becoming tobacco users, the potential effects if the MRTP serves as a gateway to smoking, and/or increases the likelihood of former users (i.e., those who quit all tobacco and those who switched from cigarettes to MRTP) relapsing back to smoking cigarettes.

Analyses using the DPM indicate that the introduction of Swedish snus, the proposed MRTP, can result in a net population-level benefit, particularly if the product is adopted by a sufficient number of smokers. If introduction of Swedish snus results in more tobacco users compared to the base case, however, a survival deficit may result. However, the latter scenario appears unlikely in this case, given the results of the premarket consumer perception research on the proposed label changes included in this Application.

The size of an effect on overall morbidity, positive or negative, depends on the particular exposure patterns evaluated. For example, tipping point analyses indicate that if some who would have quit smoking in the base case switch to Swedish snus instead, a survival deficit results. This effect is counteracted, however, if a fairly small proportion, 1% or less, of those in the base case who would have continued to smoke instead switch to Swedish snus and don't revert to smoking. Tipping point analyses also indicate a survival deficit results if base case never tobacco users initiate Swedish snus, but this can be counterbalanced by base case smoking initiators initiating Swedish snus instead of cigarettes. If only 1% of base case never tobacco users initiate Swedish snus, less than 5% of base case smoking initiators must initiate Swedish snus to counteract the survival deficit. However, if 5% of base case never tobacco users initiate Swedish snus, at least 20% of base case smoking initiators instead must initiate Swedish snus to counterbalance the survival deficit. These apparently large percent changes must be interpreted in light of the sizes of the exposure groups involved. Because the never tobacco users represent a large subgroup of the whole population, a small percent change affects a large number of individuals. Likewise, there are relatively few individuals who successfully quit smoking in the

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[25] MRTP Guidance at 27.

base case, so a large percentage of that population subgroup must shift to a different exposure for a population-level effect on survival to be observed. In modeling gateway effects, such that base case never tobacco users initiated tobacco use with the MRTP and then switched to smoking cigarettes, there was no statistically significant survival benefit in counterfactual scenarios consisting of base case smoking initiators choosing the MRTP instead of cigarettes. However, other exposure patterns that include additional exposure groups can counterbalance this population-level harm.

This conclusion is corroborated by analyses of counterfactuals based on the Swedish tobacco use patterns estimated for the 1990s compared with a base case defined by US smoking initiation rates from 2008 and cessation rates from 2005-2008. In each of the counterfactual exposure scenarios investigated, in which snus was used with similar frequency and in which snus was 10%, 25% and 50% as popular in the US as in Sweden, there was a substantial and statistically significant survival benefit compared with the US base case. The magnitude of the difference in the number of survivors vs. the base case was not greatly affected by the value selected for the ERR comparing the MRTP to cigarette smoking (0.11 or 0.055), by increasing the gateway effect or by reducing the MRTP initiation rate among those who would have otherwise remained as never tobacco users and those who would have initiated tobacco use with cigarettes. When the rate of switching to the MRTP by those who would have continued to smoke and those who would have quit smoking in the base case was reduced compared to the rates estimated for the "Swedish counterfactual", there was still a statistically significant increase in the number of survivors in the counterfactual vs. the base case, but the effect was smaller. The greater responsiveness of the results to changes that affected continuing smokers or those who would have quit smoking is a reflection of the relative sizes of the various population subgroups included in the analyses.

2.5.2.3.9. Governance and Oversight

As noted above, Swedish Match has sponsored a number of studies submitted in support of this MRTP Application. Studies funded by any regulated party are subject to extra scrutiny, but the surveillance that must be applied to research funded by the tobacco industry may be unparalleled. This was one of the findings contained in the IOM Report (IOM 2012) regarding the scientific standards for studies on MRTPs. Chapter 2 of the report details the challenging history of tobacco research and proposes the establishment of an independent third party to oversee such research.

Swedish Match understands why research funded by tobacco companies is subject to greater scrutiny, and the Company conceptually supports the findings and recommendations set forth in the IOM Report. Swedish Match is therefore committed to working toward a long-term solution to tobacco research governance which is characterized by a coordinated effort among FDA, industry, researchers and other stakeholders. In the meantime, Swedish Match is determined to take action on its own, in keeping with the Company's longstanding history of ensuring that its research is conducted in a credible manner. For example, Swedish Match's GOTHIATEK® product standard provides a foundation for a range of product stewardship-related commitments,

including generating and communicating scientific evidence. The GOTHIATEK® standard was developed in concert with scientists from the Swedish Food Agency (which regulates snus), and it reflects Swedish Match's historic and ongoing commitment to working with authorities to ensure credibility and transparency.

Swedish Match applied the principles of GOTHIATEK® and other internationally accepted guidelines when developing the protocols and conducting the clinical trials described in this Application. The protocols were developed in collaboration with individual research teams according to accepted guidelines and the studies were performed in accordance with local and national laws, ICH guidelines, and the guidelines of the Declaration of Helsinki. Further, the studies were approved by an appropriately constituted IRB[26] or IEC, and all trials were conducted according to ICH-GCP.

Management of all clinical and other study-related information, including monitoring, was conducted by CROs with extensive experience of controlled clinical trials of pharmaceutical products (e.g., i3 Research, Covance, and CROel AB). All data handling and statistical analyses were conducted by external contractors according to pre-specified statistical analysis plans, and there was prospective registration in public databases such as www.clinicaltrials.gov. From the outset, Swedish Match was committed to publishing the results of the clinical trials irrespective of study outcomes, and five (5) peer-reviewed articles based on these studies have been published to date.

In addition to the foregoing, perhaps the most significant action taken by Swedish Match to address concerns relating to tobacco research governance is the establishment of the MRTP Advisory Panel. The Company initiated the advisory panel process by soliciting advice from leaders in the research, tobacco control, and public health communities. In early 2013, Swedish Match approached two well-respected leaders in the field of tobacco research: Dr. Karl Fagerström, the President of Fagerström Consulting, and Dr. John Hughes, Professor of Psychology and Psychiatry at the University of Vermont. The two agreed to serve as founding members of an external advisory body on the condition that they would develop their own mission statement and operating principles which would be used to recruit prospective members and to "test the waters" with their colleagues in the research and tobacco control communities.

The Panel ultimately adopted the following mission statement and operating principles:

- *Mission Statement:* To present advice on matters relating to the FDA Modified Risk

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[26] Swedish Match retained the services of an IRB whenever appropriate. For example, the study protocol for the premarket consumer perception study was subject to oversight by (b) (4), and it was determined that informed consent was not required because the study did not involve the use of test articles (i.e., regulated tobacco products) and, hence, did not constitute a "clinical investigation" for purposes of FDA's Good Clinical Practice regulations.

Tobacco Product application and review process and to serve as a model for the interaction between FDA, the scientific community, and tobacco companies. The Advisory Panel's deliberations will be guided by public health interests and will advance tobacco regulatory science

- *Operating Principles:*

    - The Advisory Panel is an independent body that develops its own mission statement and operating procedures. Members do not have a contractual arrangement with Swedish Match and do not sign confidentiality agreements.
    - The Advisory Panel does not offer a consensus position; rather the members express their individual views.

    - Swedish Match staff provides administrative services to the Advisory Panel; including offering background information, arranging for calls and meetings, and providing meeting follow-up. Swedish Match staff and the Panel members work closely together in preparing meeting agendas and identifying work tasks with the Advisory Panel having the final decision.

    - Advisory Panel members are informed of Swedish Match operations in the US and globally and are encouraged to ask questions regarding policies and performance.

    - The Advisory Panel will serve as a model for how a tobacco company can interact with an external science-based group. Accordingly, it is essential that the operations of the Advisory Panel are as transparent as feasible and members continually seek opportunities to communicate its goals and operations. The Advisory Panel has an interest in informing the tobacco enterprise and the broader scientific and public health communities of its actions and principles.

    - The Advisory Panel is a new and evolving body. The members are committed to the mission statement and operating principles but the approach used to accomplish the mission will continually evolve.

In order to ensure that a wide range of perspectives was represented, it was decided the Advisory Panel would not be limited to tobacco experts only, but rather would consist of scientists and science policy experts with extensive backgrounds in toxicology, risk perception and communication, FDA regulations, and research governance. The MRTP Advisory Panel currently consists of five members,[27] all of whom have had long and accomplished careers in

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[27] In addition to Drs. Fagerström and Hughes, the Panel includes: Dr. Nancy Ostrove, a Principal of EXPRE; Dr. Mark Frankel, the Director of Scientific Responsibility at the Human Rights and Law Program at the American Association for the Advancement of Science (AAAS); and Dr. Daniel Casciano, the Science Advisor at the Center for Integrative Nanotechnology Sciences at the University of Arkansas at Little Rock.

their scientific fields and are seeking to apply their experiences and insights to improve the exchange of information and concepts in the area of tobacco regulatory science. The Panel's most immediate task was to provide advice regarding Swedish Match's MRTP Application; however, the Panel will continue to operate long after the Application is submitted and tobacco research governance will always remain a priority for Swedish Match.

The MRTP Adivisory Panel met via an inaugural conference call on March 1, 2013, and the first face-to-face meeting followed two weeks later. During that period, the Panel finalized its mission statement and operating principles and discussed how best to communicate its work to the tobacco community. The Panel met again for two-day sessions on June 24-25, 2013 and in Washington, DC, on November 13-14, 2013. CTP was notified in advance of the DC meeting and meeting minutes were provided.

Although the MRTP Advisory Panel is not the third-party research governance entity envisioned in the IOM Report, the Panel nevertheless provides important research governance-related services and is representative of the kind of progressive initiative that is needed to reach the Report's stated goals. In particular, the Panel is able to address some of the questions that CTP raised in establishing a public docket[28] and hosting a public workshop[29] on third-party governance of industry-sponsored research on MRTPs. One such question from CTP concerns the aspects of tobacco product research which may properly be subject to third-party governance. The MRTP Advisory Panel now has firsthand experience with this issue. For example, during its initial face-to-face meeting, the Panel reviewed Swedish Match's draft protocol for the premarket consumer perception research. Subsequent to the meeting, panel members provided additional comments on the protocol through a series of email exchanges. Throughout the process, the Panel did not seek a consensus view, but rather endeavored to be as transparent as possible and ensure that each member shared his or her comments with the entire group.

Swedish Match's science, policy, and marketing staff presented the MRTP Advisory Panel's input during a May 8, 2013 meeting with CTP that was focused solely on the premarket consumer perception study protocol. CTP expressed interest in the Panel's input and suggested that the Company have the Panel conduct a final review of the protocol, which was done during

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28 FDA published notice of the docket in the Federal Register (78 Fed. Reg. 19713 (Apr. 2, 2013)) and requested data, information, and comments regarding the possible role of independent third parties in industry-sponsored tobacco product research in response to the IOM's recommendations regarding third-party governance. Drs. Fagerström and Hughes submitted comments to the docket on August 14, 2013, explaining why they agreed to serve on the MRTP Advisory Panel and the Panel's relevance to governance concerns. Their submitted comments are included in Appendix 2N of the Application.

29 FDA held a Public Workshop titled "Third Party Governance of Industry-Sponosred Tobacco Product Research on March 19-20, 2013. The purpose of the workshop was to discuss the recommendation in the IOM Report that sponsors of MRTP applications use independent third parties to undertake one or more key functions in tobacco product research. *See* http://www.fda.gov/TobaccoProducts/NewsEvents/ucm336166.htm.

the June 2013 meeting. Additional input was provided during and following the meeting, and the Panel also provided a final review of the protocol before the research commenced.

The MRTP Advisory Panel has reviewed and commented upon several key components of this MRTP Application, but was not asked to approve the Application. For example, prior to its November 2013 meeting, the Panel received an early draft of Section 2.5 (Summary) and Section 6 (Summary of All Research Findings), and was provided access to the entire Application. The Application was discussed during the two-day meeting and additional comments were received following the meeting. In February 2014, the Panel received the premarket consumer perception data and various drafts of Section 6.4 (Effect of Marketing on Consumer Understanding and Perceptions). The Panel's comments on these materials were incorporated into the final text as appropriate.

2.5.2.4. Concluding Discussion of How MRTPA Meets Relevant Statutory Requirements

The Tobacco Control Act was enacted to establish a regulatory framework to address the public health and societal problems attributable to tobacco, and to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products.[30] The prospect of a less hazardous tobacco product is "not in and of itself problematic" but rather the "fundamental issue is that if a product is going to be marketed as being 'safer', then the claim must be true." (IOM 2012)

Swedish Match submits that Swedish snus, as manufactured by Swedish Match, is significantly less harmful than cigarettes, and that Congress has provided a mechanism under the Tobacco Control Act to inform adult consumers of snus's harm reduction potential. Accordingly, this MRTP Application provides a comprehensive analysis of all the relevant scientific evidence relating to the health effects of Swedish snus and the public health impact of the product for users and non-users at both the individual and population levels. In particular, this Application presents data from numerous observational epidemiologic studies showing that Swedish snus significantly reduces harm and the risk of tobacco-related disease to individual tobacco users—particularly with respect to mouth cancer, gum disease, tooth loss, CVD, and other health outcomes. The Application also summarizes data from a well-run clinical trial demonstrating that *ad lib* provision of Swedish snus to smokers who are interested in quitting (as the majority of smokers in the United States say they are[31]) will result in an increased rate of smoking cessation. Results from a Premarket Consumer Perception Study confirm that current non-users of tobacco products will not be more interested in using the Snus Products simply because of the proposed warning label changes which are the subject of this Application. Finally, dynamic population modeling of reasonable and probable scenarios associated with the of the introduction

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30 Tobacco Control Act, § 3(4).

31 CDC Fact Sheet, Smoking & Tobacco Use: Quitting Smoking, Feb. 2014, available at http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm#quitting (last accessed March 4, 2014).

of a new low-nitrosamine MRTP (such as the Snus Products) in the US market evidence a net benefit to public health in every case, including where the proportion of smokers who switched to the MRTP was assumed to be quite low. These data support the conclusion that the Snus Products 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.

This Application meets all the statutory requirements for an MRTP application as set forth in Section 911(d) of the Act. In particular, the Application contains:

(i) a description of the proposed Snus Products (Section 3.1) and any proposed advertising and labeling (Section 4.1);

(ii) the conditions for using the Snus Products (Section 3.3);

(iii) the formulation of the Snus Products (Section 3.2);

(iv) sample product labels and labeling (Section 4.2);

(v) all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by Swedish Match relating to the effect of the Snus Products on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the Snus Products to reduce risk or exposure and relating to human health (Section 7); and

(vi) data and information on how consumers actually use the Snus Products (Section 3.4).

Swedish Match has organized and synthesized all the foregoing information—along with the additional information which FDA has suggested be submitted—in accordance with the recommendations found in FDA's MRTP Guidance.

Swedish Match is confident that this submission provides FDA with conclusive evidence to show that Swedish snus as manufactured by Swedish Match—and hence, the Snus Products which are the subject of this Application—"significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and also "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." Therefore, the Company respectfully requests that the Agency grant the requested MRTP orders for the Snus Products pursuant to Section 911(g) of the Act.

2.5.3. References

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3. DESCRIPTIVE INFORMATION

The ten (10) Snus Products which are the subject of this Application are a form of Swedish snus, a world-unique oral smokeless tobacco product which originated in the Nordic region of Europe nearly 200 years ago.

This section of the Application provides descriptive information regarding the Snus Products, including their features and designs, ingredients, manufacturing processes, quality control measures, and conditions for use, and it includes information regarding how consumers actually use the products.

3.1 Description of Proposed Products

3.1.1. The brand names and, if applicable, subbrand names of the proposed modified risk tobacco products

The brand and subbrand names of the tobacco products which are the subjects of this Application are as follows:

1. General Loose (SKU 4852);
2. General Dry Mint Portion Original Mini (SKU 4800);
3. General Portion Original Large (SKU 4880);
4. General Classic Blend Portion White Large – 15 ct (SKU 4877);
5. General Classic Blend Portion White Large – 12 ct (SKU 4878);
6. General Mint Portion White Large (SKU 4352);
7. General Nordic Mint Portion White Large – 15 ct (SKU 4876);
8. General Nordic Mint Portion White Large – 12 ct (SKU 4875);
9. General Portion White Large (SKU 4881); and
10. General Wintergreen Portion White Large (SKU 4882)

(collectively, the "Snus Products" or the "Products").

3.1.2. Description of the product form

According to ESTOC, "snus" is defined as a smokeless tobacco product for oral use which is

traditionally produced and used in Sweden and manufactured using a heat treatment process.[32] This definition distinguishes Swedish snus from all other types of smokeless tobacco, including some products recently introduced as "snus" in the United States market which have distinctly different characteristics.

Swedish snus is made from selected, mainly air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. Put another way, Swedish snus consists only of finely ground tobacco mixed with water, additives (e.g., cooking salt, sodium bicarbonate, etc.) and flavors (e.g., licorice, mint). In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in premises that are hygienically suitable for food production.[33]

The Snus Products are moist (50-60% moisture) to semi-moist (30-45% moisture) oral smokeless products which are typically placed between the upper lip and the gum and do not require expectoration during use. By contrast, American moist snuff products are typically placed under the lower lip and require expectoration during use.

For more detailed descriptive information about the Snus Products generally, please see the *Swedish Snus According to GOTHIATEK®* report (SM GOTHIATEK Report 2013, attached as Appendix 3A).

3.1.3. Description of the product dimensions and the overall construction of the products

The Snus Products are currently marketed in the United States in two (2) packaging formats, namely loose snus and portion snus.

- ***Loose snus:*** Loose snus is the traditional variant of Swedish snus that is formed to a pinch at usage.

- ***Portion snus:*** Portion snus consists of pre-packed pouches wrapped in a non-woven fabric which allows for discrete and hygienic usage. The pouches are available in different sizes and weights (e.g., from 0.3g to 1.0g). Swedish Match produces two (2) types of pouch products (i.e., original and white) which differ in regard to packaging processes.

    - ***Portion Original:*** Portion original products are brown in color, (b) (4)

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32 European Smokeless Tobacco Council, http://www.estoc.org/about-smokeless-tobacco.

33 In Sweden, snus is regulated by the National Food Agency´s regulation on "snus och tuggtobak; LIVSFS 2013:7" (Regulations amending the Food Administration regulations (LIVSFS 2012:6) of snuff and chewing tobacco), and is equated with food in the Food Act (SFS 2006:804).

- ***Portion White:*** Portion white products are white in color.

The Snus Products are packaged and sold in round or square cans. The dimensions of the cans are reported in millimeters below (i.e., as diameter x height for round cans and as width x length x height for square cans). Where applicable, the dimensions of the portion snus pouches are also reported as width x length x height in millimeters.

3.1.3.1. Loose snus product

This MRTP Application covers one (1) loose snus product. The product is packed in paraffin-coated (b) (4) cans with plastic lids.

LOOSE SNUS PRODUCT						
Brand	**SKU**	**FDA Submission Tracking Number (STN)**	**Weight Per Can**	**Can Material**	**Can Dimensions**	**Can Content**
General Loose	4852	SE0000140	45.0 g	Cardboard	70.5 x 23 mm	45 g

3.1.3.2. Portion snus products

This Application covers nine (9) portion snus products. The products are packed in either round or square plastic cans with plastic lids.

Portion products are produced using a pouch material made of nonwoven fabric which is wrapped around the snus and sealed using heat and pressure. The pouch material has a thickness of 0.195 mm (+/- 0.02 mm) and a weight of 29.0 g/m^2 (+/- 2.9 g/m^2).

A tight can is a prerequisite for stability during shelf life, and can content varies from (b) (4) depending on pouch size and the number of pouches in the can.

PORTION SNUS PRODUCTS								
Portion Original								
Brand	**SKU**	**FDA Submission Tracking Number (STN)**	**Pouch Weight**	**Pouch Size**	**Pouches Per Can**	**Weight Per Can**	**Can Material**	**Can Dimensions**
General Dry Mint Portion Original Mini	4800	SE0000139	0.3 g	14 x 28 x 5 mm	20	6.0 g	Plastic	66 x 19 mm
General Portion Original Large	4880	SE0000143	1.0 g	18 x 33 x 6 mm	24	24.0 g	Plastic	70 x 24 mm
Portion White								
Brand	**SKU**	**FDA Submission Tracking Number (STN)**	**Pouch Weight**	**Pouch Size**	**Pouches Per Can**	**Weight Per Can**	**Can Material**	**Can Dimensions**
General Classic Blend Portion White Large – 15 ct	4877	SE0000138	0.9 g	14 x 34 x 5 mm	15	13.5 g	Plastic	56.6 x 86 x 18 mm
General Classic Blend Portion White Large - 12 ct	4878	SE0000138	0.9 g	14 x 34 x 5 mm	12	10.8 g	Plastic	56.6 x 86 x18 mm
General Mint Portion White Large	4352	SE0000141	1.0 g	18 x 34 x 5.5 mm	24	24.0 g	Plastic	70 x 24 mm

General Nordic Mint Portion White Large - 15 ct	4876	SE0000142	0.9 g	14 x 34 x 5 mm	15	13.5 g	Plastic	56.6 x 86 x18 mm
General Nordic Mint Portion White Large - 12 ct	4875	SE0000142	0.9 g	14 x 34 x 5 mm	12	10.0 g	Plastic	56.6 x 86 x18 mm
General Portion White Large	4881	SE0000144	1.0 g	18 x 34 x 5.5 mm	24	24.0 g	Plastic	70 x 24 mm
General Winter-green Portion White Large	4882	SE0000145	1.0 g	18 x 34 x 5.5 mm	24	24.0 g	Plastic	70 x 24 mm

3.1.3.3. Product Photographs

The following pictures clearly depict samples of the finished Snus Products and their components.

Figure 3-1. General Loose (SKU 4852)

Figure 3-2. General Dry Mint Portion Original Mini (SKU 4800)

Figure 3-3. General Portion Original Large (SKU 4880)

Figure 3-4. General Classic Blend Portion White Large – 15 ct (SKU4877)

The photograph of **General Classic Blend Portion White Large – 12 ct (SKU 4878)** has been omitted because although the product contains three fewer pouches, it does not otherwise materially differ from that of the 15-ct SKU shown above.

Figure 3-5. General Mint Portion White Large (SKU4352)

Figure 3-6. General Nordic Mint Portion White Large – 15 ct (SKU 4876)

The photograph of **General Nordic Mint Portion White Large – 12 ct (SKU 4875)** has been omitted because although the product contains three fewer pouches, it does not otherwise materially differ from that of the 15-ct SKU shown above.

Figure 3-7. General Portion White Large (SKU4881)

Figure 3-8. General Wintergreen Portion White Large (SKU4882)

3.1.4. Whether the products use a heating source and, if so, a description of the heat source

According to the MRTP Guidance, the term "heating source" refers to burning coal, electric, chemical reaction, carbon tip or other heating sources used in the consumption of the tobacco product. As a smokeless, *non-combustible* tobacco product, Swedish snus does not have a heating source. Therefore, this product characteristic is irrelevant for purposes of all the Snus Products which are the subject of this Application.

3.1.5. Description of all design features of the products (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient)

Swedish Match's Snus Products do not include design features such as ventilation holes, heat source, or paper.

From a consumer perspective, it is important that the pouch material (which is used in the portion snus products) is soft and has texture properties which facilitate the release of nicotine and flavor compounds.

The percent nicotine in each Snus Product is shown in the table below.

Table 3-1. Percent Nicotine

BRAND	SKU	SUBMISSION TRACKING NUMBER (STN)	NICOTINE CONCENTRATION
LOOSE SNUS PRODUCT			
General Loose	SKU 4852	STN SE0000140	0.75% nicotine
PORTION SNUS PRODUCTS			
PORTION ORIGINAL			
General Dry Mint Portion Original Mini	SKU 4800	STN SE0000139	1.5% nicotine
General Portion Original Large	SKU 4880	STN SE0000143	0.8% nicotine
PORTION WHITE			
General Classic Blend Portion White Large – 15 ct	SKU 4877	STN SE0000138	0.75% nicotine
General Classic Blend Portion White Large – 12 ct	SKU 4878	STN SE0000138	0.75% nicotine

General Mint Portion White Large	SKU 4352	STN SE0000141	0.8% nicotine
General Nordic Mint Portion White Large – 15 ct	SKU 4876	STN SE0000142	0.75% nicotine
General Nordic Mint Portion White Large – 12 ct	SKU 4875	STN SE0000142	0.75% nicotine
General Portion White Large	SKU 4881	STN SE0000144	0.8% nicotine
General Wintergreen Portion White Large	SKU 4882	STN SE0000145	0.8% nicotine

There is significant inter- and intra-individual variation in nicotine extraction and uptake, but on average 10-20% of the nicotine in snus is absorbed after 30 minutes of use (Lunell and Lunell 2005).

Other product characteristics, including moisture and pH value, are shown in **Table 3-2** below.

Table 3-2. Additional Product Characteristics

Products	SKU	FDA SE Application No.	Tobacco Recipe	Heat treatment process	Moisture (%)	pHvalue
LOOSE SNUS PRODUCT						
General Loose	4852	SE0000140	(b) (4)	(b) (4)	58.0	8.4

Products	SKU	FDA SE Application No.	Tobacco Recipe	Heat treatment process	Moisture (%)	pH value
PORTION SNUS PRODUCTS						
PORTION ORIGINAL						
General Dry Mint Portion Original Mini	4800	SE0000139	(b) (4) (b) (4)	(b) (4)	51.0	7.5

Products	SKU	FDA SE Application No.	Tobacco Recipe	Heat treatment process	Moisture (%)	pH value
General Portion Original Large	4880	SE0000143	(b)	(b) (4)	53.5	8.7
PORTION WHITE						
General Classic Blend Portion White Large - 15 ct	4877	SE0000138	(b)	(b) (4)	53.5	8.7
General Classic Blend Portion White Large - 12 ct	4878	SE0000138	(b)	(b) (4)	53.5	8.7
General Mint Portion White Large	4352	SE0000141	(b)	(b) (4)	53.6	8.7
General Nordic Mint Portion White Large - 15 ct	4876	SE0000142	(b)	(b) (4)	53.5	8.7
General Nordic Mint Portion White Large - 12 ct	4875	SE0000142	(b)	(b) (4)	53.5	8.7
General Portion White Large	4881	SE0000144	(b)	(b) (4)	53.5	8.7
General Wintergreen Portion White Large	4882	SE0000145	(b)	(b) (4)	53.5	8.7

3.1.6. Any other information relevant to describing the tobacco products, such as whether the tobacco products require special handling or storage

Refrigeration of the finished snus products (at 6-8 centigrade) is recommended as this prevents

or slows down loss of humidity, a drop in pH, and oxidation of nicotine (Rutqvist et al. 2011).

3.2 Description of Formulation of the Products

3.2.1. A complete list of uniquely identified components, ingredients, and additives by quantity in the tobacco products as well as the applicable specifications and a description of the intended function for each

Swedish Match defines ingredients as raw materials, additives, and flavors (i.e., essential oils, flavor compounds, or compounded flavors). A processing aid is not regarded as an ingredient since it is not intended to remain in the finished product.

Each ingredient in Swedish Match's Snus Products complies with applicable legislations and internal standards, such as GOTHIATEK® specification requirements for additives and policies such as *Swedish Match Negative List for Flavors*.

3.2.1.1. GOTHIATEK®

Although Swedish Match's current manufacturing methods for snus build upon those that were introduced more than a century ago, the high quality of modern Swedish snus is largely due to improvements in production techniques and selection of raw materials in combination with programs for quality assurance and quality control that were successively introduced by Swedish Match since the early 1970s. In 2001 these developments formed the basis for a codified, voluntary quality standard named GOTHIATEK® (Rutqvist et al. 2011).

Developed and owned by Swedish Match, GOTHIATEK® draws upon the best available knowledge regarding selection of raw materials and manufacturing practices. It encompasses a standardized manufacturing process that controls every aspect of the production chain, from seed to finished can. In particular, GOTHIATEK® sets the standard for:

- Swedish Match internal requirements for maximum permitted levels of undesirable substances found naturally in the tobacco plant;
- raw material quality requirements;
- manufacturing process requirements; and
- consumer product information requirements.

3.2.1.2. Raw Materials

All raw materials in Swedish Match's Snus Products (with the exception of tobacco, which is specifically addressed in Section 3.2.2 of this Application) fulfill Swedish Match's raw material specification requirements. These requirements are specific to each raw material and comprise detailed data about component characteristics, field of application, governing directives, purity, physical properties, microbiological assays, genetically modified organisms ("GMO") statements, allergen statements, statements of origin, and manufacturing practices. See Section 6 of the SM GOTHIATEK Report 2013 for more information about raw materials specifications

for the Snus Products.

Swedish Match also obtains information from suppliers to confirm that raw materials fulfill Swedish Match's requirements. If such information is unavailable or incomplete, Swedish Match performs chemical analyses to ensure that the raw materials conform to the internal specifications.

Table 3-3. Suppliers of Raw Materials Included in Product Recipes for the Snus Products Marketed by Swedish Match in the United States

Compound	Company	Supplier Address
(b) (4)	(b) (4)	(b) (4)

3.2.1.3. Additives

All additives in the Snus Products comply with Swedish Match's ingredient material specification requirements. These requirements are specific to each additive and comprise detailed data about component characteristics, field of application, governing directives, purity, physical properties, microbiological assays, GMO statements, allergen statements, statements of origin, and manufacturing practices when applicable.

Swedish Match obtains information from suppliers to determine whether additives fulfill Swedish Match's requirements. If such information is incomplete or unavailable, Swedish Match performs chemical analyses to ensure that the additive conforms to the internal specifications.

Table 3-4. Suppliers of Additives Included in Product Recipes for the Snus Products Marketed by Swedish Match in the United States

Compound	Company	Supplier Address
(b) (4)		

3.2.1.4. Flavors

Swedish Match has developed a procedure for assessment of ingredients, which includes a negative list for flavors. This list is sent to each flavor supplier with whom Swedish Match conducts business. The list is divided into sub-categories comprising different types of flavors which cannot be included in snus recipes in accordance with Swedish Match's internal ingredient policy. Swedish Match's Negative List for Flavors for 2010 consists of the following:

An ISO 9001 description for assessment of ingredients describes the procedure used by Swedish Match for the approval of flavors, additives and raw materials (other than tobacco) in snus. In order to manage information about ingredients, relevant legislation and acceptable use levels, Swedish Match has created an internal database: Swedish Match Ingredient Management System ("SIMS"). This database includes information about all flavors in Swedish Match products as well as product recipes. It is continuously updated with modifications of the flavor recipes, Swedish Match's Negative List for Flavors, product recipes, and country specific legislation relating to ingredients.

Swedish Match has signed confidentiality agreements with all of its flavor suppliers. These agreements stipulate that the supplier will provide Swedish Match with full disclosure of all flavor recipes.

Table 3-5. Suppliers of Flavors Included in Product Recipes for the Snus Products Marketed by Swedish Match in the United States

Compound	Company	Supplier Address
(b) (4)		

		(b) (4)
(b) (4)		

3.2.1.5. Processing Aids

According to current EU regulations on food additives, a "processing aid" shall mean any substance which: (i) is not consumed as a food by itself; (ii) is intentionally used in the processing of raw materials, foods or their ingredients, to fulfil a certain technological purpose during treatment or processing; and (iii) may result in the unintentional but technically unavoidable presence in the final product of residues of the substance or its derivatives provided they do not present any health risk and do not have any technological effect on the final product.[34] Processing aids, and other substances that are not consumed as food itself but used intentionally in the processing of foods, are not subject to the aforementioned regulation. Accordingly, Swedish Match does not classify processing aids as ingredients, but rather requires that the former comply with Swedish Match ingredient material specification requirements as described in Section 3.2.1.3. Raw Materials.

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[34] *See* REGULATION (EC) No 1333/2008 OF THE EUROPEAN PARLIAMENT AND THE COUNCIL, Official Journal of the European Union, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0016:0033:en:PDF.

Table 3-6. Suppliers of Processing Aids Included in Product Recipes for the Snus Products Marketed by Swedish Match in the United States

Compound	Company	Supplier Address
(b) (4)		

3.2.1.6. List of Ingredients

3.2.1.6.1. Basic Formulation

The basic formulation for all the Snus Products consists of ground tobacco, salt and water. Additives are added during production to ensure shelf-life, taste, and, quality.

Table 3-7. Ingredients Used in the Snus Products Marketed by Swedish Match in the United States

Ingredient Name	Ingredient Type	Ingredient Function	Reason for Usage
(b) (4)			

**Additives with an E-number are additives which are generally permitted for use in foods in the EU*

3.2.1.6.2. General Loose (SKU 4852)

Table 3-8. Listing of Ingredients in General Loose

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure

(b) (4)

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
(b) (4)					

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
					(b) (4)

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
(b) (4)					

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
					(b) (4)

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
					(b) (4)

Ingredient Name	Unique scientific name or code	Type of code	Ingredient function	Quantity of ingredient	Unit of measure
(b) (4)					

3.2.1.6.3. General Dry Mint Portion Original Mini (SKU 4800)

Table 3-9. Listing of Ingredients in General Dry Mint Portion Original Mini

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.4. (b) (4)

Table 3-10. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.5. (b) (4)

Table 3-11. Listing of Ingredients in General (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.6. (b) (4)

Table 3-12. Listing of Ingredients in General (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.7. (b) (4)

Table 3-13. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.8. (b) (4)

Table 3-14. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.9. (b) (4)

Table 3-15. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.10. (b) (4)

Table 3-16. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.6.11. (b) (4)

Table 3-17. Listing of Ingredients in (b) (4)

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

Ingredient name	Unique scientific name or code	Type of code	Ingredient function	Quantity of Ingredient	Unit of measure
(b) (4)					

3.2.1.7. Packaging

3.2.1.7.1. Loose Snus Product

The cardboard cans used for the packaging of General Loose (SKU 4852) and other Swedish Match portion loose products are assembled by (b) (4) . (b) (4) The can design takes into account consumer acceptance, facility of the cardboard manufacturing process, geometrical stability, and appropriate general tightness of the can.

3.2.1.7.2. Portion Snus Products

The plastic cans used for the packaging of all Swedish Match portion Snus Products are (b) (4) (b) (4) The can design takes into account consumer acceptance, facility of the injection molding process, geometrical stability, and appropriate general tightness of the can.

The pouch material used in all portion Snus Products is a (b) (4) All materials in the portion pouch fabric are in compliance with the following FDA regulations for indirect food additives:

- Paper and paperboard components (21 CFR §§ 176.170, 176.180) and
- Adhesives (21 CFR § 175.105).

The exact composition of the binder is a trade secret of the supplier, and Swedish Match has signed a confidentiality agreement with the supplier for disclosure of the binder composition.

3.2.2. A description of tobacco blending, reconstitution, or manipulation

More detailed information on Swedish Match's routines for procurement and handling of raw tobacco is found in Section 3 of the SM GOTHIATEK Report 2013.

3.2.2.1. Procurement

Swedish Match Leaf Operations, Swedish Match North Europe AB, is responsible for the procurement of all tobacco for the production of Swedish snus. The tobacco blends for production are comprised of mixtures of selected tobacco qualities. Tobacco quality differs depending on country of origin, curing procedure, and plant position, and it is characterized by taste, aroma, texture, and chemical composition. The concept of "tobacco grade" is used to characterize the quality by country of origin, curing process, and plant position. Each tobacco blend comprises a mixture of different tobacco grades.

At present the tobacco used for snus production originates from several countries, includin (b) (4)

(b) (4)

In order to ensure that the supply of stem tobacco contains low and controlled levels of TSNAs, stem tobacco is procured separately and on markets for by-products.

3.2.2.2. Curing

Curing is the process required to prepare the harvested tobacco leaf for consumption. Curing methods vary according to tobaco type, and can include curing by air, sun, flue, or fire.[35]

Air curing is a natural drying process in which harvested tobacco leaves are hung to dry in an air-curing barn. Air cured tobacco undergoes three (3) stages in the curing process. The first stage lasts for 2-5 days, during which time the chlorophyll degrades and gives way to the second stage, called the yellowing stage. The yellowing stage lasts 5-10 days, depending on the curing conditions, as the yellow pigments degrade more slowly than the chlorophyll. At the end of the yellowing stage, when the plant cell membranes break down, many chemical reactions occur before the leaf becomes dehydrated. These reactions include, at uncontrolled conditions of temperature and humidity, microbial reduction of nitrate to nitrite and chemical nitrosation of the alkaloids by nitrite.

The third stage of curing, the browning stage, follows as the yellow pigments degrade and the leaf dies. The main factors that control the air curing rate are temperature, humidity, air flow, and sunlight.

Sun curing is similar to air curing, with the main difference being that the tobacco is cured outside with no protection from sun or rain. Sun curing is often practiced in dry and hot areas. Such conditions are favorable for the production of low TSNA tobaccos.

Flue curing requires 5-7 days for completion. It is an artificial curing process in which temperature, time, and airflow are controlled. The first stage, which is commonly referred to as "yellowing," is a physiological process in which the biochemistry of the harvested leaf is changed. The process is terminated by drying, referred to as "fixing color." This stage takes about two (2) days, during which the leaf is almost completely dehydrated. Generally, flue curing produces lamina tobacco of high sugar content which, in most cases, is unsuitable for snus production. However, Swedish Match buys flue cured stem tobacco, since it, like sun cured stem tobacco, typically contains low levels of undesired constituents such as TSNAs, as compared to air cured stem tobacco.

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[35] Fire curing is not discussed herein because it is not used in the manufacture of Swedish snus. The fire curing process produces undesirable smoke components, typically B(a)P, that stick to the tobacco leaves.

3.2.2.3. Producing High Quality Raw Tobacco

The final quality of the raw tobacco is determined by a combination of factors, including seed variety, growing and curing conditions, and handling by the farmers and suppliers. Swedish Match has developed proprietary procedures to control these variables in order to obtain high quality tobacco and ensure the consistency, integrity, consumer acceptance, and regulatory compliance of the final products.

Swedish Match has a longstanding commitment to reduce TSNAs and other undesired constituents in raw tobaccos through research and development and in cooperation with suppliers and growers. This commitment has resulted in a range of recommendations and instructions governing the production of the tobacco at several locations around the world. The procedures for achievement of tobacco suitable for the production of snus according to Swedish Match's standards vary slightly among different areas in the world depending on local conditions, but the main principles are the same.

Basic actions to secure high quality tobacco for snus production are as follows:

- No usage of dark fired tobacco (because the curing process causes undesirable high levels of several unwanted constituents, such as, B(a)P);
- No usage of fermented tobacco (because fermentation may be associated with formation of TSNAs);
- Increased usage of certified seed varieties with low converter frequency;
- Establishment of an "Early Warning System" to assess the quality of a specific crop;
- Removal of stem/midrib from the lamina in *Nicotiana Tabacum* varieties;
- Reduction of moisture in the packed raw tobacco (b) (4) to reduce formation of TSNAs during storage before the manufacturing process; and
- Control of temperature and relative humidity during storage before the manufacturing process.

In addition, Swedish Match requirements for farmers and suppliers include:

- Good sanity practices during tobacco handling;
- The shortest possible lead time between farmer baling and processing of the raw tobacco;
- The ability to produce raw tobacco compliant with Swedish Match requirements on an annual basis; and
- Implementation of Swedish Match's general instructions for packing of tobacco for snus production.

Swedish Match also provides instructions to farmers and suppliers in the following areas:

- *Seed varieties*: Growers are advised to use only certified seed varieties. New varieties are continuously being developed. The following table shows the varieties used at the various tobacco production locations where Swedish Match purchased raw tobacco in 2011.

Table 3-18. Seed Varieties

Type	Variety
(b) (4)	

- *Growing conditions*: (b) (4)
- *Harvesting*: (b) (4)
- *Curing*: (b) (4)
- *Handling of the* tobacco *by the farmers with a focus on sanity*: (b) (4)
- *Handling of the tobacco by the suppliers*: (b) (4)
- *Processing of the tobacco by the suppliers*: (b) (4)

(b) (4)

3.2.2.3.1. Choosing Source of Origin

Swedish Match strives to maintain diversified sources of leaf tobacco to minimize reliance on any one growing or sourcing area. Swedish Match selects geographical areas that present the right conditions in terms of:

- Consistent quality and volume over time;
- Appropriate soil conditions;
- Established infrastructure, including tobacco processing facilities;
- Presence of a farming community open to changing its growing and curing practices;
- Dry and stable climate during the curing period; and
- Access to irrigation.

3.2.2.3.2. Criteria for Choosing Suppliers

Swedish Match buys tobacco through tobacco suppliers that have pre-plant contracts with growers to produce tobacco which the supplier then markets to Swedish Match. Swedish Match provides indications for future requirements of tobacco qualities and quantities to the suppliers in order to permit them to determine the extent of pre-plant grower contracts. Indication quantities are based on existing inventories, current planned production, and estimated future production volumes.

Swedish Match buys tobacco from a small number of suppliers, who are all major international organizations with their own regulatory frameworks and controls regarding social and environmental issues. Swedish Match requires that these companies have strict policies with regard to human rights, child labor, and farming practices.

Swedish Match does not perform social audits, but all suppliers of tobacco are informed about the company's Code of Conduct and are required to sign and return the document titled "Social commitment for suppliers to Swedish Match." They must also complete an agronomy questionnaire. Swedish Match representatives visit the suppliers each year and proactively discuss social issues, such as child labor, human rights, and other matters central to the Company's Code of Conduct.

Swedish Match uses only suppliers that have an integrated compliance system. The following components should be included in the system:

- *Good agricultural practices*, which involve promoting, using, and further developing sound leaf production techniques and strategies which meet with the Cooperation Centre for Scientific Research Relative to Tobacco ("Coresta") Guide No 3

(http://www.coresta.org/Guides/Guide-No03-GAP_Feb05.pdf), as well as promoting farmer success and supporting a sustainable environment;

- *Good manufacturing practices*, which involve using best practices and developing improved technologies to optimize results in the processing facilities;

- Practices related to *environmental performance*, which involve monitoring the supplier's industrial activities and implementing strategies to reduce environmental impacts and comply with all laws and regulations;

- Practices related to *product integrity and traceability*, which involve ensuring product quality, integrity, and traceability throughout the supply chain; and

- A *social responsibility program*, which includes a commitment to address child labor issues; the protection of contractors, visitors, and the workforce by creating and maintaining a workplace free of recognized hazards; contributions to surrounding communities through volunteer services and financial support of community improvement initiatives; and adherence to the conventions of the International Labour Organization ("ILO") and continuously training and developing employees.

3.2.2.3.3. Criteria for Acceptance and Approval of Raw Tobacco

3.2.2.3.3.1. Tolerance and Guidance Levels for Constituents in Raw Tobacco

Swedish Match adheres to a detailed set of criteria for acceptance and approval of raw tobacco. In particular, Swedish Match has established a quality standard, GOTHIATEK® (Rutqvist et al. 2011), with requirements for constituents, ingredients, agrochemical residues and GMO in finished products. Swedish Match tobaccos for snus production have therefore been assigned maximum tolerance levels for TSNAs, nitrite and GMO, as well as guidance levels for B(a)P, mycotoxins, heavy metals, sugars, nicotine and agrochemical residues.

Despite measures taken by farmers and suppliers, unfavorable growing and/or curing conditions over a given year may result in raw tobacco that has levels close to or exceeding these tolerance or guidance levels. In exceptional cases Swedish Match may buy tobacco for snus production that has constituent levels slightly above the tolerance and/or guidance levels. However, by strict control of the blending process, constituent levels in the finished products are not allowed to exceed the GOTHIATEK® limits.

To meet the GOTHIATEK® standard and internal tolerance levels, certain tolerances and guidelines have been set on constituents in raw tobacco. Neither the tolerance nor the guidance levels for raw tobacco are mandatory. However, the tolerance level is a purchase condition that has to be fulfilled and, if not, may lead to the rejection of an order. The guidance level is a maximum level for action and improvement in the development of future supply of raw tobacco.

Both may lead to the termination of tobacco supply from markets that are not able to adjust or improve.

- Tolerance levels (dry weight):
  (b) (4)

- Guidance levels (dry weight):
  (b) (4)

3.2.2.3.3.2. Raw Tobacco Buying Process

The initial stage of Swedish Match's raw tobacco buying process consists of planning. In addition to sales forecasts, storage levels, and inventory policy, the results of chemical analyses in previous crops are also considered. Tobacco is procured throughout the calendar year when the tobacco is ready at the source of origin. The suppliers purchase the tobacco directly from the contracted growers. Generally, the supplier provides growers with guidance, fertilizers, agrochemicals and other materials necessary for production. The supplier is responsible for sorting, threshing, drying and packing the tobacco according to Swedish Match's specifications.

Tobacco processing facilities are usually located in the regions of the growing areas. When the farmer bales arrive from the growers to the processing plants, the tobacco is classified according to the supplier's internal grades describing the tobacco's characteristics such as plant position, maturity, uniformity, and cleanliness.

During processing, tobacco grades are blended to meet Swedish Match's quality specifications in terms of organoleptic and chemical properties. The tobacco is threshed and separated into lamina and stem. Both products undergo a redrying process before being packing into cardboard cartons in order to obtain adequate conditions for shipment and storing. (b) (4)

Over the course of a tobacco crop season, representatives from Swedish Match are present at different stages of the tobacco growing, buying and processing cycles. Laboratory tests for quality control are performed throughout the whole process, ensuring that the tobacco meets Swedish Match's criteria for approval before a final purchase decision is made.

3.2.2.3.4. Control of Chemical Components

To ensure that tobacco quality meets Swedish Match's standards for chemical constituents in the final product, thorough chemical quality control of the tobacco is performed at different stages of the tobacco procurement process.

- *Early Warning Samples ("EWS")*: Swedish Match has implemented an "Early Warning System" to obtain an early indication of the chemistry and cleanliness of the tobacco for a given crop year. Representatives from Swedish Match visit tobacco growing areas on a regular basis and instruct the dealers on how to collect tobacco samples for chemical analysis directly after curing. (b) (4)

- *Offer samples*: Before buying tobacco from areas where Swedish Match has not previously conducted business, offer samples are collected by suppliers and sent to Swedish Match for thorough investigation. The tobacco undergoes inspection for physical, chemical and sensory properties to determine its usability for snus production.

- *Packed tobacco samples*: Chemical quality control is performed throughout the entire tobacco packing process. (b) (4)

3.2.2.3.5. Shipment and Storage

The tobacco is shipped to Sweden after final approval of the chemical analysis results. Before shipment, the tobacco is fumigated against pests according to the Coresta Guide No 2 for fumigation (http://www.coresta.org/Guides/Guide-No02-Fumigation_June09.pdf). (b) (4)

3.2.2.3.6. Inspections at the Swedish Match Warehouse in Sweden

Upon arrival in Sweden, the quality of the delivered tobacco is inspected according to codified routines. The tobacco is also inspected for the presence of non tobacco-related material. The tobacco is then stored under controlled conditions until released for snus production. The storage warehouse is temperature-controlled throughout the year, (b) (4)

(b) (4)

3.2.3. A description of manufacturing steps, including the sources of all components, and quality control measures in place

The Snus Products described in this Application are produced in three (3) manufacturing steps, namely tobacco flour grinding, snus blend processing, and packing of finished product.

- Step 1: In the grinding process, a blend of different raw tobacco qualities, specified by a tobacco blend recipe, is ground and blended to tobacco flour (b) (4) .
- Step 2: In the snus blend process, tobacco flour is mixed with ingredients (b) (4) (b) and heat treated (b) (4)
- Step 3: The packing of finished products includes packing of the snus blend into cans as loose snus products, or packing of pouches which are packed into cans as a portion snus products. (b) (4)

Swedish Match produces finished Snus Products in the form of loose snus and portion snus pouches wrapped in non-woven fabric. Portion snus pouches have differing properties such as size, weight, moisture content and color of the pouches. Pouches which are dry on the surface, and therefore have a white appearance if white fabric is used, are referred to as white portions. Pouches which are moist on the surface, and therefore have a brown appearance, are referred to as original portions.

Pouches are produced using two different techniques. (b) (4)

Swedish Match has two (2) production sites in Sweden: one (1) is located in Gothenburg and one (1) is located in Kungälv. (b) (4)

3.2.3.1. Tobacco Blend Formulation

Raw tobacco for Swedish Match's snus production consists of air cured, sun cured and flue-cured (or "bright") tobacco types of different qualities. The compositions of different tobacco types used for grinding of tobacco flour for snus production are specified by tobacco blend recipes. (b) (4)

Each individual tobacco blend recipe is regulated by (b) (4) To achieve desired product features, such as consistency, of the finished Snus Products.(b) (4)
(b) (4) Tobacco blend recipes, (b) (4) ristics, are used for ordering raw tobacco from the raw tobacco storage for grinding of tobacco flour.

(b) (4)
.

(b) (4)
.

Swedish Match's process for tobacco blend recipe composition is described in the ISO 9001 and adheres to the following specifications:

- (b) (4)
-
-

3.2.3.2. Grinding

Tobacco flour is produced from compressed lamina strips, loose leaf, and stems by batch

grinding. (b) (4) . A machinery flow chart is shown in **Figure 3-9**. A detailed explanation of the various steps is as follows:

Start-up: (b) (4) .

Pre-grinding: (b) (4)

Drying: (b) (4)

Grinding and sieving: (b) (4) :

(b) (4)

(b) (4) .

(b) (4)

Quality assurance: (b) (4)
(b) (4)

(b) (4)

(b) (4)

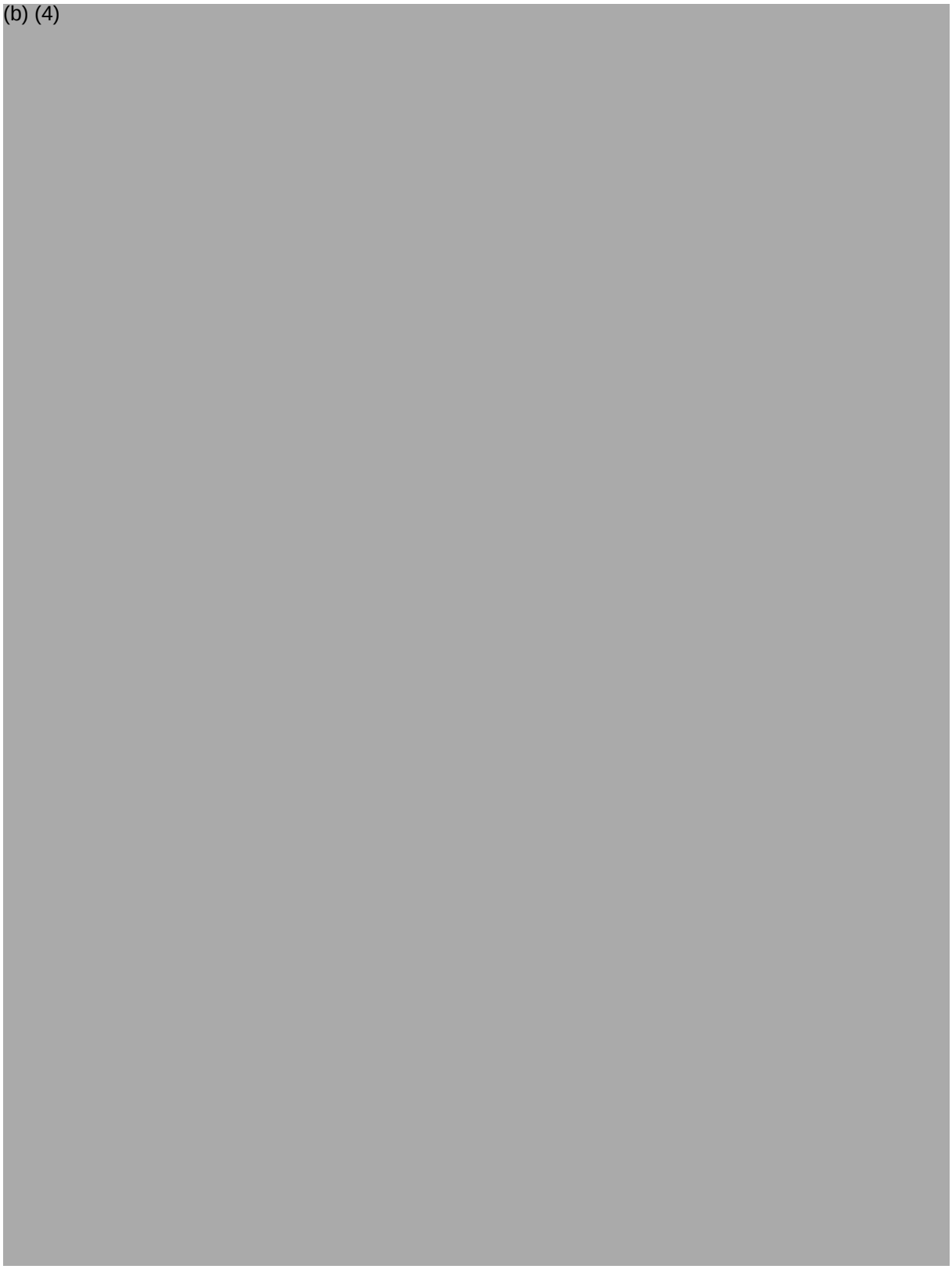
Storage of Tobacco Blends: (b) (4)

The grinding procedure is described in the ISO 9001 and controlled according to the appropriate specifications.

Figure 3-9. Tobacco Grinding Flow Chart

See the following page for an overview of the tobacco grinding process.

(b) (4)



3.2.3.3. Snus blend processing

In the snus blend process, (b) (4)

The heat treatment, (b) (4)

After heat treatment, the blend is chilled (b) (4)

Swedish Match uses several different heat treatment processes. Each process type is defined by parameters such as time and temperature for heating with steam and/or jacket heating, time for resting periods between heating, time and speed of mixing at different steps, air ventilation control and time and/or temperature for cooling.

(b) (4)

In production, the process recipe used is (b) (4)

A snus blend process generally includes the following steps:

- *Loading*: (b) (4)
- *Heating*: (b) (4)
- *Heat treatment and resting*: (b) (4)

(b) (4)

- *Cooling*: (b) (4) .
- *Adding of ingredients*: (b) (4)

  (b) (4) .

  (b) (4)
- *Quality assurance:* (b) (4)
- *Emptying*: (b) (4) .

(b) (4)

(b) (4) Detailed descriptions of these processes are set forth below.

3.2.3.3.1. (b) (4) heat treatment, supported by steam

The (b) (4) heat treatment snus blend process, supported by steam, is used for all loose and moist white portion snus products, including the following Snus Products sold in the United States:

- *Loose Snus Product:* General Loose (SKU 4852)
- *Moist White Portion Snus Products:* General Classic Blend Portion White Large - 15 ct (SKU 4877); General Classic Blend Portion White Large - 12 ct (SKU 4878); General Mint Portion White Large (SKU 4352); General Nordic Mint Portion White Large - 15 ct (SKU 4876); General Nordic Mint Portion White Large - 12 ct (SKU 4875); General Portion White Large (SKU 4881); and General Wintergreen Portion White Large (SKU 4882).

Loading: (b) (4)

Heating: (b) (4)

.

Heat treatment and resting: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) of the natural bacterial flora in the tobacco and brings texture, taste and color to the snus blend.

Cooling: (b) (4) he process recipe. The chilled blend at this stage is referred to as a semi-finished snus blend.

Additives and mixing: (b) (4)

(b) (4)

Quality assurance: (b) (4)

Emptying and storage: (b) (4)

Figure 3-10. Typical temperature profile, (b) (4) heat treatment, supported by steam

Figure 3-11. General flow chart, snus blend processing for Loose Snus Products

(b) (4)

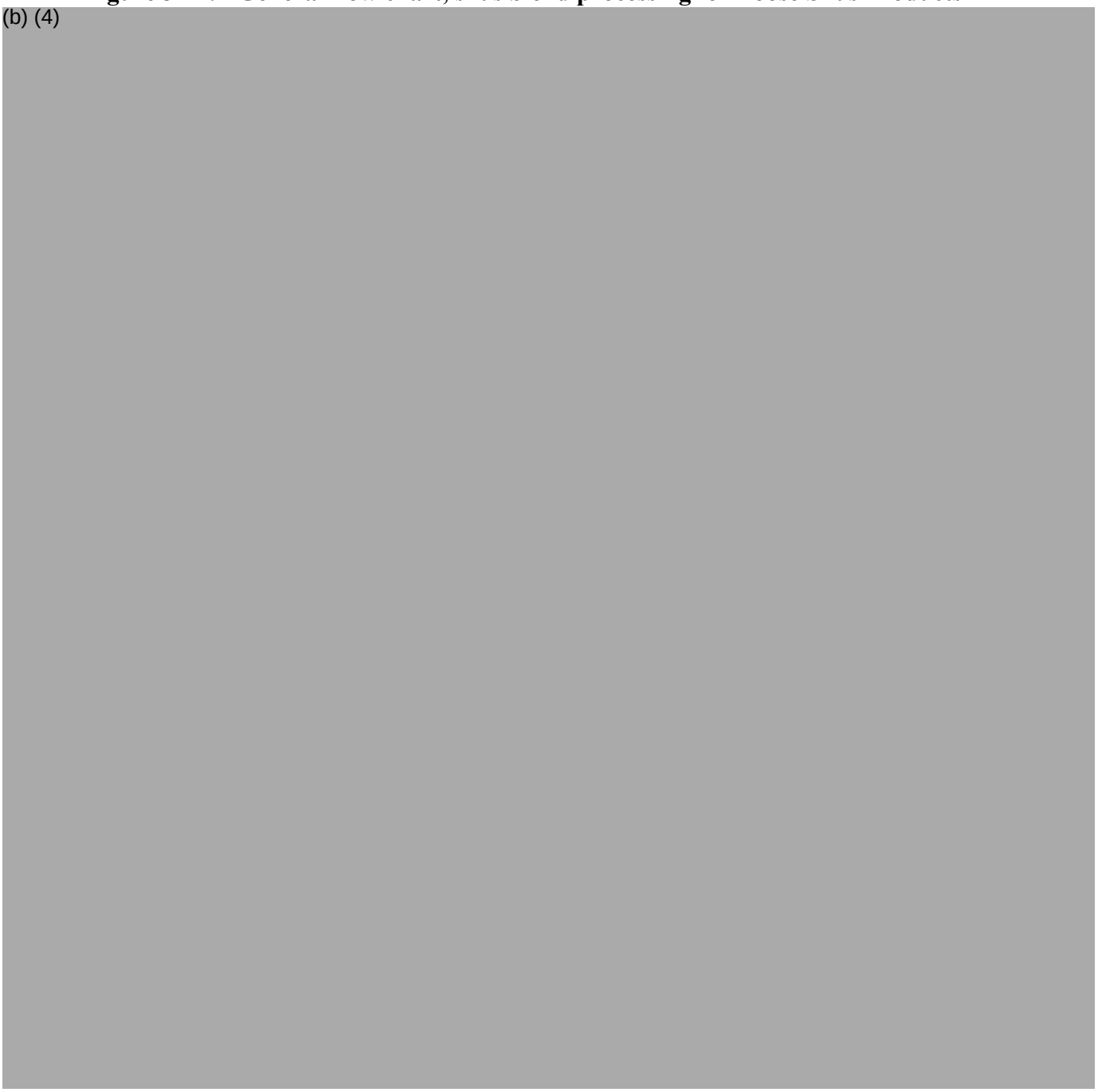
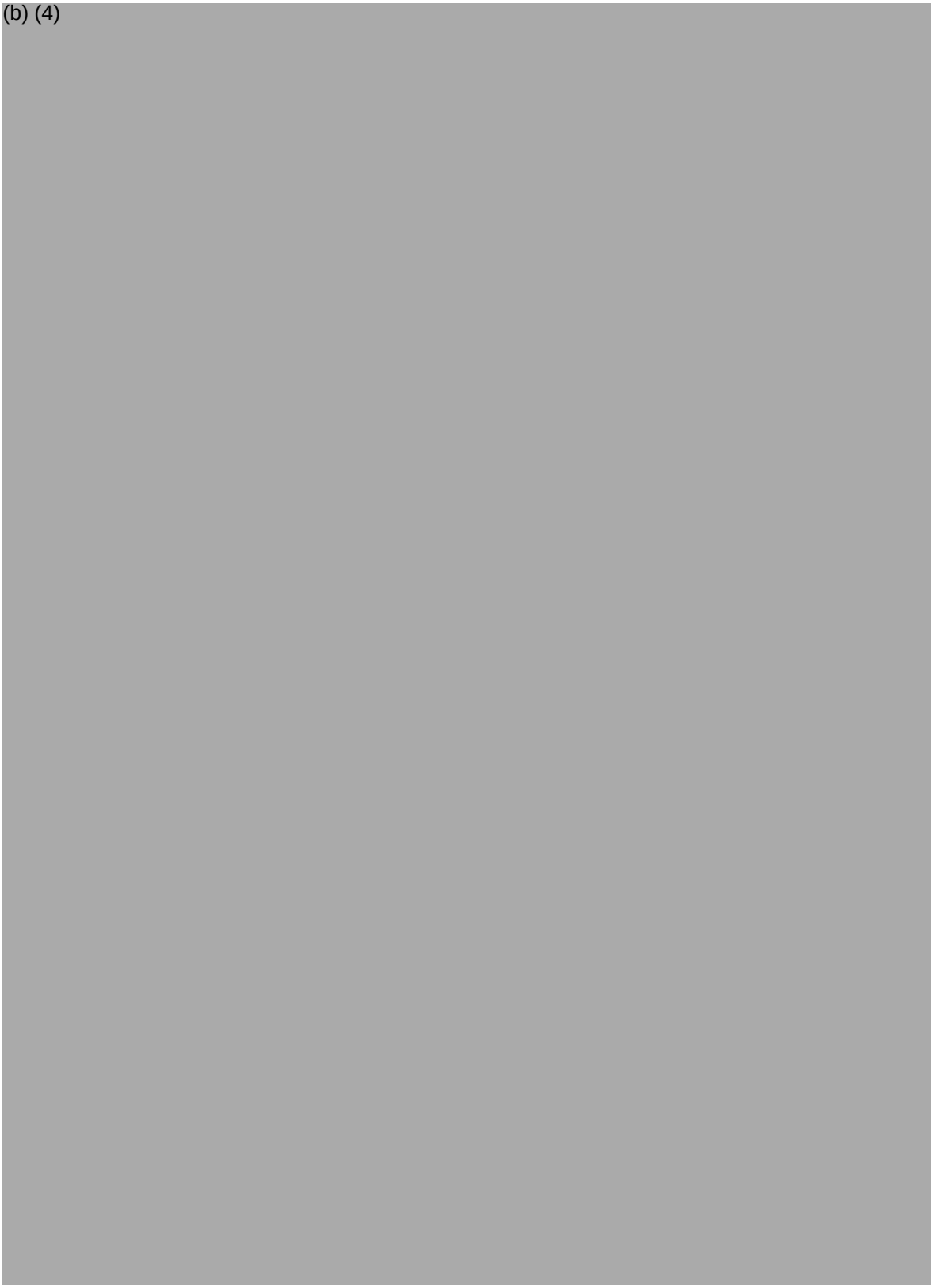


Figure 3-12. General flow chart, snus blend processing for Moist White Portion Snus Products

See the following page for an overview of the snus blending process for Moist White Portion Snus Products.

(b) (4)



3.2.3.3.2. (b) (4) heat treatment, supported by steam

The snus blend process for General Portion Original Large (SKU 4880) is as follows:

Loading: (b) (4)

Heating: (b) (4) .

Heat treatment and resting: (b) (4) .

(b) (4)

(b) (4)

Cooling: (b) (4)

Additives and mixing: (b) (4)

(b) (4)

(b) (4)

Quality assurance: (b) (4)

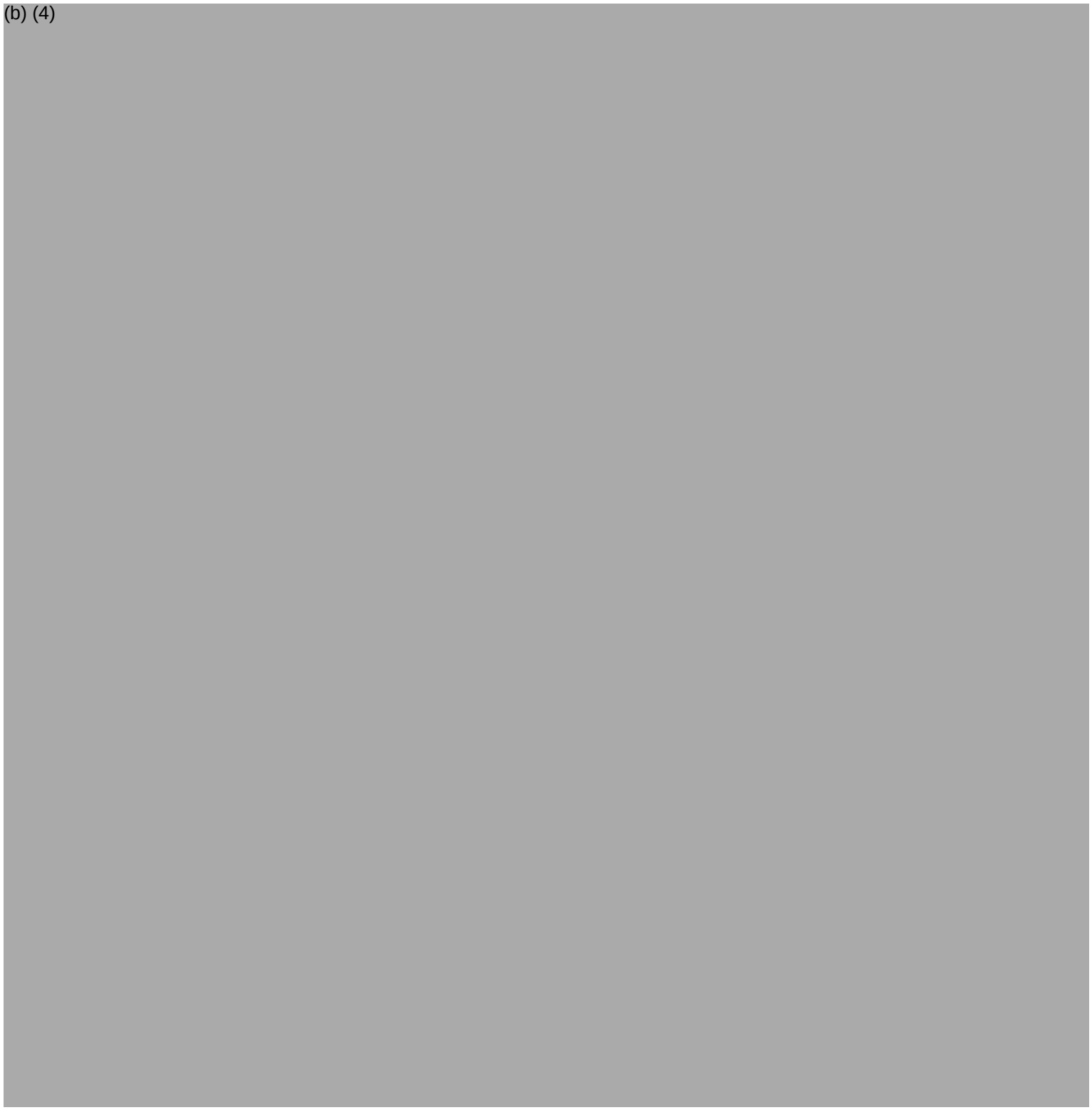
.

Emptying and storage: (b) (4)

Figure 3-13. Typical temperature profile, (b) (4) heat treatment, supported by steam

(b) (4)

Figure 3-14. General flow chart, snus blend processing for Original Portion Snus Products



3.2.3.3.3. (b) (4) alkaline heat treatment, supported by jacket heating

The snus blend process for General Dry Mint Portion Original Mini (SKU 4800) is as follows:

Pre-heating and loading: (b) (4)

Heating: (b) (4)

Heat treatment: (b) (4)

Cooling: (b) (4)

Additives and mixing: (b) (4)

(b) (4)

Quality assurance: (b) (4)

Emptying and storage: (b) (4)

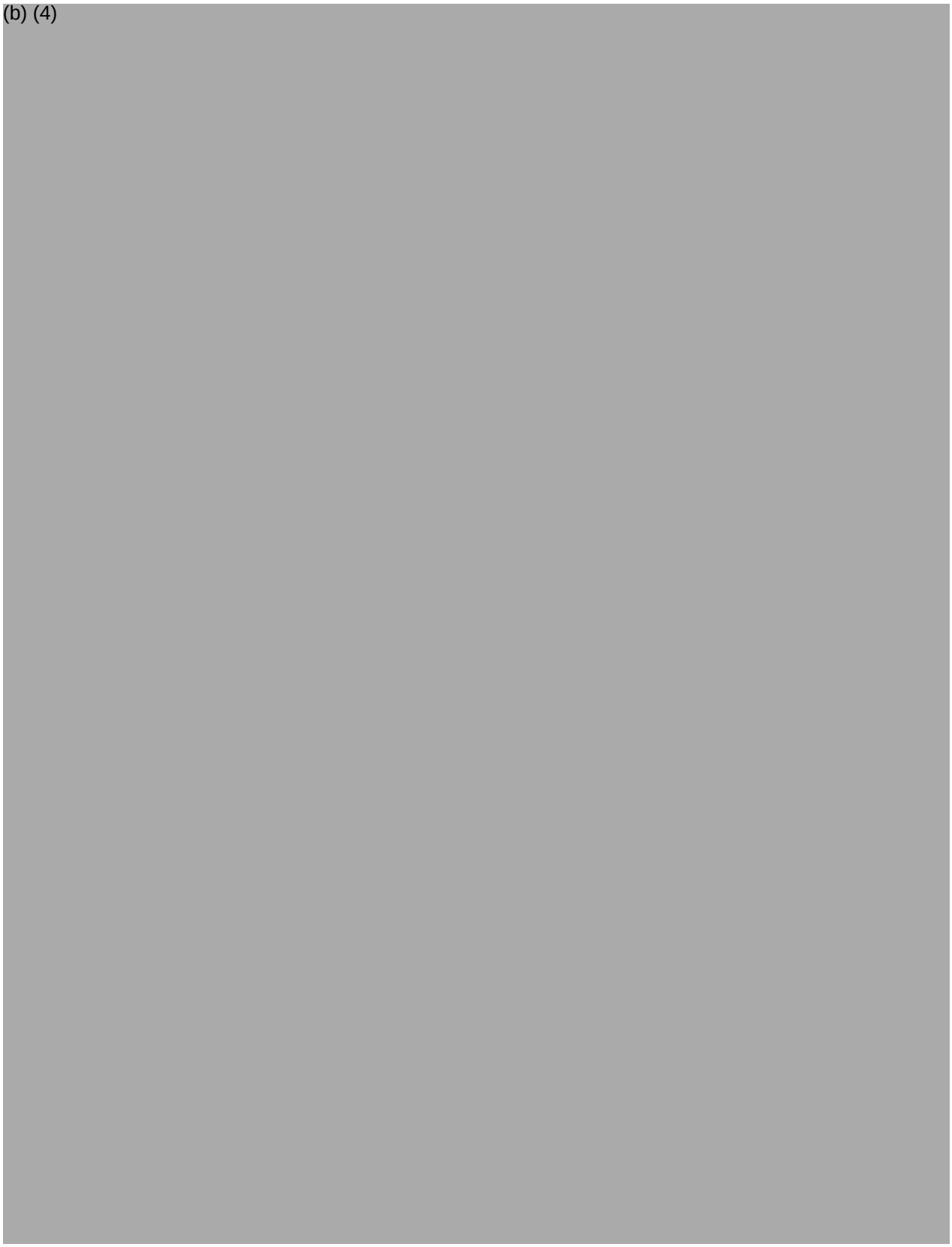
Figure 3-15. Typical temperature profile, (b) (4) alkaline heat treatment, supported by jacket heating

(b) (4)

Figure 3-16. General flow chart, snus blend processing for Dry White Portion Snus Products

See the following page for an overview of the snus blending process for Dry White Portion Snus Products.

(b) (4)



3.2.3.4. Packing

3.2.3.4.1. Packing of Loose Snus Products

The procedures for packing General Loose (SKU 4852) are as follows:

(b) (4)

Figure 3-17. General flow chart, packing of Loose Snus Products

(b) (4)

3.2.3.4.2. Packing of Moist White Portion Snus Products

The procedures for packing General Classic Blend Portion White Large - 15 ct (SKU 4877); General Classic Blend Portion White Large - 12 ct (SKU 4878); General Mint Portion White Large (SKU 4352); General Nordic Mint Portion White Large - 15 ct (SKU 4876); General Nordic Mint Portion White Large - 12 ct (SKU 4875); General Portion White Large (SKU 4881); and General Wintergreen Portion White Large (SKU 4882) are as follows:

(b) (4)

Figure 3-18. General flow chart, packing of Moist White Portion Snus Products

(b) (4)

3.2.3.4.3. Packing of Dry White Portion Snus Products and Original Portion Snus Products

The procedures for packing General Dry Mint Portion Original Mini (SKU 4800) and General Portion Original Large (SKU 4880) are as follows:

(b) (4)

(b) (4)

Figure 3-19. General flow chart, packing of Dry White Portion Snus Products and Original Portion Snus Products

(b) (4)

3.2.3.4.4. Cold storage and shipping

(b) (4)

3.2.3.4.5. Sources of All Components

Swedish Match's current suppliers of packaging materials, such as cans, lids, labels and pouch material, are listed in the following table.

Table 3-19. Current Suppliers of Packaging Materials for Swedish Match Snus Products

(b) (4)

3.2.3.4.6. Quality Control Measures

During the packaging process for the loose snus product, (b) (4)

(b) (4)

During the packaging process for original pouch snus products, (b) (4)

(b) (4)

During the packaging process for white pouches, (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Other testing parameters are:

(b) (4)

If all tests are approved, the cans and lids are released for use in the production.

Microbiological testing (b) (4)

Hazards involving the storage facility for packaging includes flying insects and high microbiological presence. All packaging materials are well sealed until ready to use in production. In order to prevent contamination of the hygiene zone, the storage areas are kept free from vermin. The following precautions are taken:

- (b) (4)

(b) (4)

3.2.3.5. Chemical Analysis and the GOTHIATEK® Standard

Swedish Match uses analytical methods, chemical quality control programs, brands testing programs, and agrochemical management programs to manufacture snus according to GOTHIATEK®, the company's proprietary quality standard for snus products. More details can be found in Section 7 of the SM GOTHIATEK Report 2013. The following descriptions apply to all of the Swedish Match products marketed in the US.

The principal components of the GOTHIATEK® standard are:

- Constituent standards:
  - Maximum levels ("MLs") which must not be exceeded, for selected, undesired constituents in the finished product (see **Table 3-20** below); and
  - Guidance Residue Levels ("GRLs") for agrochemical residues in finished products, which serve as guidance for tobacco purchase and product quality.
- Manufacturing standards:
  - Standard for selection of raw material:
    - Leaf tobacco selection and an "early warning" chemical analysis program designed so that the limits for undesired constituents in finished products are met; and
    - An ingredient policy consistent with the Swedish Food Act for additives and flavors.
- Manufacturing process requirements:
  - Tobacco comminuted in a controlled process satisfying the requirements for specific particle size distribution;
  - Controlled heat treatment that reduces the natural microbial flora of the tobacco to specified residual limits;
  - Manufacturing in a closed system to prevent the product from being contaminated (e.g. by external microflora);
  - Hygienic conditions complying with the Swedish Food Act; and
  - Consumer information.
- Consumer package labeling which includes a "best before" date, recommended

storage conditions, and a declaration of ingredients in accordance with requirements for the labeling of processed food stuffs; and

- A public website with detailed information based on scientific evidence about health effects of snus use and brand-specific product characteristics. (The health effect part is not implemented in the United States or towards US consumers as that might be viewed as inconsistent with the Tobacco Control Act's prohibition against unapproved modified risk claims).

The current levels of GOTHIATEK® constituents in Swedish Match's Snus Products are far below the maximum levels included in the standard. Swedish Match has therefore introduced internal tolerance limits for the GOTHIATEK® constituents together with some additional constituents and additives. The GOTHIATEK® limits and the internal tolerance limits are shown in **Table 3-20** below.

Swedish Match's internal tolerance limits are not static, but rather continue to evolve as techniques and processes are improved and more scientific data become available. Swedish Match has developed a procedure to control chemical components, to evaluate and revise existing internal tolerance limits, as well as to propose new internal tolerance limits for undesirable substances, including many of the harmful and potentially harmful constituents ("HPHCs") for smokeless tobacco products that FDA has identified to date.

Table 3-20. GOTHIATEK® Limits and Swedish Match Internal Tolerance Limits for Constituents in Snus Products

2014 limits are based on dry weight except for propylene glycol, water activity, and bacteria.

Constituents	Internal tolerance limits	GOTHIATEK® limits	Legislation limits
(b) (4)			

Constituents	Internal tolerance limits	GOTHIATEK® limits	Legislation limits
(b) (4)			

** Swedish National Food Agency, LIVSFS 2012:6*
*** Swedish Medical Products Agency SFS2010:1622*

Compliance with the GOTHIATEK® limits and the internal tolerance limits is verified on a regular basis in the Chemical Quality Control Program, (b) (4)

The GOTHIATEK® standard also includes limits for agrochemical residues in snus products.

- GRLs are described in the Swedish Match Agrochemical Management Program. GRL is a well established concept in the field of crop protection, and CORESTA has published a GRL list (available at www.coresta.org) to provide guidance to tobacco growers and the tobacco industry generally. The guidance levels are based on the levels of residues that may be present after application of agrochemical using Good Agricultural Practice (GAP), international legal and regulatory Maximum Residue Levels ("MRLs") and on the Limits of Quantification.

- Maximum Levels ("MLs") are also used for GOTHIATEK® constituents.

The Swedish Match Chemical Laboratory, or SCL, in Stockholm (Swedish Match North Europe

AB, R&D, Chemical Analysis, Stockholm) is accredited according to ISO/EIC 17025:2005 (Accreditation certificate) by the Swedish Board for Accreditation and Conformity Assessment, SWEDAC. Swedish Match's internal quality assurance system is based on this standard. The methods included in the accreditation are:

- Alkaloids (nicotine, nornicotine);
- Loss on drying;
- Mycotoxins (Ochratoxin A, Aflatoxins B1, B2, G1 and G2);
- Nitrite ion;
- Nitrate ion;
- N-Nitrosodimethyl amine;
- Tobacco specific nitrosamines (NNN, NNK, NAT, NAB);
- Water;
- Metals (Arsenic, Cadmium, Chromium, Lead, Nickel);
- Benzo(a)pyrene;
- Moisture; and
- pH.

Analyses not yet accredited but reported by SCL to regulatory authorities are performed in accordance with the ISO 17025:2005 standard.

The Chemical Laboratory Quality Assurance System includes(b) (4)

The documentation of the laboratory quality assurance system includes:

- The Quality Manual of Chemical Analysis, Stockhom ("Quality Manual");
- Process descriptions, method descriptions, procedure descriptions, instructions, and forms; and
- References to standards and recommended methods.

Conformance to the laboratory quality system is supervised by an internal quality system function ("QSF"), which examines and approves all quality documents and recommends improvements and changes.

Each analytical method is summarized in a method description together with a validation document in a standardized format in accordance with ISO 17025. The SCL's Quality Manual describes the quality system and linked documents. Instructions exist for sample handling, sample registration and the reporting of results, management of instruments and equipment, and

management of data software. All method descriptions – including a summary of the validation results, descriptions, and instructions – are stored in QEMS as electronic documents. These documents are available for employees involved in the ISO certification of the Swedish Match Smokefree Products Division.

Standardized and/or recommended analytical methods are primarily considered for further development and/or implementation at SCL, although the requirements of Swedish Match Chemical Quality Control Program, trade associations, and other authorities are also highly relevant to such decisions.

SCL is equipped with modern and appropriate analytical instruments and equipment. (b) (4)

(b) (4)

3.2.3.5.1. Short Descriptions of Methods

This section includes short descriptions of the analytical methods done at SCL for the analysis of tobacco blends and snus products included in the Chemical Quality Control Program (b) (4) (b) (4), analytical methods used for the analysis of snus products included in the Brands Testing Program and methods used for the analysis of raw tobaccos.[36]

[36] Additional information about the test methods described herein can be provided to CTP upon request.

Table 3-21. Chemical Analyses Performed at SCL

	Method	Analyte	Comments
(b) (4)			

	Method	Analyte	Comments
(b) (4)			

Method 1 (b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2:	

Analyte: (b) (4) Validation parameters	
Method measurement interval	

Limit of quantification (LOQ)	(b) (4)
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 2 (b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 3 (b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 4 (b) (4)

(b) (4)

.

Analyte: (b) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters:	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage	

Analyte: (b) (4) Validation parameters:	
factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 5 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
	(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 6 (b) (4)

(b) (4)

Analyte (b) (4)

Validation parameters	(b) (4)
Method measurement interval	
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 7 (b) (4))

(b) (4)

Analyte: (b) (4) Validation parameters	(b) (4)
Method measurement interval	
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 8 ((b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 9 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	

Analyte: (b)	
Validation parameters	
Total relative measurement uncertainty with a coverage factor of 2	(b) (4)

Method 10 ((b) (4))

(b) (4)

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	

Relative standard deviation under within laboratory reproducibility condition (RSD_R)	(b) (4)
Total relative measurement uncertainty with a coverage factor of 2	

Analyte (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) (b **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 11 ((b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	

Relative standard deviation under repeatability condition (RSD_r)	(b) (4)
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 12 ((b) (4)

(b) (4)

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 13 (b) (4)

(b) (4)

Analyte (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition	

(RSD_r)	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	(b) (4)
Total relative measurement uncertainty with a coverage factor of 2	

Method 14 ((b) (4)

(b) (4)

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 15 ((b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 16 ((b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Reproducibility, within laboratory relative standard deviation (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method (b) (4)

(b) (4)

(b) (4)

(b) (4) Validation parameters:	
Limit of quantification (LOQ)	(b) (4)

Method 18 ((b) (4) **s)**

(b) (4)

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	

Analyte: (b) (4)	
Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	

Some analyses included in the quality control of raw tobacco, tobacco blends, and products are performed by external contractors (**Table 3-22**), which are accredited for the analysis of food and/or tobacco products.

Table 3-22. Chemical Analyses Performed by Contract Laboratories

#	Method	Analyte	Comments	Laboratory
19	(b) (4)			
20				

#	Method	Analyte	Comments	Laboratory
	(b) (4)			
21				
22				
23				
24				
25				
26				
27				

#	Method	Analyte	Comments	Laboratory
	(b) (4)			
28				
29				
30				
31				

Method 19 ((b) (4)

(b) (4)

Analyte: (b) (4) **Validation parameters**	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Total relative measurement uncertainty with a coverage factor of 2	

Method (b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	(b) (4)
Total relative measurement uncertainty with a coverage factor of 2	(b) (4)

Method 21 ((b) (4)

(b) (4)

(b) (4)

. Limits of quantification are shown in **Table 3-23**.

Analyte: See Table 3-23, below. Validation parameters	
Method measurement interval	(b) (4)
Total relative measurement uncertainty with a coverage factor of 2	(b) (4)

Table 3-23. Limit of Quantification (LOQ) for Agrochemicals

Analyte	LOQ µg/g		Analyte	LOQ µg/g		Analyte	LOQ µg/g
(b) (4)							

Analyte	LOQ µg/g		Analyte	LOQ µg/g		Analyte	LOQ µg/g

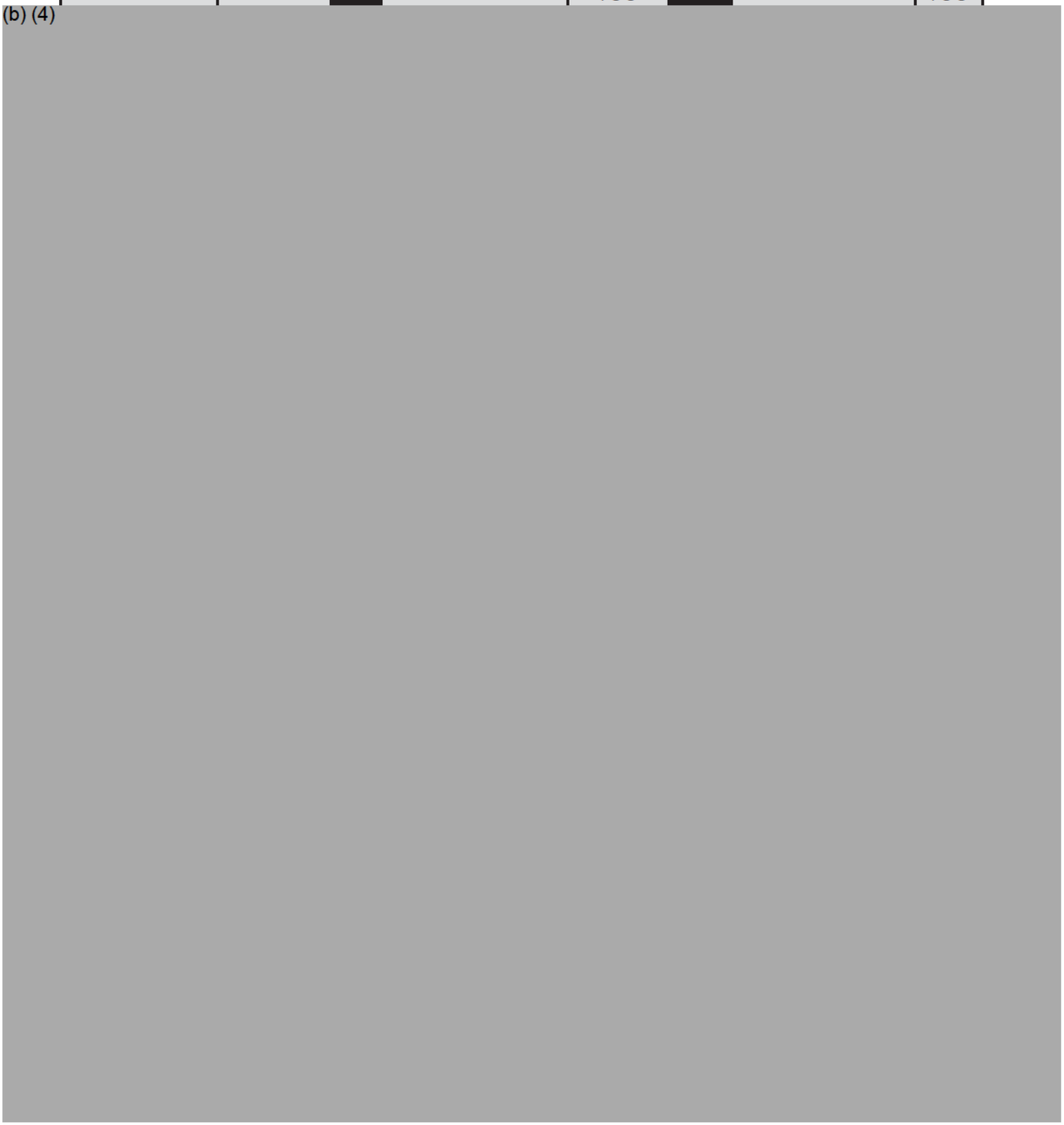
(b) (4)

Analyte	LOQ µg/g	[redacted]	Analyte	LOQ µg/g	[redacted]	Analyte	LOQ µg/g

(b) (4)

Analyte	LOQ µg/g		Analyte	LOQ µg/g		Analyte	LOQ µg/g

(b) (4)



Analyte	LOQ µg/g		Analyte	LOQ µg/g		Analyte	LOQ µg/g

(b) (4)

Analyte	LOQ µg/g		Analyte	LOQ µg/g		Analyte	LOQ µg/g

(b) (4)

Analyte	LOQ µg/g	[redacted]	Analyte	LOQ µg/g	[redacted]	Analyte	LOQ µg/g

(b) (4)

Method 22 (b) (4))

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r)	
Relative standard deviation under within laboratory reproducibility conditions (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 23 (b) (4)

(b) (4)

Analyte: Dithiocarbamates Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 24 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Relative standard deviation under repeatability condition (RSD_r):	
Relative standard deviation under within laboratory reproducibility condition (RSD_R)	
Total relative measurement uncertainty with a coverage factor of 2	

Method 25 (b) (4)

(b) (4)

Analyte: (b) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Measurement uncertainty	

Analyte: (b) Validation parameters

Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Measurement uncertainty	

Analyte: (b) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Measurement uncertainty	

Analyte: (b) Validation parameters	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Measurement uncertainty	

Method 26 ((b) (4)

(b) (4)

Analyte:(b) Validation parameters:	
Method measurement interval	(b) (4)
Limit of quantification (LOQ)	
Measurement uncertainty	

Method 27 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: N(b) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte:(b) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Method 28 ((b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Method 29(b) (4)

(b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Method 30 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	1 (b) (4)

Method 31 (b) (4)

(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Analyte: (b) (4) Validation parameters	
Limit of quantification (LOQ)	(b) (4)

Chemical Quality Control Program for Tobacco Blends in 2011: A total of 218 batches of tobacco blends were analyzed in 2011, out of which the results for 166 batches showed all constituents below the internal tolerance limits ("TL") (**Table 3-24**). (b) (4)
(b) (4)

(b) (4)

Table 3-24. (b) (4))

(b) (4)

(b) (4)

in Table 3-25. (b) (4)

(b) (4)

Table 3-25. US Products with Corresponding Tobacco Blend Number

SKU	Product name	Tobacco Blend Number
4852	General Loose	(b) (4)
4800	General Dry Mint Portion Original Mini	
4880	General Portion Original Large	
4877	General Classic Blend Portion White Large – 15 ct	
4878	General Classic Blend Portion White Large – 12 ct	
4352	General Mint Portion White Large	
4876	General Nordic Mint Portion White Large – 15 ct	
4875	General Nordic Mint Portion White Large – 12 ct	
4881	General Portion White Large	
4882	General Wintergreen Portion White Large	

Table 3-26. Chemical Results for Tobacco Blends Produced and Analyzed in 2011: (b) (4)

Values in bold are outside the tolerance limits.

		(b) (4)					(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**	**n**	**Min**	**Mean**	**Max**	**Median**
(b) (4)											

		(b) (4)					(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**	**n**	**Min**	**Mean**	**Max**	**Median**
(b) (4)											

Table 3-26. Continued: (b) (4)

		(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**
(b) (4)						

		(b) (4)				
Compound	Unit	n	Min	Mean	Max	Median
(b) (4)						

Table 3-26. Continued: (b) (4)

		(b) (4)				
Compound	Unit	n	Min	Mean	Max	Median
(b) (4)						

		(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**

(b) (4)

Table 3-26. Continued: R(b)

		(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**

		(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**
(b) (4)						

		(b) (4)				
Compound	**Unit**	**n**	**Min**	**Mean**	**Max**	**Median**
(b) (4)						

Historical Data on Tobacco Blends: Chemical data on tobacco blends collected between 2002 and 2011 from the Chemical Quality Control Program are summarized below. The average nicotine content in the tobacco blends was nearly constant during this period (**Figure 3-15**). (b) (4)

tent (**Figure 3-16**). (b) (4)

(**Figure 3-17**).

The content of nitrite ion has varied slightly over the years (**Figure 3-18**). The average level of TSNA has decreased over the years and has reached a stable level of approximately 1.7 µg/g. The same is true of the sum of NNN + NNK, which has stabilized at just over 1 µg/g (**Figure 3-19**). (b) (4) , it has been possible to lower the content of ochratoxin in recent years (**Figure 3-20**). (b) (4) (b) (4) (**Figure 3-21**).

Figure 3-15. Average Nicotine Content Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year

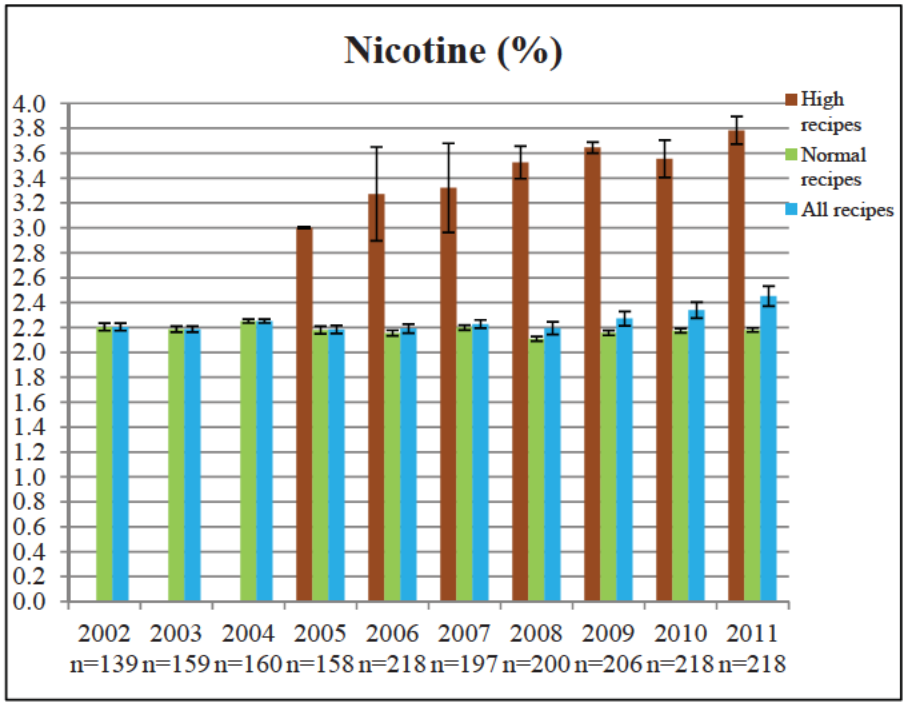


Figure 3-16. Average Nitrate Ion Content Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year

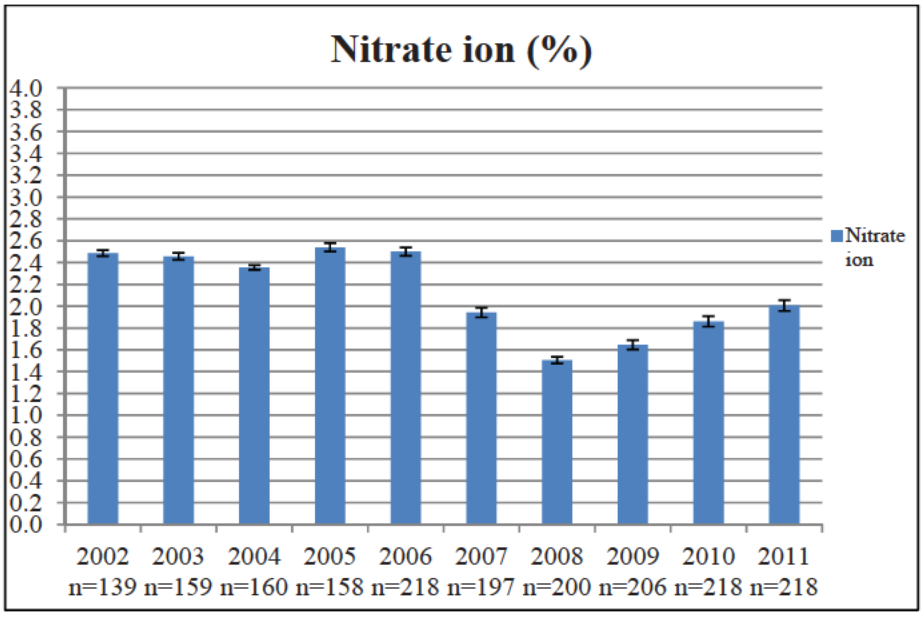


Figure 3-17. Average Sugar Content Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year

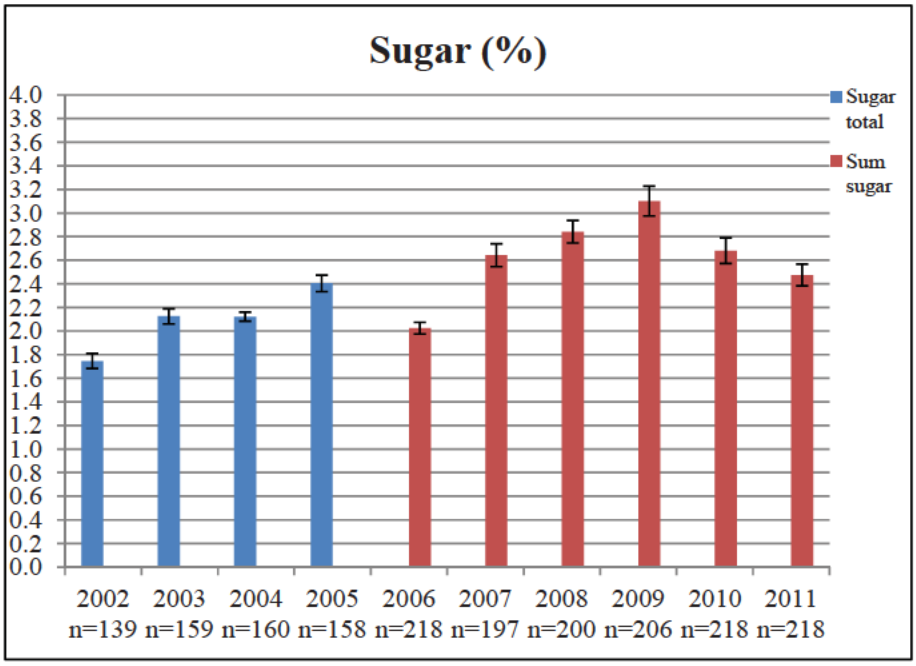


Figure 3-18. Average Nitrite Ion Content Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year

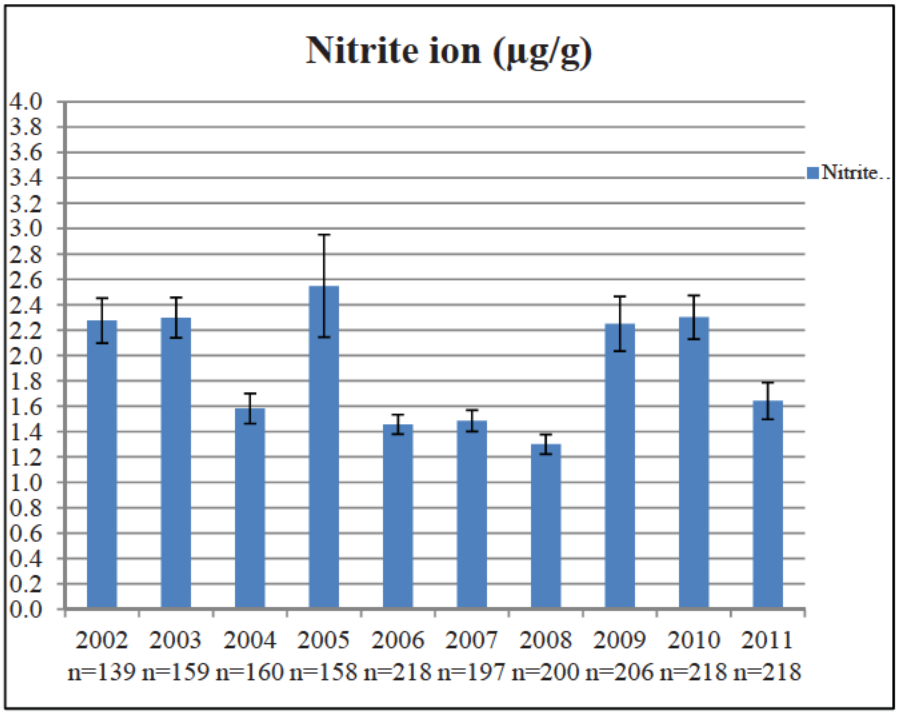


Figure 3-19. Average TSNA Content Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested per Year

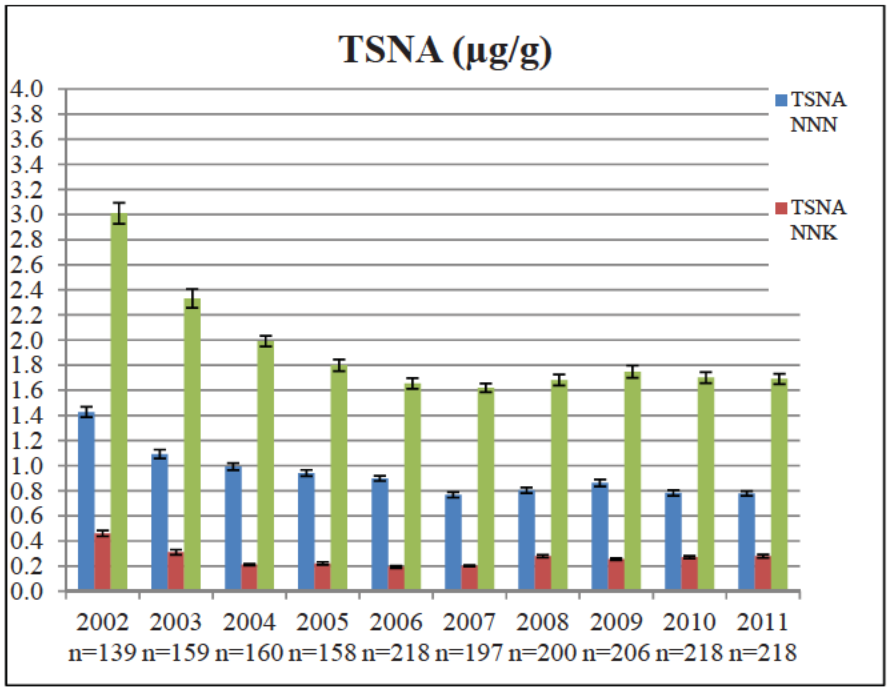


Figure 3-20. Average Content of Mycotoxins Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year

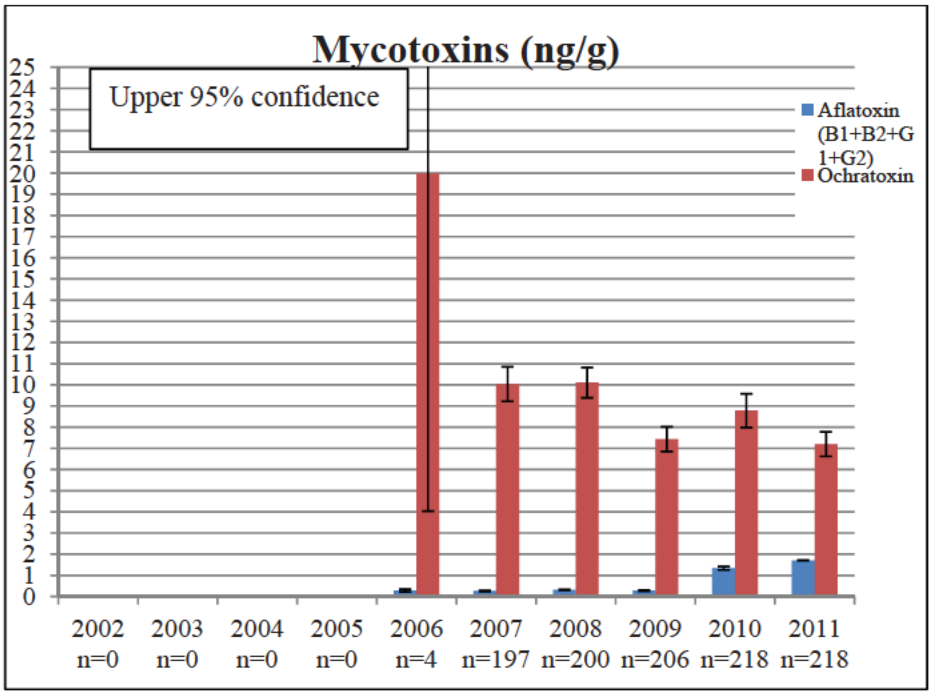
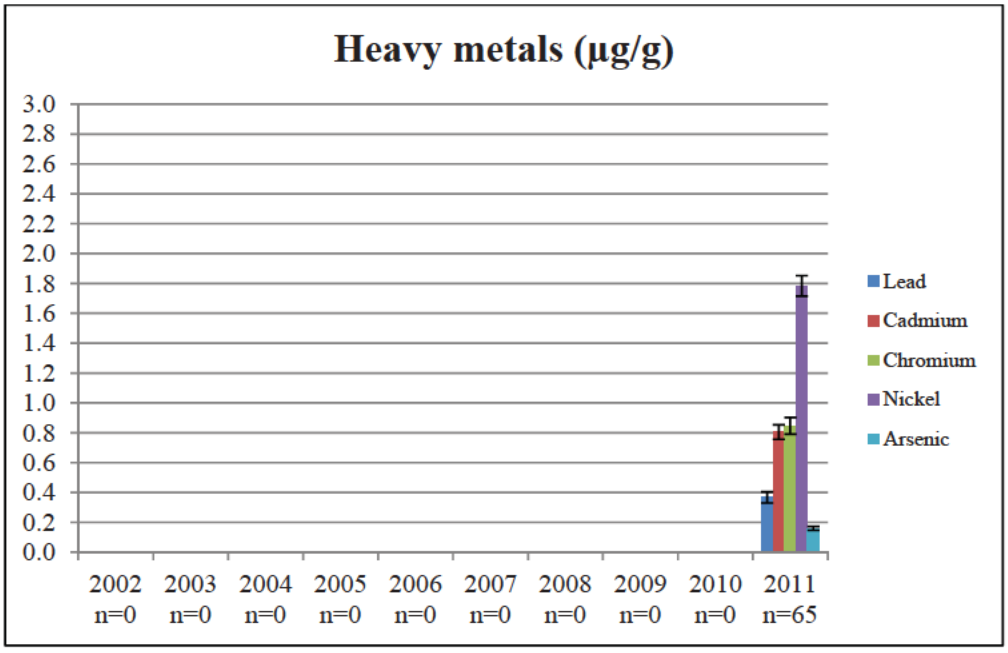


Figure 3-21. Average Content of Heavy Metals Together with 95% Confidence Intervals for the Total Number of Tobacco Blends (n) Tested Per Year



Chemical Quality Control Program – Finished Products: (b) (4)

(b) (4)

Sampling Procedure: (b) (4) . The products are stored in a refrigerator or freezer according to CORESTA guidelines. (b) (4)

(b) (4)

Table 3-27(
b

(b) (4)

Table 3-27. (b) (4)

(b) (4)

Analyte	Reason for inclusion
(b) (4)	

Analyte	Reason for inclusion
(b) (4)	

*TPSAC proposed list dated 07/07/2010

IARC Classification
(b) (4)

NTP Carcinogen Classification Abbreviations
(b) (4)

EPA Carcinogen Classification Abbreviation
(b) (4)

Chemical Quality Control Program in 2011: In 2011, a total of (b different snus products were tested (**Table 3.28**). (b) (4)

Table 3-28. Snus Products Tested in the Chemical Quality Program 2011

Snus product	SKU
(b) (4)	

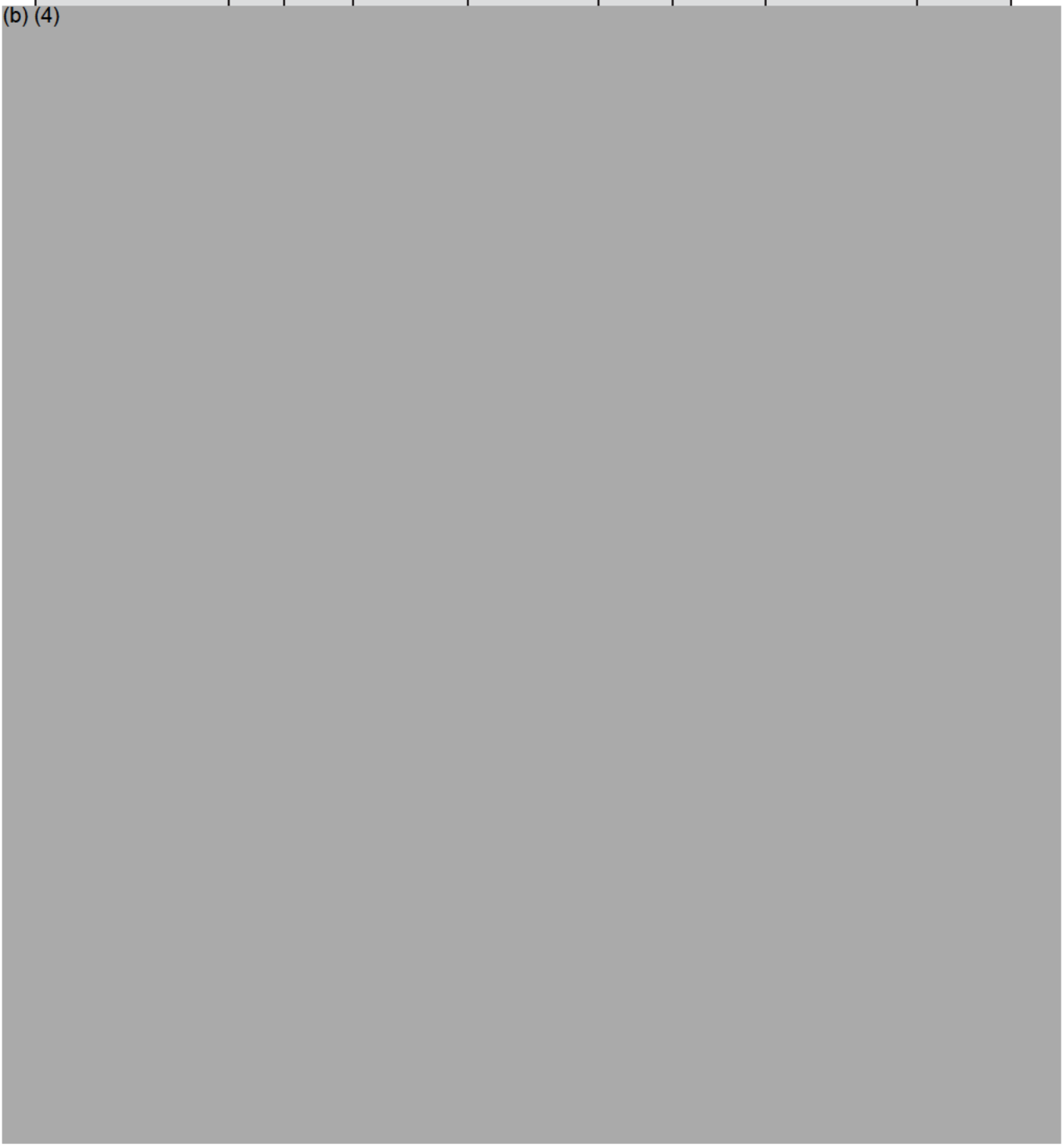
Snus product	SKU
(b) (4)	

Table 3-29. Results for Selected Analytes for Swedish Match Snus Products Tested in 2011 Chemical Quality Control (all results are from testing on dry weight products)

Compound	n	Min 2011	Mean 2011 (Mv ± 2 stdev)	Mean 2010 (Mv ± 2 stdev)	Max 2011	Median 2011	GOTHIATEK® limits	Internal limits
(b) (4)								

Compound	n	Min 2011	Mean 2011 (Mv ± 2 stdev)	Mean 2010 (Mv ± 2 stdev)	Max 2011	Median 2011	GOTHIATEK® limits	Internal limits

(b) (4)



Compound	n	Min 2011	Mean 2011 (Mv ± 2 stdev)	Mean 2010 (Mv ± 2 stdev)	Max 2011	Median 2011	GOTHIATEK® limits	Internal limits
(b) (4)								

(b) (4)

(b) (4)

(b) (4)

The chemical results for each product and analyte are presented in the report "Chemical Quality Control of Snus Products in 2011" (R&A Report No: 2012/02).

Table 3-30. (b) (4) **Table 3-29**. The results were in general similar to those presented in **Table 3-29**. (b) (4) (b) (4) . (b) (4)

The US products (b) (4) were tested according to the Swedish Match Agrochemical Management Program. Results are presented below under the heading "Agrochemical Residues in Tobacco and Snus Products."

Table 3-30. Chemical Results From 2011 for Snus Products Marketed by Swedish Match in the US ([redacted])

		General Loose n=4	General Dry Mint Portion Original Mini n=4	General Portion Original Large n=4	General Classic Blend Portion White Large n=3	General Mint Portion White Large n=4	General Nordic Mint Portion White Large n=4	General Portion White Large n=4	General Wintergreen Portion White Large
		4852	4800	4880	4878	4352	4875	4881	4882
[redacted]									

		General Loose n=4	General Dry Mint Portion Original Mini n=4	General Portion Original Large n=4	General Classic Blend Portion White Large n=3	General Mint Portion White Large n=4	General Nordic Mint Portion White Large n=4	General Portion White Large n=4	General Wintergreen Portion White Large
		4852	4800	4880	4878	4352	4875	4881	4882

(b) (4)

		General Loose n=4	General Dry Mint Portion Original Mini n=4	General Portion Original Large n=4	General Classic Blend Portion White Large n=3	General Mint Portion White Large n=4	General Nordic Mint Portion White Large n=4	General Portion White Large n=4	General Wintergreen Portion White Large
		4852	4800	4880	4878	4352	4875	4881	4882

(b) (4)

		General Loose n=4	General Dry Mint Portion Original Mini n=4	General Portion Original Large n=4	General Classic Blend Portion White Large n=3	General Mint Portion White Large n=4	General Nordic Mint Portion White Large n=4	General Portion White Large n=4	General Wintergreen Portion White Large
		4852	4800	4880	4878	4352	4875	4881	4882
[redacted]									

(b) (4)

Reporting of Harmful and Potentially Harmful Constituents ("HPHCs") to FDA in 2012: In March 2012, FDA requested that nine (9) of the constituents on FDA's established list of HPHCs be reported for smokeless tobacco products. The quantities of these constituents found in the ten (10) Swedish Match snus products marketed in the US were reported prior to September 22, 2012.

(b) (4)

All analyses were performed by Swedish Match, R&D, Chemical Analysis in Stockholm, which is a laboratory accredited for the testing of most of the HPHC analytes.

Table 3-31. Levels of Selected HPHCs in Snus Products Marketed by Swedish Match in the US According to a Report Submitted to FDA in 2012 (mean values with standard deviations are reported within parentheses)

		Loose snus product	Pouch snus products							
	Unit	General Loose (n=12)	General Dry Mint Portion Original Mini (n=18)	General Portion Original Large (n=18)	General Classic Blend Portion White Large (n=18)	General Mint Portion White Large (n=12)	General Nordic Mint Portion White Large (n=18)	General Portion White Large (n=18)	General Wintergreen Portion Large (n=18)	Unit
SKU		**4852**	**4800**	**4880**	**4878, 4877**	**4352**	**4875, 4876**	**4881**	**4882**	
Pouch weight	G		0.335 (0.0136)	0.981 (0.0189)	0.870 (0.0746)	0.999 (0.0477)	0.900 (0.0141)	0.966 (0.0523)	0.977 (0.0524)	
Acetaldehyde	µg/unit of use	12.6 (1.42)	2.50 (0.709)	13.9 (2.24)	11.6 (1.40)	16.9 (5.39)	10.5 (1.84)	17.3 (4.84)	13.4 (2.60)	µg/g
Arsenic	µg/unit of use	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	<0.10 (0.00)	µg/g

BaP	ng/unit of use	<0.6 (0.0953)	<0.6 (0.00)	<0.6 (0.00)	<0.6 (0.199)	<0.6 (0.218)	<0.6 (0.00)	<0.6 (0.00)	<0.6 (0.00)	ng/g
Cadmium	µg/unit of use	0.190 (0.0387)	0.107 (0.00923)	0.197 (0.0110)	0.243 (0.0274)	0.210 (0.0175)	0.231 (0.0225)	0.229 (0.0159)	0.235 (0.0241)	µg/g
Crotonaldehyde	µg/unit of use	<0.25 (0.00)	<0.25 (0.00)	<0.25 (0.00)	<0.25 (0.0485)	<0.25 (0.00)	<0.25 (0.00)	<0.25 (0.00)	<0.25 (0.00)	µg/g
Formaldehyde	µg/unit of use	4.89 (0.369)	3.31 (0.582)	6.33 (0.883)	6.92 (0.765)	6.56 (0.853)	6.15 (1.26)	6.03 (0.750)	4.99 (0.663)	µg/g
Nicotine (Free)	mg/unit of use	5.64 (0.107)	0.973 (0.269)	6.21 (0.295)	5.69 (0.433)	6.39 (0.346)	5.66 (0.252)	6.37 (0.402)	6.43 (0.374)	mg/g
Nicotine (Total)	mg/unit of use	7.04 (0.116)	4.95 (0.205)	7.54 (0.240)	6.66 (0.540)	7.16 (0.441)	6.85 (0.305)	7.37 (0.426)	7.62 (0.436)	mg/g
NNK	µg/unit of use	0.0911 (0.00902)	0.0923 (0.0639)	0.106 (0.0130)	0.144 (0.0147)	0.142 (0.00635)	0.162 (0.0188)	0.143 (0.0155)	0.151 (0.0186)	µg/g
NNN	µg/unit of use	0.215 (0.0109)	0.332 (0.213)	0.273 (0.0145)	0.291 (0.0225)	0.301 (0.0200)	0.315 (0.0250)	0.313 (0.0207)	0.336 (0.0332)	µg/g

Historical data collected from the Chemical Quality Control Program from 2002 to 2011 are shown in **Figures 3-22 to 3-28**. All data are on dry weight basis. A long term strategy to continuously reduce the level of TSNA has resulted in low and stable TSNA levels (<2 µg/g) since 2003-2004 (**Figure 3-22**). The level of B(a)P has been low since the use of fire-cured tobacco was discontinued in the late 1990s (Rutqvist et al. 2011). The low levels of B(a)P found in the products in recent years (1- 2 ppb) are probably due to environmental pollution of the raw tobacco (**Figure 3-23**). Nitrite content has been consistently below 3 µg/g which accords with the GOTHIATEK® limit (**Figure 3-24**). The levels of the five (5) GOTHIATEK® metals have remained stable over the past decade, and all values are below the GOTHIATEK® limits (**Figure 3-25**). The content of NDMA has consistently been below 1 ng/g (**Figure 3-26**).

The average nicotine content and pH value in all Swedish Match snus products has been constant over the past decade (**Figures 3-28** and **Figures 3-29**).

Figure 3-22. Average Content of TSNAs (NNN, NNK, and Total TSNAs) based on dry weight in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated)

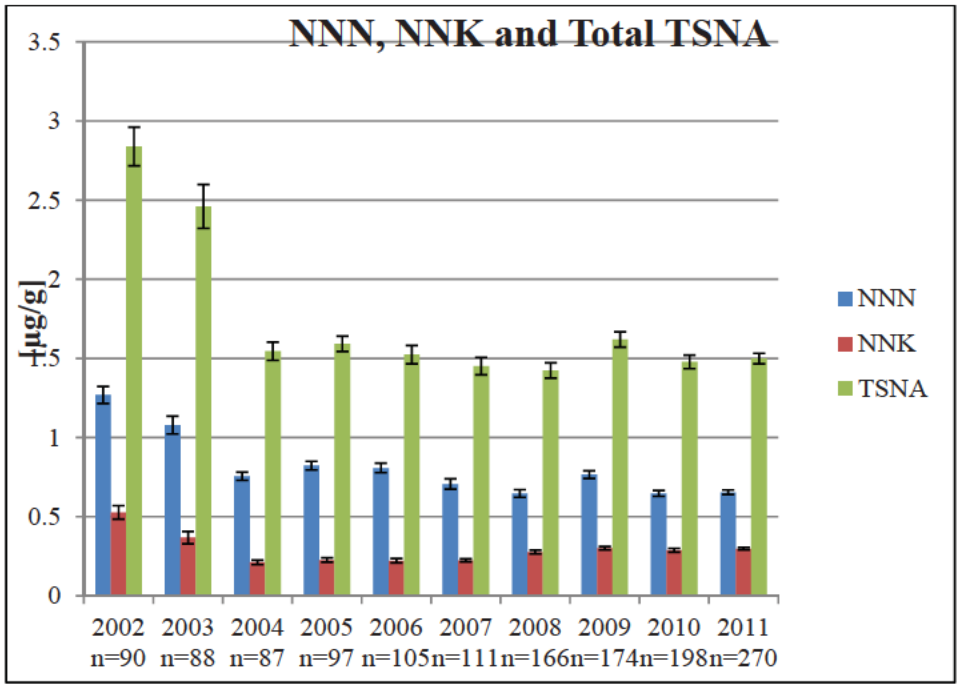


Figure 3-23. The Average Content of B(a)P, based on dry weight, in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated)

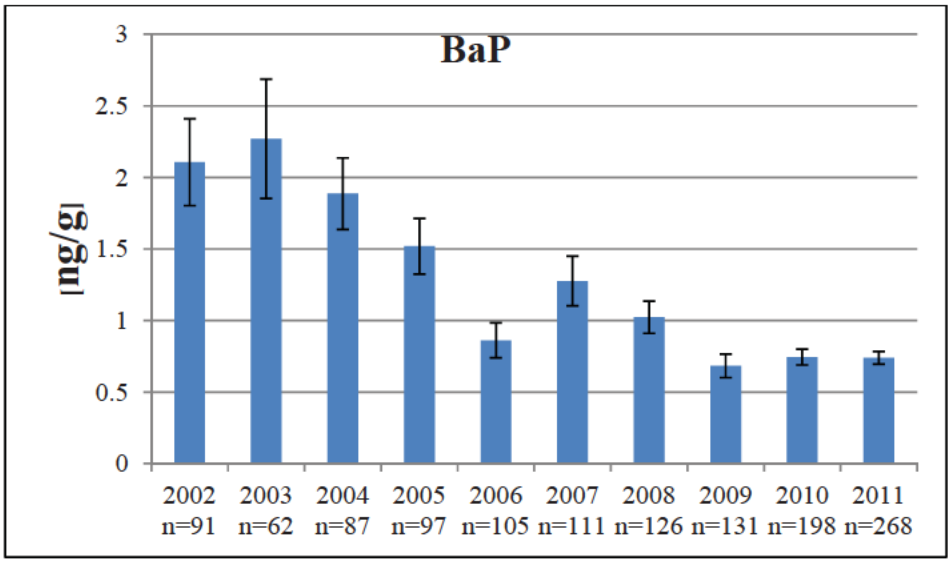


Figure 3-24. **The Average Content of Nitrite Ion, based on dry weight, in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated).**

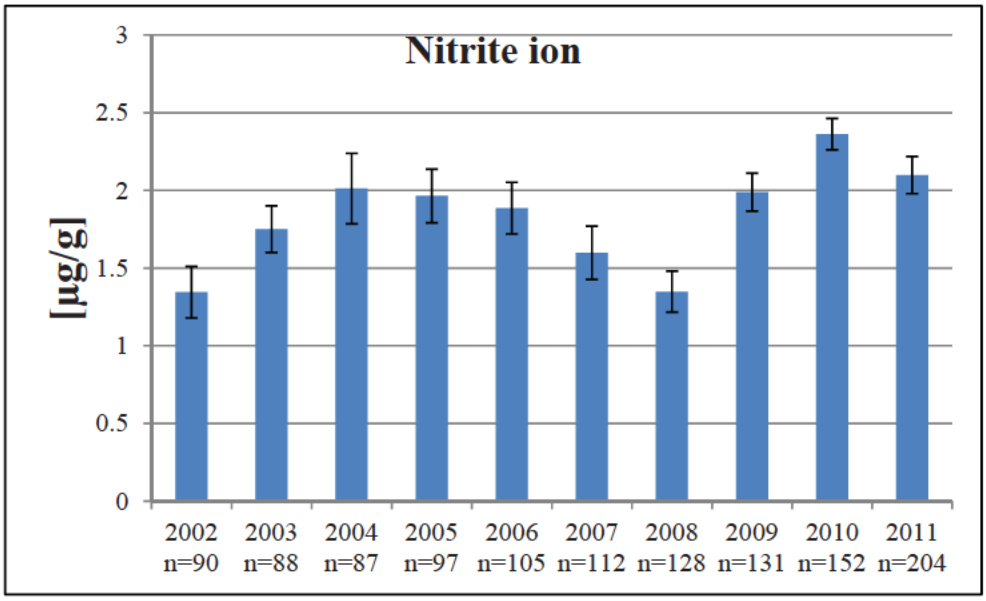


Figure 3-25. **The Average Content of Selected Metals, based on dry weight, in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated)**

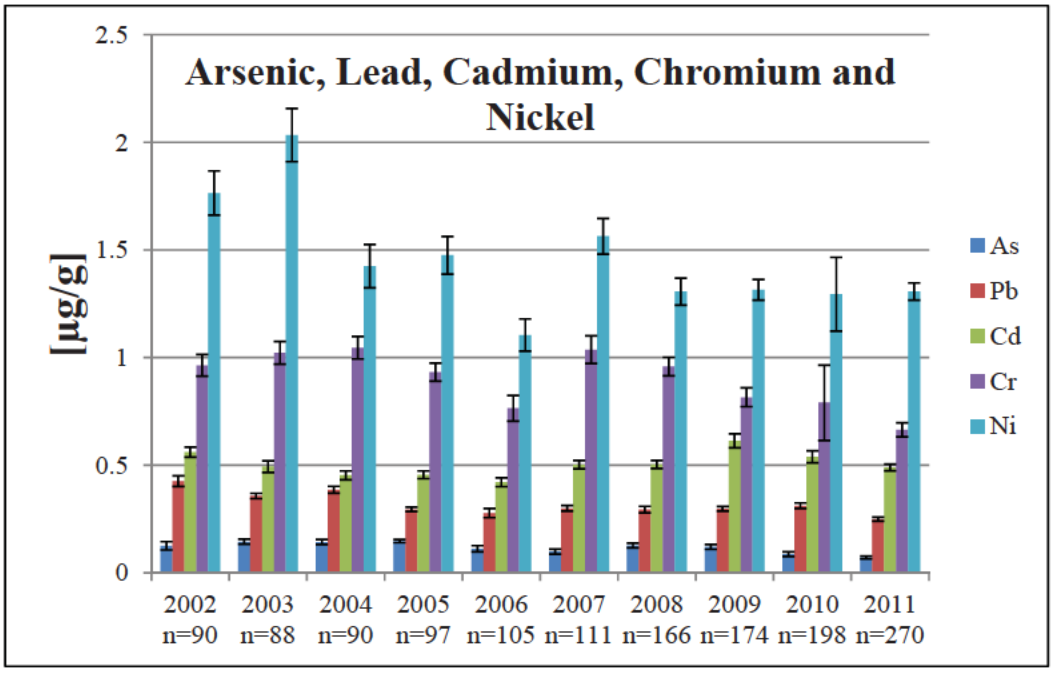


Figure 3-26. The Average Content of NDMA, based on dry weight, in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated)

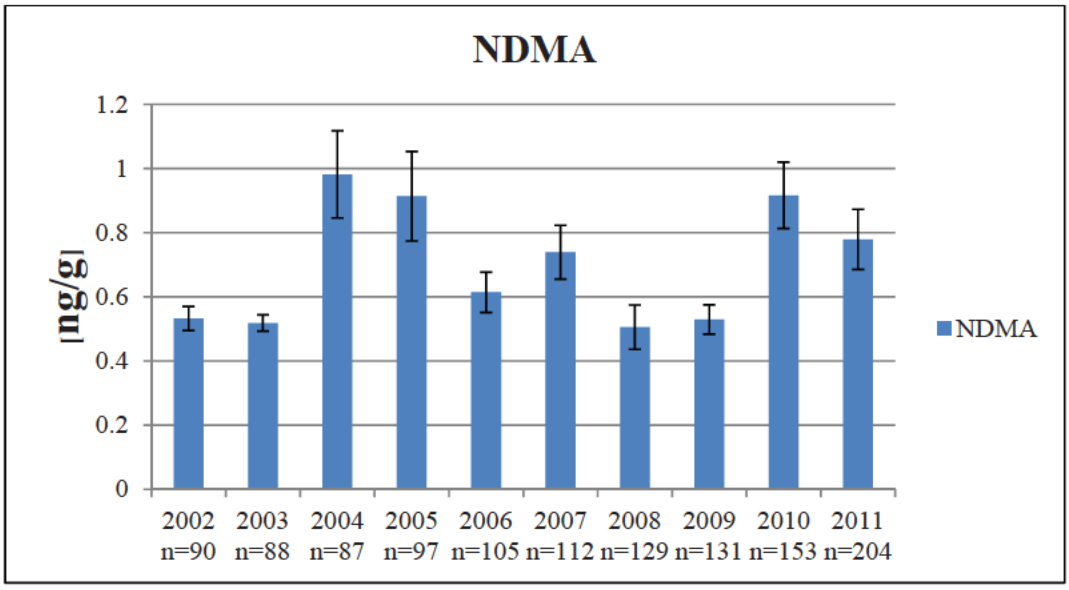


Figure 3-27. The Average Content of Nicotine in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated).

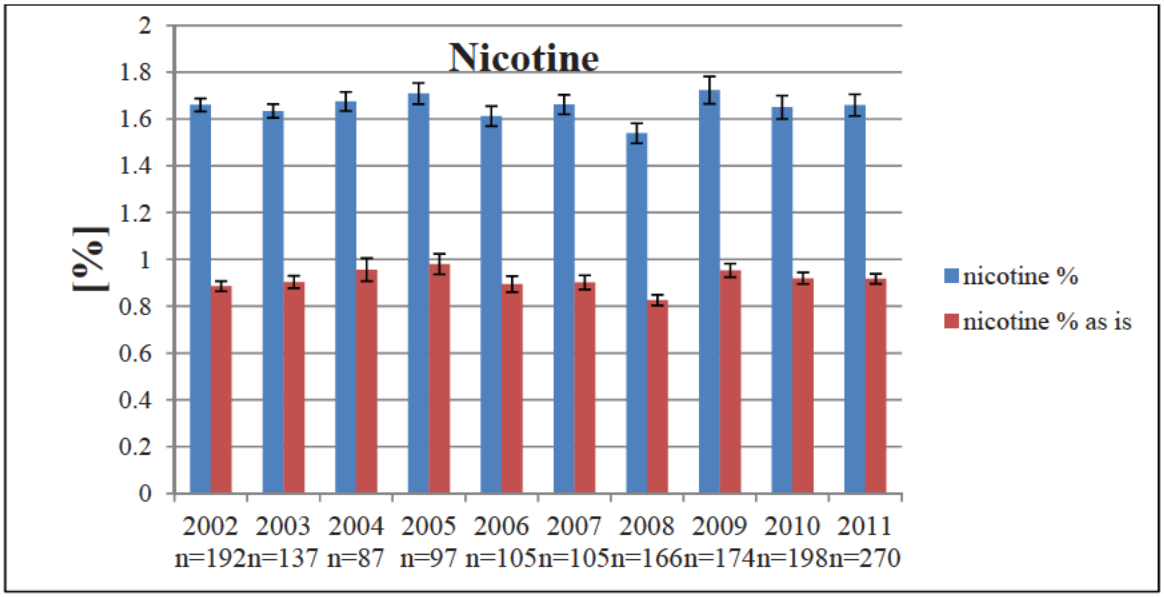
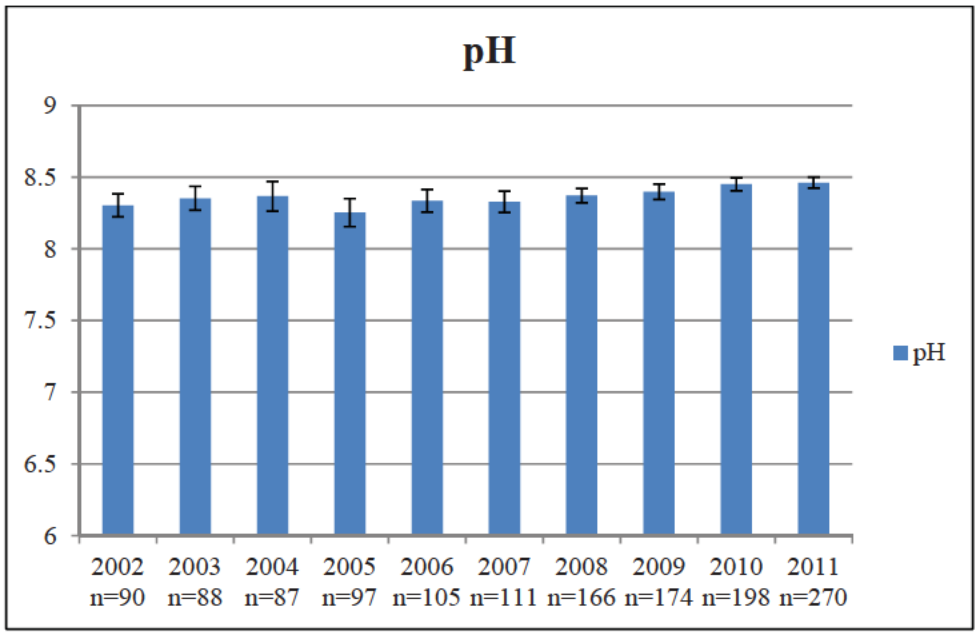


Figure 3-28. The Average pH Level in All Snus Products Included in Swedish Match's Chemical Quality Program From 2002-2011 (the number of tested products (n) and 95% confidence intervals are indicated)



Brands Testing Program of Snus Products: Brands testing of Swedish Match snus products has been performed annually since 1988. (b) (4)

(b) (4)

2011 Brands Testing Program of Swedish Match Snus Products: In 2011, the Brands Testing Program included (b (b) (4) snus products produced by Swedish Match (*Brands Testing 2011,*

In 2011, (b) (4)

(b) (4) (b) (4)

(b) (4)

Table 3-32. Results of the 2011 Brands Testing Program for Analytes Tested in (b) (4) Snus Products. All data presented are on dry weight except when otherwise stated.

Analyte	Min	Arithmetic Mean	Max	n
(b) (4)				

Analyte	Min	Arithmetic Mean	Max	n
(b) (4)				

Analyte	Min	Arithmetic Mean	Max	n
(b) (4)				

Analyte	Min	Arithmetic Mean	Max	n
Water activity	(b) (4)			
Water content [%]				
Moisture [%]				
Unit Weight [g]				

*4 PAHs suggested by EU, B(a)A, B(b)F and Chrysene + BaP.
BDL: Below Detection Limit

As of 2012, all Swedish Match snus products currently marketed in the US are included in the Brands Testing Program. **Table 3-33** summarizes the results for these products. (b) (4)
(b) (4)

Table 3-33. 2012 Brands Testing Program Results for Swedish Match Snus Products Marketed in the US

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882
(b) (4)									

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882

(b) (4)

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882

(b) (4)

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882
(b) (4)									

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882

(b) (4)

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882
(b) (4)									

Analyte	Unit	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
		4852	4800	4880	4877, 4878	4352	4876, 4875	4881	4882
(b) (4)									

All values are given on a dry matter basis unless otherwise stated.

3.2.3.5.2. Additional Chemical Quality Control Measures

Swedish Match Agrochemical Residue Management Program:

Swedish Match has established an Agrochemical Residue Management Program that includes a formalized process for inclusion of agrochemicals to be tested, decisions about Guidance Residue Limits ("GRLs"), and procedures concerning the company's stewardship and dealing with agrochemical residues in raw tobacco and snus products.

(b) (4)

(b) (4)

The agrochemicals included for testing under the Agrochemical Residue Management Program (pesticides, fungicides, and herbicides) are either:

- (b) (4)
-
-
-

(b) (4)

Swedish Match's procedure for setting agrochemical GRLs: (b) (4)

. When setting a GRL for a particular agrochemical, the following circumstances are considered and the lowest value is selected:

- (b) (4)
-
-
-

(b) (4)

(b) (4)

The list of agrochemicals and Swedish Match internal GRLs for tobacco and oral smokeless tobacco products in 2012 is presented in Section 7 of the SM GOTHIATEK Report 2013. The list comprises about 200 agrochemical residues known to be used on tobacco worldwide. About 170 of those residues for which there are available and certified analytical methods are included in the GOTHIATEK® standard.

(b) (4)

All testing of agrochemical residues in raw tobacco (as well as in finished products) is done at the Swedish consultant laboratory "Eurofins AB" in Lidköping, Sweden. Eurofins AB is a certified laboratory contracted by the National Food Agency in Sweden to perform testing in food products. It uses methods approved by the Swedish National Food Agency which are developed and validated for agrochemical analyses of food, and which have been modified for the analysis of tobacco and tobacco products.

(b) (4)

(b) (4)

(b) (4)

Agrochemical Residues in 2011: (b) (4) (different agrochemical residues were found in 2011 (**Table 3-34**). (b) (4)

b

Table 3-34. Frequency of Agrochemicals Found in (b) Snus Products Tested in 2011

Agrochemical residue	Found	
	Frequency	Freq. > GRL
(b) (4)		

Agrochemical residue	Found	
	Frequency	Freq. > GRL
(b) (4)		

The snus products marketed in the US were tested in 2011 for approximately 340 agrochemical residues. The results are presented in **Table 3-35**. All detected agrochemicals had levels below Swedish Match's internal GRLs. One agrochemical which does not have a Swedish Match GRL value, mandipropamide (0.016 µg/g), was detected in the General Nordic Mint PSWL) product.

Table 3-35. Agrochemical Residues Found in 2011 in Snus Products Marketed in the US

SKU	Product	Agrochemical	Amount (µg/g)	SM GRL (snus) (µg/g)
4852	General Loose	(b) (4)		
4800	General Dry Mint Portion Original Mini			

SKU	Product	Agrochemical	Amount (µg/g)	SM GRL (snus) (µg/g)
		(b) (4)		
4880	General Portion Original Large			
4877	General Classic Blend Portion White Large			

SKU	Product	Agrochemical	Amount (µg/g)	SM GRL (snus) (µg/g)
		(b) (4)		
4876	General Nordic Mint PSWL			

SKU	Product	Agrochemical	Amount (µg/g)	SM GRL (snus) (µg/g)
4352	General Mint Portion White Large	(b) (4)		
4875	General Nordic Mint Portion White Large			

SKU	Product	Agrochemical	Amount (µg/g)	SM GRL (snus) (µg/g)
4881	General Portion White Large	(b) (4)		
4882	General Wintergreen Portion White Large			

(b) (4)

Historical data (b) (4)

(b) (4) (Table 3-36).

Table 3-36. Frequency of Detected Residues and Total Residue Amount in Two Snus Products From 2002-2011

SKU Product	Year	No. of found residues	No. of analyzed residues	Total amount of residue (µg/g)
(b) (4)				

SKU Product	Year	No. of found residues	No. of analyzed residues	Total amount of residue (µg/g)
(b) (4)				

3.2.3.6. Hygiene, Cleaning, and Vermin Control

In Sweden, snus is regulated as a food product according to the Swedish Food Law. The manufacturing of the snus products marketed in the US therefore complies with the same regulatory requirements as those for Swedish food stuffs. In particular, Swedish Match's manufacturing process complies with the Swedish Food Regulations, Food Act, as well as the Swedish Food Agency Directives on Snus and Chewing Tobacco, and on Drinking Water, SLVFS 2011:3. It also complies with EU requirements for hygiene of foodstuffs. More details are found in Section 5 of the SM GOTHIATEK Report 2013.

To meet the requirements of these regulations, Swedish Match applies a comprehensive hygiene and environmental control program that consist of hygiene rules, cleaning procedures, and vermin control. The various aspects of the program, including processes, descriptions, procedures, and protocols, are described in QEMS.

Swedish Match classifies heat-treatment and packaging process areas as hygiene zones subject to strict hygiene rules and specific procedures for employees and process equipment. All employees involved in product production are trained in food hygiene and Hazard Analysis and Critical Control Points ("HACCP").

In addition, process equipment is adapted such that the criteria for the manufacturing of food stuffs are satisfied. Cleaning and maintenance operations are therefore critical in equipment and process design. Machines, process equipment, and production premises are cleaned daily. Cleaning routines are described in the QEMS documents.

A HACCP program designed in accordance with "Codex Alimentarius CAC/RCP 1-1969" is implemented in all production stages.

Actions and precautions that are taken during the tobacco grinding processes to fulfill hygiene requirements set by the Swedish food regulations and internal rules include daily cleaning with removal of dust and tobacco waste and mechanical cleaning of floor surfaces. In addition, the

following actions and precautions are taken during the heat-treatment and packaging processes to fulfill the hygiene requirements:

- Daily cleaning of floor surfaces;
- Microbiological testing of equipment and packaging material intended to be in contact with the product;
- Microbiological testing of room air; and
- Cleaning of equipment after every production batch.

The automatic cleaning programs for the equipment in the heat treatment and packaging processes comprise (b) (4)

To prevent microbiological contamination in the heat-treatment and packaging process areas, microbiological activity is checked on equipment surfaces and in the ambient air. The testing of microbiological activity on equipment surfaces is done to verify the efficacy of the cleaning process.

The occurrence of vermin is checked according to an internal vermin control program as well as by an external contractor. Swedish Match's indoor vermin control program includes checks of the occurrences of rats, mice, tobacco bugs, flying insects, and birds at different sites within the production area. An outdoor environmental control program is also implemented to help prevent the occurrence of rats, mice and birds inside the factories.

Traps are installed in different parts of the factories to prevent and alert of infestations. These include:

- Pheromone traps for the detection of tobacco bugs;
- Mice traps; and
- Halogen traps for flying insects.

3.2.3.7. Traceability and Recall Processes

3.2.3.7.1. Internal Tracking Processes

Swedish Match has established internal processes and inventory management controls that track ingredients,[37] components, packaging, and labels through their receiving, manufacturing and holding activities. Various functional units, including procurement, regulatory affairs, R&D,

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[37] Ingredients are defined as raw materials and additives per Directive 2000/12/EC of the European Parliament and of the Council of 20 March 2000 on the approximation of the laws of the Member States relating to the labeling presentation and advertising of foodstuffs.

engineering, production, quality control, logistics, storage and affiliate companies work together to ensure internal traceability. Swedish Match's traceability processes comply with EU regulations as well as with the Swedish Food Agency directives on snus and chewing tobacco. More detailed information is provided in Section 9 of the SM GOTHIATEK Report 2013. Swedish Match's GOTHIATEK® standard further stipulates that manufacturing processes must comply with Swedish laws on food production and must meet the requirements of the quality standard ISO 9001:2000.

In addition, the Swedish general food law requires manufacturers to follow "Codex Alimentarius, General Principles of Food Hygiene CAC/RCP 1-1969," which is an internationally recognized process for food safety. The Hazard Analysis Critical Control Point (HACCP) based quality assurance system ensures that employees are HACCP qualified, that each critical control point of the production chain is identified, and that the critical control limits are determined, monitored and recorded. Swedish Match's HACCP program addresses microbiological, chemical and physical potential hazards and has established appropriate controls for hazards identified as reasonably likely to occur during manufacturing. Further, hygiene procedures require pre- and post-processing contamination prevention activities. Control measures for metal fragments are established and involve the use of on-line metal detection equipment and daily equipment checks. After heat treatment, contamination is prevented by the use of a closed tubing system. Production approval of the manufacturing, packaging and labeling are documented and records are stored.

The minimum requirement for traceability is that each traceable unit be uniquely labeled and thus capable of being identified. Toward this end, Swedish Match uses a standardized graphic that is machine- and human-readable and which conforms to recognized international standards. This graphic has a batch identification number and displays the product's "best before" date. The batch identification number contains the product information that Swedish Match considers relevant for traceability of the final tobacco product, and which would be used in the event of a recall. This batch number references the tobacco product itself and the items contained within it.
(b) (4)

What follows are examples of the labels that Swedish Match uses for cans, rolls, and cases (in this example, for the Snus Product, General Wintergreen Portion White Large):

3.2.3.7.1.1. Can Label

The batch number is affixed via a round, paper adhesive sticker to the bottom of each can. All inks and adhesives are approved for indirect food contact. In addition, the adhesives have size requirements, are self-adhesive, and in some cases are synthetic to withstand moisture. These markings are used as part of the traceability process. More details of the snus packaging process can be found in Section 8 of the SM GOTHIATEK Report 2013.

A product's can label displays key elements of the product, including the best before date, the batch number, and a letter that identifies the manufacturing facility. In the example below, 01 24

2014 is the best before date, 14129 is the batch number, and K is the letter that identifies the manufacturing facility (i.e., K represents the Kungälv factory). The remaining numbers on the label (i.e., 50, 1, and 3 in the example below) represent the production line, the shift and the labeling machine, respectively, used to produce the can.

Figure 3-29. Can Label

3.2.3.7.1.2. Roll Label

Cans are packaged into a roll and a white label is affixed to the side of the roll. The key elements of the roll label are the product name and the machine- and human-readable GTIN 128 code combination number, which includes the batch number. The key elements of the roll label example shown below are as follows:

Internal Item no:	4882
Info:	Keep refrigerated
DC No:	8878
Product Name:	General Wintergreen
UPC- Code:	6 09249 64024 6
GTIN 128 Code:	(01)073 10870148829(10) 0351375014129

Figure 3-30. Roll Label

3.2.3.7.1.3. Case Label

Rolls are placed into a case and a white label with a yellow frame is affixed on top. Case labels enable trading partners to identify products. A case label shows the product's identification information including the product name, the batch number, the best before date and the GTIN number (GS1-128) in bar code and human readable form. The GTIN code allows the case to be identified quickly at any point in the supply chain, both manually and electronically. It links to the master item data file kept by Swedish Match in Sweden.

The key elements of the case label example shown below are as follows:

Place of Issue:	4882
Production week and day:	V36-5
Current production time:	09:51
Country:	United States
Product Name:	General Wintergreen
DC Number:	640530
Item no:	640530
Batch No:	035137 (production order number) 501 (50 = Line 550, 1=shift 2) 4129 (heat treatment batch no)
Best before:	01.24.2014 (MMDDYYYY)
PCS (Number of packages):	18
UPC Code:	6 09249640536
GTIN Code 128:	(02) 07310870148829 (37) 18 (10) 0351375014129

Figure 3-31. Case Label

Visual product audits of the batch number are performed before the tobacco product is packed into a case. Reference products from the same batch are maintained past the best before date to permit investigational analyses if necessary. These reference samples are kept in the same container and closure system as a finished tobacco product, and are stored in a secured refrigerator.

The logistic unit is a pallet composed of cases. This unit has a GTIN code that is located on the pallet label, and constitutes the traceable and identifiable unit that can be identified in the event of a recall.

3.2.3.7.2. Coordination with External Partners

Swedish Match has established and maintains inventory management controls with external trading partners. Swedish Match's suppliers are obligated to satisfy EU regulations and Swedish Match's internal specifications. Suppliers are evaluated and approved by a documented evaluation process and major suppliers are periodically audited.

The receiving process is managed by trained employees who visually verify and ensure that specifications are consistent with the purchase orders. (b) (4)

(b) (4)

Flavor suppliers are evaluated for conformance with EU and Swedish regulations and Swedish Match's internal requirements. (b) (4)

Logistic units are transported by a third-party logistic carrier on trucks to Landvetter Airport, Gothenburg, Sweden. An airline, usually (b) , is contracted to fly the shipments to the United States. (b) (4)

Upon the arrival at the Owensboro facility, each logistic unit is received, segregated in the warehouse and scanned into the Dynamic AX system to verify the contents of the shipment by batch number and quantity. Quality control staff review, approve and release the logistic unit both electronically and manually. Nonconforming products are quarantined in a secured cage area.

(b) (4)

(b) (4)

Orders are shipped to distributors and retailers using one of two different modes of shipping. Third-party logistic carriers are used to transport products to distributors and retailers that are

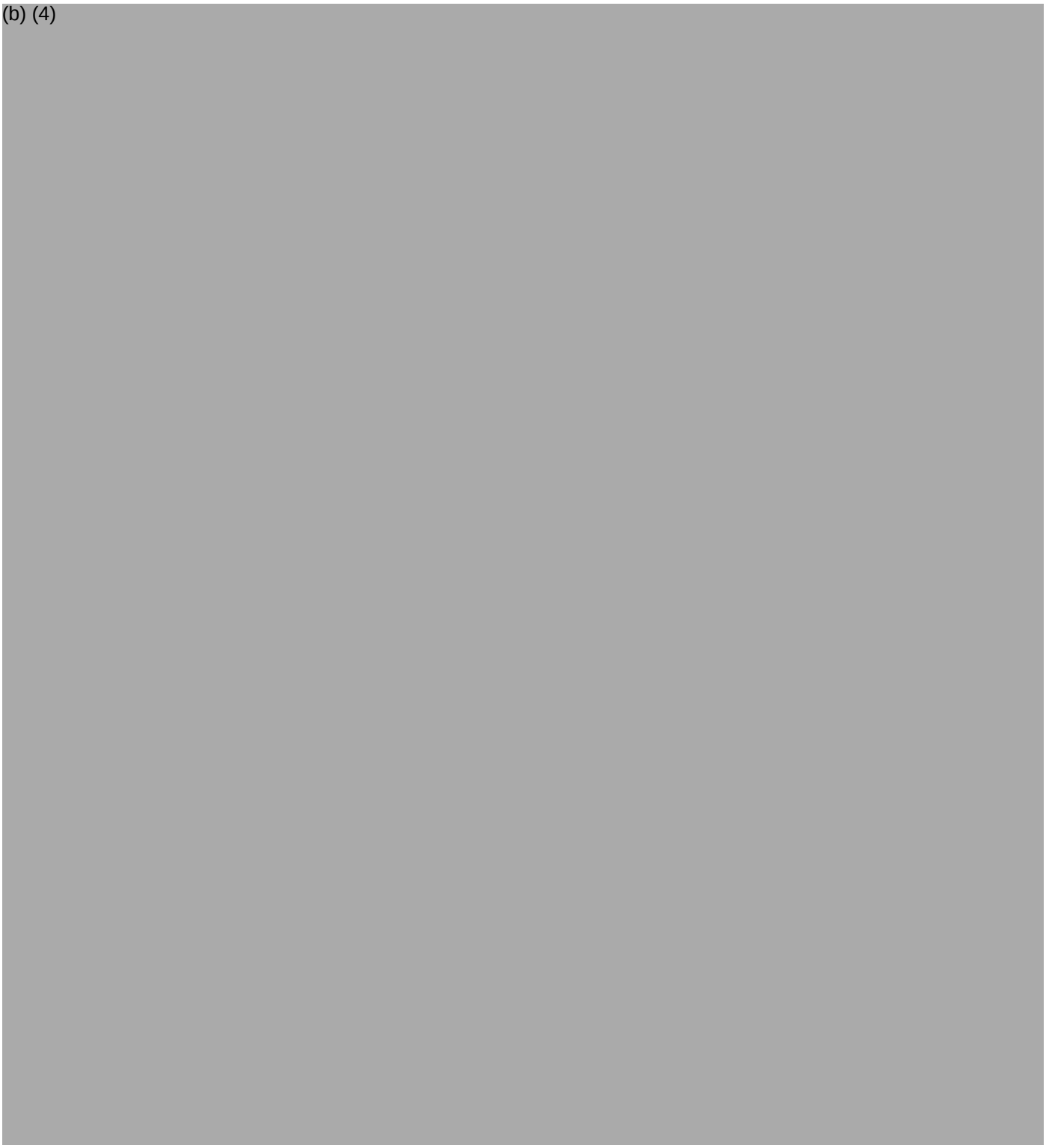
high volume customers. The bill of lading identifier links the shipment to the Dynamic AX picking list, and consequently also to the batch number and corresponding information. Low-volume product orders are shipped via UPS. The UPS airway bill number is linked to the batch number. For both shipping methods, signed proofs of delivery are required, and Swedish Match Owensboro maintains a list of consignees and corresponding contact information. External and internal audits are performed to verify inventory accuracy of orders.

Swedish Match also implements and maintains disposition processes to remove non-conforming, elapsed, unwanted, or unused components, packaging and labels at its Gothenburg and Kungälv manufacturing facilities to prevent their use in manufacturing. In addition, final products that do not meet specifications after being manufactured, packaged and labeled and that have not been delivered for introduction into commerce are quarantined. These processes are based on Swedish Match's internal requirements of responsibility, certification, safety and security. The processes futher meet all applicable local and federal regulations and laws. (b) (4)

Swedish Match implements and maintains similar disposition processes to remove nonconforming, elapsed, unwanted or unused product at its Owensboro, Kentucky, manufacturing facility. These processes are based on Swedish Match's internal requirements of responsibility, safety and security. Further, they meet all applicable local, state, and federal regulations. (b) (4)

Figure 3-32. Traceability Chain

(b) (4)



3.2.3.7.3. Recalls

Each snus can features the identity of the product, batch number, best before date, and Swedish Match's contact information. In the event of a recall, Swedish Match will use the product's batch number, and a combination of automated and manual processes to accurately identify the affected snus products.

For products sent to Swedish Match's Owensboro, Kentucky, manufacturing facility, the contact information on the product cans includes the relevant phone number for the US Consumer Contact Center (the "Contact Center"). Thus, all US consumer contacts are initiated at the Contact Center (Product Recall, QP 8.3.3) which, in turn, uses the original batch number on the reported can for traceability in the United States and in Sweden.

The Contact Center is staffed by quality control employees who are trained in the customer complaint handling process. A recall process review is routinely initiated when the Contact Center receives three complaints about defects in the same brand with the same production date and production code. Defective products may include products that:

- do not match the product specifications;
- have the wrong smell or taste;
- have microbiological activity above the upper limit value;
- have an incorrect date of production listed on the product;
- are adulterated in a way that might increase toxicity; or
- any other reasonable cause.

Any information collected from the consumer is compiled and sent to Swedish Match North Europe AB. There, Swedish Match has a cross-functional team that serves as a recall group (the "Recall Group"). This group performs recall assessments on a case-by-case basis, and all decisions are documented. The root cause of the defect is determined and preventative actions are considered. The Recall Group determines whether a recall will occur and how information regarding the defect will be relayed. In particular, it decides whether to recall the product and/or take some other customer/consumer-facing action. Ultimately, the Recall Group formulates the information that is to be provided to customers, consumers, and the Consumer Contact Center. The process is documented and follow-up is monitored.

If a deficiency in product quality is considered to be potentially harmful to an individual consumer's health, or if for any other reason a consumer should be contacted, the decision and related information will be communicated internally by the recall team to all departments and units concerned.

3.2.4. A description of how the design, materials, ingredients, and heating source (if applicable) combine to produce the final products

A detailed description of how the tobacco, ingredients and packaging are combined is provided in above in Sections 3.2.1 – 3.2.3.

3.2.5. A quantitative description of the performance criteria for the tobacco products (e.g., burn rate, ventilation criteria, dissolution rate).

3.2.5.1. Snus Blends

(b) (4)

The analyses are performed in accordance with the respective analytical procedures described in Subsection 3.2.3.5.1 of this Application.

(b) (4)

(Table 3-37). (b) (4)

.

(b) (4)

Table 3-37. Specifications of Snus Blends (After Processing but Before Packaging)

	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
	4852	4800	4880	4878, 4877	4352	4875, 4876	4881	4882
Moisture (%)	(b) (4)							
• Target								
• Toleranc								
pH								
• Target								
• Toleranc								

	General Loose	General Dry Mint Portion Original Mini	General Portion Original Large	General Classic Blend Portion White Large	General Mint Portion White Large	General Nordic Mint Portion White Large	General Portion White Large	General Wintergreen Portion White Large
Water activity	(b) (4)							
• **Max**								

3.2.5.2. Finished products

(b) (4)

3.2.5.2.1. Loose snus

(b) (4)

3.2.5.2.2. Portion Snus

(b) (4)

(b) (4)

Table 3-39. Edana Test Methods

	Supplier Test Method	EDANA Method	Unit	Target	Tolerance
For all widths					
Base Unit Weight	(b) (4)				
Thickness (E)					
Dry MD Tensile					
Wet MD Tensile					
Wet TD Tensile					
Heat seal					
Web quality					

(b) (4)

There is no EU legislation on pouch materials used in smokeless tobacco products. Some ingredients in the pouch material are considered plastic materials and must therefore fulfill the EU-regulation 10/2011, which concerns plastic materials and articles intended to come in contact with food. There are also regulations concerning pouch materials issued by FDA, as well as recommendations from the BfR Federal Institute for Risk Assessment in Germany.

Swedish Match requires that pouch paper suppliers certify that paper and all in-going components conform to relevant EU and FDA regulations. Therefore, the pouch material and its ingredients must fulfill the requirements in the following directives:

- US FDA 21 CFR 176.170: Components of paper and paperboard in contact with aqueous and fatty foods;
- US FDA 21 CFR 176.180: Components of paper and paperboard in contact with

dry foods;

- US FDA 21 CFR 173.340: Secondary direct food additives permitted in food for human consumption (Defoaming agents);
- US FDA 21 CFR 175.105: Indirect Food Additives: Adhesives and components of coatings (Adhesives);
- BundesInstitüte für Risikobewertung, BfR; BfR XXXVI paper and board for food contact;
- Regulation (EC)1333/2008 OF THE EUROPEAN PARLIAMENT AND THE COUNCIL of 16 December 2008 on food additives;
- LIVSFS 2012:6, Livsmedelsverkets föreskrifter om snus och tuggtobak (Swedish National Food Agency´s directive on snus and chewing tobacco);
- COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food (replaces 2002/72/EG); and
- Color Additive Status Listing: http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm106626.htm.

The film used directly to wrap the bobbins with the pouch material complies with the Commission Directive 2002/72/EC of August 2002 relating to "Plastic materials and articles intended to come into contact with foodstuffs."

Material selection for the can and plastic lids are determined by the following quality requirements:

- (b) (4)

When the choice of packaging material is plastic, the above requirements are met by using (b) (4) for both the can and the lid of the package. (b) (4)

3.2.6. Data establishing the stability of the products through the stated shelf lives

The recommended shelf lives for snus products in cool storage differ based on product category. (b) (4) This testing is part of the

Chemical Quality Analysis Program (b) (4)

All products tested for product stability in 2011 are listed in **Tables 3-40** and **3-41**, below. (b) (4)

.

Results from the 2011 testing show (b) (4)

Table 3-40. Analytical Results for Products Sampled in 2011: Water Content, pH Level and Nicotine Content in Selected Snus Products During Storage Until Best Before Date (in refrigerator for 3 weeks, thereafter at ambient room temperature and relative humidity. Nicotine values are given as dry weight.)

Product, SKU	Batch	Water %	pH	Nicotine, %
(b) (4)				

Product, SKU	Batch
(b) (4)	

Product, SKU	Batch	Water %		pH		Nicotine, %	
		3 w	14 w	3 w	14 w	3 w	14 w
(b) (4)							

Table 3-41. Analytical Results for Products Sampled in 2011: Content of TSNAs, Nitrite Ions, NDMA, and Bacterial Activity in Selected Snus Products During Storage Until Best Before Date (in refrigerator during 3 weeks, thereafter at ambient room temperature and relative humidity. Values of TSNA, NDMA and nitrite ion are given as dry weight.)

Product, SKU	Batch	TSNA µg/g	Nitrite ion µg/g	NDMA ng/g	Bacteria log cfu/g

(b) (4)

Product, SKU	Batch

(b) (4)

(b) (4)

(b) (4)

Historical data: Results from testing conducted in 2007 through 2011 for selected snus products stored at ambient conditions are shown in **Tables 3-42 and 3-43.** (b) (4)

Table 3-42. Analytical Results From the Years 2007 to 2011 Showing the pH Value and the Content of Water and Nicotine in Snus Products Stored in Refrigerator for Three (3) Weeks and at Ambient Room Temperature and Relative Humidity Until Best Before Date (nicotine values are given as dry weight)

Year	Product, SKU	Water %	pH	Nicotine %
	(b) (4)			
2007				
2008				
2009				
2010				
2011				
2007				

Year	Product, SKU	Water %	pH	Nicotine %
2008	(b) (4)			
2009				
2010				
2011				
2007				
2008				
2009				
2010				
2011				

Table 3-43. Analytical Results From the Years 2007 to 2011 Showing the Content of TSNA, Nitrite Ion, NDMA and Colony Forming Bacteria Count in Snus Products Stored in Refrigerator for 3 Weeks and at Ambient Room Temperature and Relative Humidity Until Best Before Date (values of TSNA, NDMA and nitrite ion are given as dry weight)

Year	Product	TSNA µg/g	Nitrite ion µg/g	NDMA ng/g	Bacteria log cfu/g
	(b) (4)				
2007					
2008					
2009					
2010					
2011					
2007					
2008					
2009					
2010					
2011					
2007					
2008					
2009					
2010					
2011					

(b) (4)

(b) (4)

As of 2012, all snus brands produced by Swedish Match are included in the product stability testing (b) (4)

The results for the ten (10) products marketed in the US are shown in **Tables 3-44** and **3-45**. (b) (4)

(b) (4)

Table 3-44. Analytical Results From the Year 2012 Showing the pH and a_w Values and the Content of Water, Moisture, Nicotine and Colony Forming Bacteria Count for Products Marketed in the US, Stored Both in Refrigerator and at Ambient Room Temperature and Relative Humidity Until Best Before Date (nicotine values are given as dry weight)

		a_w	Water %	pH
Product, SKU	(b) (4)			
General Loose, 4852				
Product, SKU				
General Dry Mint Portion Original Mini, 4800				

Product, SKU	(b) (4)
General Portion Original Large, 4880	
General Classic Blend Portion White Large, 4878	
General Mint Portion White Large, 4352	
General Nordic Mint Portion White Large, 4875	
General Portion White Large, 4881	
General Wintergreen Portion White Large, 4882	

		Moisture %	Nicotine %	Bacteria log cfu/g
Product, SKU	(b) (4)			
General Loose, 4852				
Product, SKU				
General Dry Mint Portion Original Mini, 4800				
Product, SKU				
General Dry Mint				

Portion White Mini, 4800										
General Portion Original Large, 4880	(b) (4)									
General Classic Blend Portion White Large, 4877										
General Mint Portion White Large, 4352										
General Nordic Mint Portion White Large, 4876										
General Portion White Large, 4881										
General Wintergreen Portion White Large, 4882										

Table 3-45. Analytical Results From the Year 2012 Showing the Content of Acrylamide, TSNA, NDMA, Nitrite Ion and Ethyl Carbamate for Products Marketed in the US, Stored Both in Refrigerator and at Ambient Room Temperature and Relative Humidity Until Best Before Date (values of acrylamide, TSNA, NDMA, nitrite ion, and ethyl carbamate are given as dry weight)

		Acrylamide* ng/g			TSNA* µg/g			NDMA* ng/g		
Product, SKU	(b) (4)									
General Loose, 4852										
Product, SKU										
General Dry Mint Portion Original Mini, 4800										

Product, SKU	(b) (4)
General Portion Original Large, 4880	
General Classic Blend Portion White Large, 4878	
General Mint Portion White Large, 4352	
General Nordic Mint Portion White Large, 4876	
General Portion White Large, 4881	
General Wintergreen Portion White Large, 4882	

	(b) (4)
Product, SKU	
General Loose, 4852	
Product, SKU	
General Dry Mint Portion Original Mini, 4800	
Product, SKU	

General Dry Mint Portion White Mini, 4800	(b) (4)
General Portion Original Large, 4880	
General Classic Blend Portion White Large, 4877	
General Mint Portion White Large, 4352	
General Nordic Mint PSWL, 4875	
General Portion White Large, 4881	
General Wintergreen Portion White Large, 4882	

3.3 Description of Conditions for Use

3.3.1. A full narrative description of the way in which a consumer will use the tobacco product, including a description of how a consumer operates the products

All of the Snus Products that are the subject of this Application are a form of Swedish snus. Upon usage, a pouched snus or a pinch of loose snus is typically placed between the gum and the upper lip at the front of the oral cavity. The pouch may be pre-wet on the tongue before being placed in the mouth and is most often worked on orally during use. The pinch is typically prepared by forming a small dough with the thumb and index fingers. Neither the pouched or loose snus products require expectoration during use.

3.3.2. A quantitative description of the length of time it takes a consumer to consume a single unit of the product, including information about the pattern of use during that time

A recent population-based telephone survey of 2,914 randomly selected respondents in Sweden investigated snus use patterns and behaviors (Digard et al. 2009). It found that the typical usage time for one portion snus pouch is 60-70 minutes, and the total usage time is 10-12.5 hours per day. The study further found that the typical usage time is approximately the same among users of loose snus products and users of pouched snus products.

Nicotine is absorbed into the body mainly via the oral mucous membrane. Compared to cigarettes, the nicotine uptake is slower but lasts as long as the snus is kept in the mouth (Lunell and Lunell 2005).

3.3.3. Specific instructions on how to use and store the product to get the proposed reduction in risk or exposure

None of the products that are the subject of this Application require specific instructions for use or storage to get the proposed reduction in risk.

3.3.4. Specific instructions on how to avoid using the product in a way that could reduce or eliminate the potential benefit or increase the risk of using the product

None of the Snus Products that are the subject of this Application require specific instructions on how to avoid using the products in a way that could reduce or eliminate the potential benefit or increase the risk of use the products. However, Swedish Match notes that a used pinch or pouch should be discarded, as the product is not intended to be swallowed or reused.

3.4 Description of How Consumers Actually Use the Product

3.4.1. Data and information regarding whether consumers can and are likely to comply with any instructions for product use

Not applicable. None of the Snus Products that are the subject of this Application require instructions for use.

3.4.2. Data and information regarding consumer use in both controlled and natural environments, including the number of units of the product consumed per day and the way in which individuals consume each unit of the product

Upon usage a pinch of loose snus or the pouched snus is placed between the gum and the upper lip. Expectoration during use is not required.

Data on snus product usage in natural environments come from the aforementioned population-based, telephone survey to investigate the patterns and behaviors of snus use among 2,914 randomly selected respondents (Digard et al. 2009). The survey found that on average, users of pouched snus products use approximately 11-12 g/day, while users of loose snus products use approximately 29-32 g/day. Although the number of packages (c. 0.5) and portions used per day (c. 12) are similar among users of loose and pouched snus, the portion weights are approximately three (3) times greater among the loose snus users than the pouched snus users. The typical usage time is approximately the same among users of loose snus products and users of pouched snus products. The typical usage time for one pinch or pouch is 60-70 minutes, and the total usage time is 10-12.5 hours per day.

Some information on usage patterns in natural environments also comes from studies of dual use of snus and smoking, as such studies typically collected information on amount of product used among snus users, smokers, and dual users of the two products. The available data are presented in **Table 6-8**. In summary, the results for those who used snus alone showed an average consumption of 3.2-3.7 cans per week which roughly accords with the mentioned findings by (Digard et al. 2009). Dual users generally reported less consumption of snus (2.2-3.4 cans per week).

Data on snus product usage in controlled conditions come from two (2) randomized, double-blind trials of snus as a smoking cessation aid, one conducted in the United States (Fagerstrom et al. 2012) and the other in Serbia (Joksic et al. 2011). Participants in the US study (n=250) were daily smokers of more than nine (9) cigarettes per day, while participants in the Serbia study (n=319) were smokers of over 10 cigarettes per day. In both studies, participants were randomly allocated to use active or placebo snus *ad libitum* as a smoking cessation aid. Product usage was much lower in these trials than in the Digard et al. population-based survey discussed above. In the US trial, participants in the active snus cohort used on average 2-4 g/day. In the Serbian trial, these participants used 3.5-4.7 g/day. The substantially lower consumption observed in the trial setting is likely explained by the fact that only 13% of the snus users in the Digard et al. survey reported dual daily use of both snus and combustible tobacco products, whereas most of the participants in the controlled trials were dual users of both cigarettes and snus.

3.4.3. Data and information regarding concurrent use of multiple products containing nicotine or tobacco

3.4.3.1. Studies in Scandinavia

3.4.3.1.1. Dual Use by Adults

According to the 2011 Swedish National Tobacco Survey, the prevalence of daily snus and daily cigarette use is 2%, a rate which has remained stable since 2004. Cross-sectional studies in Sweden and Norway have reported similar prevalence rates, ranging from 2% to approximately 10%. Among adult male participants in the Swedish "Your Country and Your Life" survey, dual daily use of both snus and cigarette was low (2%), and no such use was observed among female tobacco users (Ramström and Foulds 2006). When occasional dual use of combustible tobacco products among snus users was considered, (Digard et al. 2009) found that 12.6% reported dual use of a smokeless tobacco product and a combustible tobacco product and 9.8% of daily snus users also smoked cigarettes (whether daily or occasionally), among male and female study participants. Among dual users of daily snus and occasional or daily use of cigarettes, 53.5% reported that they smoked daily.

In the northern Sweden-based MONICA cohort study of 25-64 year-olds, dual use was reported among 2-5% (Rodu et al. 2002; Stegmayr et al. 2005). This prevalence of dual use was stable for the study period, from 1986 to 1999. Dual use was classified as "use" of both products; the authors did not further elaborate on the definition. According to the authors, dual use reflects a temporary transition between cigarette and snus as an unstable and transient period.

Rodu et al. (2003) examined the stability of dual users compared to other tobacco use groups to assess whether participants who were dual users at baseline remain in the dual use category at follow-up. They reported that combined use (smoking and snus) was the least stable category (39%), as 43% switched to snus and 6% switched to cigarettes. Former users of both products were also much less stable than former users of either cigarettes or snus.

In the Malmö study conducted in southern Sweden, Janzon and Hedblad (2009) reported an overall prevalence of snus use of 7% among men (mean age 59 years) and less than 1% among women (mean age 57 years). Among the male snus users, 34% were also current smokers, 57% were ex-smokers, and 9% were never smokers.

Among all age groups (16-74 years) surveyed as part of the Norway Tobacco Statistics (n = 3,145), 27% of respondents were exclusive smokers, 8% were exclusive snus users, and 7% both smoked and used snus (Lund and Lindbak 2007; SCENIHR 2010). Dual use was defined as daily or occasional use of both snus and cigarettes. In addition, in a meta-analysis by Lund et al. (2011) of seven cross-sectional data sets from Norway, 3.1% to 10.6% of snus users smoked daily, while a higher percent of participants reported that they smoked occasionally (16-35%). Tobacco consumption was not quantified. The authors noted that it is difficult to draw conclusions about whether this combined use was more or less damaging than the amount of smoking that would have taken place without the influence of snus.

3.4.3.1.2. Dual Use by Youth

In Norway, Grotvedt et al. (2013) examined patterns of tobacco use among tenth graders living in Oslo County who were surveyed as part of the Oslo Health study in Norway (n=1395), with a three-year follow-up. Prevalence of dual use was 10%, where 6% of respondents were snus users, and 13% of respondents smoked.

In addition, Hamari et al. (2013) conducted a study among young male military recruits (n = 1174) living in Northern Finland. The prevalence of daily snus use in this study was 15.6%, which was higher than the 2.1% rate observed in the general male population (Statistics Finland 2008). The authors found daily use of both snus and cigarettes to be 6.9%. Occasional smokers were twice as likely to be daily snus users than daily smokers, at rates of 30.1% vs. 15.1%, respectively. The authors concluded that concomitant snus use seemed to increase cigarette dependence in dual users, albeit not at a statistically significant extent. They also noted that snus did not seem to serve as a substitute for cigarettes in adult daily smokers; instead, snus served as an additional habit. This study did not collect information on duration of use and daily tobacco consumption.

3.4.3.1.3. Discussion and Conclusions

Overall, dual use was more common in all age groups among men than women (Norberg et al. 2011; Ramström and Foulds 2006; Rodu et al. 2002; Stegmayr et al. 2005). Norberg and colleagues examined other factors that affected dual tobacco use, and concluded that being male and having a low educational background seemed to increase the likelihood of being a dual user,

as also observed by Engstrom et al. (2010). Additionally, as compared to non-tobacco users, dual users were more likely to be skilled and/or unskilled workers, binge drink, and engage in risky alcohol consumption. Compared to smokers, dual tobacco users were less likely to be binge drinkers, and more likely to engage in risky alcohol consumption (Engstrom et al. 2010). There were no significant differences in dual use prevalence across all age groups (Engstrom et al. 2010; Ramström and Foulds 2006). Digard et al. (2009) reported a slightly higher prevalence of cigarette smoking among pouched snus users (10.5%) in comparison with loose snus users (8.7%).

There is evidence to suggest that the amount of tobacco consumed by dual tobacco users may differ from that used by exclusive users of either product (Galanti et al. 2008; Gilljam and Galanti 2003; Rodu et al. 2002). In particular, dual users appear to consume less tobacco than exclusive snus or cigarette users. In one study (2002), exclusive snus users reported average daily consumption of 0.41 packages among ex-smokers and 0.44 packages amongst those who never smoked. With regard to smoking, former snus users averaged 15.1 cigarettes daily and those who never used snus smoked 16.0 cigarettes. In comparison, dual users consumed 0.25 packages of snus daily and smoked an average of 10.8 cigarettes daily (Rodu et al. 2002). Digard et al (2009) also investigated the frequency of cigarette use among daily snus users; all daily snus users who also smoked reported doing so at least once per week, and 53.5% of them did so daily. In the Malmö study, Janzon and Hedblad (2009) reported that male dual users smoked significantly less (12.3 cigarettes per day) than exclusive smokers (16.1 cigarettes per day). This trend was also observed among female dual users, who smoked on average 7.8 cigarettes per day compared to 12.9 cigarettes per day among exclusive smokers. Similarly, Gilljam and Galanti reported that the proportion of current smokers smoking fewer than 10 cigarettes per day was nearly twice as high among users of snus than among nonusers (44% versus 24%, respectively) (Gilljam and Galanti 2003).

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

In summary, the frequency of daily dual use has been assessed in several studies, and has been reported to be approximately 2% in men and less than 1% in women. However, these rates appear to vary slightly depending on whether the criterion is daily dual use or occasional use of one tobacco type. Other studies have reported a slightly higher prevalence of dual use in Sweden. For example, 3.2% of male and 4.4% of female snus users in northern Sweden were found to smoke regularly in the VIP cohort (2009), and Digard et al. (2009) reported a prevalence of about 9.8% (for daily and/or occasional use). Taken together, among adults and adolescents, the range of dual use appears to be less than 10% in the Swedish population of snus users. Some evidence suggests slightly lower overall tobacco use among dual tobacco users.

3.4.3.2. Studies in the United States

3.4.3.2.1. Dual Use By Adults

In the United States, population data from the 2005 National Health Interview Survey ("NHIS") reflect a low prevalence of dual tobacco use.[38] Approximately 1.4% of the male population were dual tobacco users (Rodu and Cole 2009). In this survey, dual use was defined as subjects who had used either chewing tobacco or snuff 20 times in their life, and who used another tobacco product either every day or some days (classified as current STP users). In an older 1998 NHIS survey analyzed by Tomar (2002), dual tobacco use during the survey period was found to be 1.1%.

Tomar et al. (2010) analyzed results from the 2006 to 2007 CPS-TUS survey. The prevalence of dual tobacco (daily use of STPs and cigarettes) among respondents 25 years or older was 0.6%. Men who used snuff on a daily basis had the lowest prevalence of daily smoking (7.3%), compared to the prevalence of smoking among men who had never used snuff (14.9%). Similar results were obtained from the 2002 to 2003 CPS-TUS survey analysis by Zhu et al. (2009). Prevalence rates of dual tobacco use in this study ranged from 0.3 to 2.9%. Additionally, Backinger and colleagues (2008) examined trends and patterns of tobacco use among adults 18 years or older, using the 1995 to 2002 CPS survey. Prevalence of snuff use among cigarette smokers was found to be 0.97%.

From the 2010 BRFSS survey, Mushtaq et al. (2012) reported that the prevalence of dual use among adults 18 years or older was 1.6% among males and 0.3% among females. Dual use was categorized as the use of both STPs and cigarettes, irrespective of the frequency of use. Such dual use was reported among 8.5% of male smokers and 2.3% of female smokers; and 28% of male STP users and 42.4% of female STP users reported cigarette smoking.

Rath et al. (2012) assessed the prevalence of tobacco use in a longitudinal sample of young adults, ages 18 through 34 years (n = 4,201). The study collected use information on dip, snuff, and snus products in addition to other tobacco types such as little cigars, cigarillos, bidis and hookah. The prevalence of ever use and current use of electronic cigarettes, chewing tobacco, pipes, dip/snuff (Skoal or Copenhagen), snus (Camel snus), dissolvable products, and nicotine products were all 10% or less. In particular, the prevalence of past 30-day snus use in this group was 7%. Twenty-three percent (23%) reported current use of any tobacco products, while 7% reported dual tobacco use. (The authors did not assess dual tobacco use specific to STPs).

Several studies have investigated tobacco use among US military personnel (Cooper et al. 2010;

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[38] Due to the low prevalence of Swedish snus use in the United States, US studies often the investigated dual use of cigarettes and other STPs which are not the subject of this Application. These studies are nonetheless instructive of tobacco use behaviors because Swedish snus products, including the Snus Products that are the subject of this MRTP Application, are currently available in the US market.

Grier et al. 2010; Klesges et al. 2010). Among Air Force men exposed to a 6-week period of enforced tobacco abstinence, the prevalence of baseline dual use (defined as daily or nondaily users of both cigarettes and STP) was 0.5% (Klesges et al. 2010). In another analysis (the same cohort as Klesges et al. 2010) and among intermittent non-daily and light daily smokers (<10 cigarettes smoked per day), Cooper et al. (2010) examined baseline predictors associated with tobacco use. Smokeless tobacco use was found to be associated with intermittent smoking and not daily smoking. Relative to never use, the use of smokeless tobacco products either intermittently (OR= 1.98, $p < .001$) or daily (OR= 5.39, $p < .001$) increased the odds of being an intermittent smoker versus being a daily smoker. The authors concluded that more smokeless tobacco use was associated with less smoking. In a separate study among new US Army personnel, the odds of cigarette use were high among occasional (OR=4.03; 95% CI 3.57–4.54) and frequent (OR=2.90; 95% CI 2.67–3.14) smokeless tobacco users compared to non-users in the same category (Grier et al. 2010).

3.4.3.2.2. Dual Use by Youth

Using data from the 2002 to 2004 NYTS survey, Bombard et al. (2008) showed that among students (grades 6 through 12) who were current smokers, 26.4% (estimated 1.9 million youth) used one tobacco product in combination with cigarettes and 19.7% (estimated 1.4 million youth) used more than one. Of the students who used cigarettes and one other tobacco product, 17.7% concurrently used STPs and cigarettes. Concurrent use of smokeless tobacco and cigarettes was defined as use of either form of tobacco in the preceding 30 days.

3.4.3.2.3. Discussion and Conclusions

Dual use was mostly observed among males (Rath et al. 2012; Tomar et al. 2010). Young adults aged 25–34 years were significantly more likely to use cigarettes only, or cigarettes and other tobacco products, as compared to those aged 18–24 years (RR = 1.48; CI: 1.07–2.06 and RR =1.60, CI: 1.03–2.49, respectively) (Rath et al. 2012). Other authors have reported that rates of dual use increased as age decreased decreased (McClave-Regan and Berkowitz 2011; Mushtaq et al. 2012; Rodu and Cole 2009). Heavy alcohol consumption was associated with increased odds of being a dual user (Klesges et al. 2010; Mushtaq et al. 2012). Rates of dual use among military personnel have also been reported, and the overall prevalence of tobacco use is also higher among this subpopulation than among civilian populations. (Peterson et al. 2007; Trent et al. 2007).

There are also apparent differences in the combined use of STPs and cigarettes across US regions. Polytobacco (or dual) use was associated with residing in the Midwest, South or West (Bombard et al. 2008; McClave-Regan and Berkowitz 2011). Boyle et al (2012) examined trends in dual tobacco use among tobacco users participating in the Minnesota Adult Tobacco Survey, 1999 - 2010. Their results showed that the prevalence of dual use was essentially unchanged through 2007, but increased significantly between 2007 and 2010 (4.4% to 9.6%). The authors attributed this increase to an October 2007 Minnesota workplace indoor smoking ban (including bars and restaurants) which may explain the opportunity for some smokers to consider smokeless alternatives to smoking; thereby increasing STP use during this period.

A limited number of studies have been identified in which the quantity of cigarettes smoked by dual tobacco users was compared to the quantity smoked by exclusive smokers. Some studies showed that, on average, the number of cigarettes consumed by dual users was lower than the number of cigarettes consumed by exclusive smokers (Rodu and Cole 2009; Tomar 2002; Wetter et al. 2002). For example, Rodu and Cole (2009) compared the number of cigarettes consumed daily by dual users with the quantity consumed by exclusive smokers in the 2000 and 2005 NHIS surveys. Every-day smokers who also used STPs daily consumed significantly fewer cigarettes on average (13 cigarettes/day) than exclusive smokers (approximately 20 cigarettes/day). However, no significant difference in cigarette consumption was observed between exclusive smokers and every-day smokers who used STPs on some days. Cigarette consumption among some-day smokers was very low in both survey years, and no differences were observed between some-day smokers who used STPs and exclusive some-day smokers.

Among adults 18 or older (1998 NHIS survey), Tomar (2002) reported that smokers who used snuff tended to smoke fewer cigarettes per day, on average, than those who never used snuff. Similar to Rodu and Cole (2009), Tomar (2002) found that cigarette consumption among smokers who used snuff only on some days did not differ from consumption among never snuff users (19.3 vs. 18.4; p 0.42), while those who used snuff every day smoked, on average, significantly fewer cigarettes per day (11.4; p 0.0001). Additionally, the number of cigarettes per day was found to be higher among exclusive smokers compared to concomitant users in adult males participating in the Working Well cancer prevention trial in the southeastern United States (24.6 vs. 19.5 cigarettes/day, respectively) (Wetter et al. 2002).

In a cohort of adult concurrent tobacco users in Minnesota, light smokers (1-9 cigarettes/day) were significantly more likely to report use of STPs than smokers using half a pack or more (10-19 cigarettes/day), at 13.7% vs. 5.5%, respectively. However, smokers using a pack or more per day reported similar STP use as light smokers, 11.1% vs. 13.7%, respectively (Boyle et al. 2012).

Tomar and colleagues (Tomar et al. 2010) reported that, among adults surveyed as part of the 2006 – 2007 CPS survey, there were no statistically significant differences in the quantity of cigarettes smoked by exclusive cigarette smokers or STP users compared to dual users. Daily smokers who also used STP every day smoked approximately the same mean number of cigarettes per day as did daily smokers who used STPs on some days, or who had never used STP. Similarly, Rath and colleagues (2012) found that participants who reported using cigarettes only had a mean daily use of 9.20 cigarettes per day (95% CI: 8.18–10.23) and those who reported using cigarettes and other tobacco products had a mean daily use of 8.73 cigarettes per day (95% CI: 6.66–10.80). These figures were not statistically different. The authors concluded that the use of other tobacco products does not replace cigarette smoking or decrease the mean number of cigarettes smoked daily among young adults.

Among adolescents, Tomar et al. (2010) reported that 8th grade students surveyed in the 2005-2006 MTF survey who used STPs daily had a much higher prevalence of smoking one half pack of cigarettes or more per day (10.8%) than did those who did not use STPs at all (1.3%). This suggests that cigarette consumption was higher among STP users; however, these students were surveyed at ages 13 or 14 years, which represents a period of experimental tobacco use.

In sum, the rates of dual tobacco use in the United States appear to be low, in the range of <1 to 3%, but may be higher among males, among those in the military, in certain US regions, and in certain age groups (i.e., adolescents and young adults appear to have higher rates of dual use). Prospective studies on dual use patterns among adolescents are limited. Cross-sectional studies among adolescents showed that dual users were inclined to use STP or smoke cigarettes either daily or occasionally. This evidence suggests that, in the United States, daily dual users consume fewer cigarettes than exclusive smokers, but some uncertainty exists as to whether dual users have lower rates of tobacco consumption.

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4. LABELS, LABELING, AND ADVERTISING

4.1 Description of Proposed Advertising and Labeling

The labeling and advertising for each of the Snus Products covered by this Application currently contain the four warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act. These statutorily mandated warnings are as follows:

1. WARNING: This product can cause mouth cancer.

2. WARNING: This product can cause gum disease and tooth loss.

3. WARNING: This product is not a safe alternative to cigarettes.

4. WARNING: Smokeless tobacco is addictive.

Although these warnings may be appropriate for customarily marketed smokeless tobacco products, they do not account for the scientific evidence demonstrating the individual and population-level public health benefit of Swedish snus with respect to risk reduction. Accordingly, this MRTP Application seeks certain product-specific modifications to the statutorily-mandated health warnings in order to better communicate to consumers the risks of snus as compared to other commercially marketed tobacco products.

In particular, this MRTP Application seeks the following product-specific modifications to the required warnings:

- The revised labeling will not carry the mouth cancer warning.

- The revised labeling will not carry the gum disease and tooth loss warning.

- The revised labeling will change the "not a safe alternative warning" to "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

- The revised labeling will keep the current addiction warning.

In other words, there would be two warning labels (and hence, two modified risk claims) subject to the MRTP order, and they would read as follows:

1. WARNING: This product is addictive.

2. WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.

These proposed modified risk claims will be communicated to consumers through the product label. Any advertising for the Snus Products will necessarily carry warnings identical to those

shown on the product label. However, Swedish Match does not plan to otherwise communicate, highlight, or promote the proposed modified risk claims to consumers using other labeling or advertising.

Swedish Match believes that the scientific evidence submitted in support of this Application permits CTP to issue an order permitting the use of the modified risk statements proposed above. In fact, Swedish Match considers these warning label adjustments wholly appropriate given the global acceptance of the Swedish epidemiological and other data which demonstrate the reduced risk to individual users and the population-level public health benefits of Swedish snus and, hence, the Snus Products.

4.2 Sample Product Labels and Labeling

An MRTP application must include sample product labels and labeling. In the MRTP Draft Guidance, FDA recommends the submission of copies of each package label variation (including inserts and onserts) proposed to be used for the MRTP, except that copies of package label variations for each health warning required by law may be omitted. In accordance with the Agency's recommendations, and subject to the disclaimer below, Swedish Match submits copies of the labels which have been developed by the time of the filing of this Application.

WARNING: This product is addictive
In accordance with the MRTP Guidance, and because this warning label does not materialy differ from the health warning required by law, a copy of this warning label has been omitted for each of the Snus Products.

WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes
In accordance with the MRTP Guidance, a copy of this warning label has been provided for each of the Snus Products.

4.2.1. General Loose (SKU 4852)

4.2.2. General Dry Mint Portion Original Mini (SKU 4800)

4.2.3. General Portion Original Large (SKU 4880)

4.2.4. General Classic Blend Portion White Large – 15 ct (SKU 4877)

Please view the photograph for the General Classic Blend Portion White Large – 12 ct (SKU 4878) product, as the label is identical in every way, with the exception of the specified pouch count.

4.2.5. General Classic Blend Portion White Large – 12 ct (SKU 4878)

4.2.6. General Mint Portion White Large (SKU 4352)

4.2.7. General Nordic Mint Portion White Large – 15 ct (SKU 4876)

Please view the photograph for the General Nordic Mint Portion White Large – 12 ct (SKU 4875) product, as the label is identical in every way, with the exception of the specified pouch count.

4.2.8. General Nordic Mint Portion White Large – 12 ct (SKU 4875)

4.2.9. General Portion White Large (SKU 4881)

4.2.10. General Wintergreen Portion White Large (SKU 4882)

Figure 4.2.1. General Loose (SKU 4852)

Warning is 20% of selling panel
Warning Text is 66% (17pt) of Warning Area

= Emboss

Warning is 20% of selling panel
Warning Text is 70% (11.3pt) of Warning Area

PMS 8585 LOOSE brown

Figure 4.2.2. General Dry Mint Portion Original Mini (SKU 4800)

Warning is 20% of selling panel
Warning Text is 62% (14pt) of Warning Area

= Emboss

Warning is 22% of selling panel
Warning Text is 70% (10pt) of Warning Area

PMS 314 Mini Mint Blue

Figure 4.2.3. General Portion Original Large (SKU 4880)

Warning is 30% of selling panel
Warning Text is 60% (13pt) of Warning Area

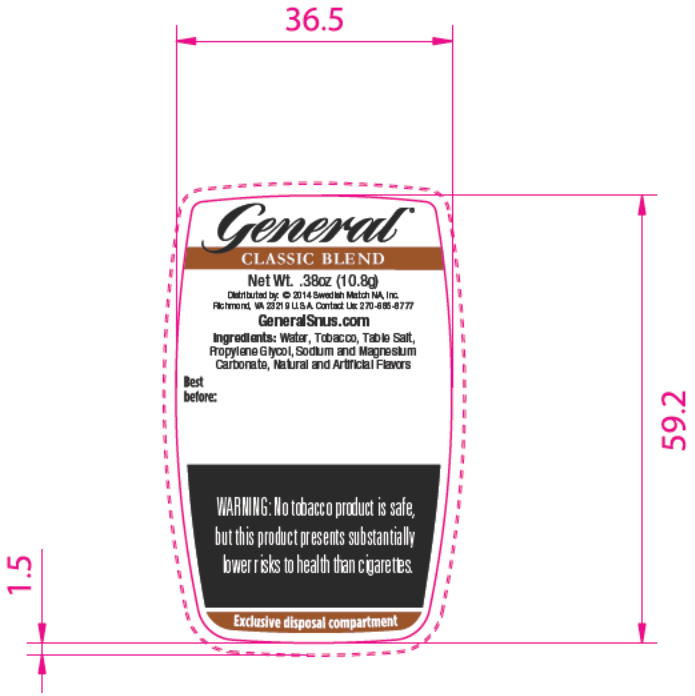
= Emboss

Warning is 30% of selling panel
Warning Text is 70% (12pt) of Warning Area

PMS 8005 ORIGINAL brown

Figure 4.2.5. General Classic Blend Portion White Large – 12 ct (SKU 4878)

Warning is 30% of selling panel
Warning Text is 70% (13pt) of Warning Area



Warning is 30% of selling panel
Warning Text is 70% (9pt) of Warning Area

PMS 7516: Classic Blend Brown

Figure 4.2.6. General Mint Portion White Large (SKU 4352)

Warning is 30% of selling panel
Warning Text is 60% (13pt) of Warning Area

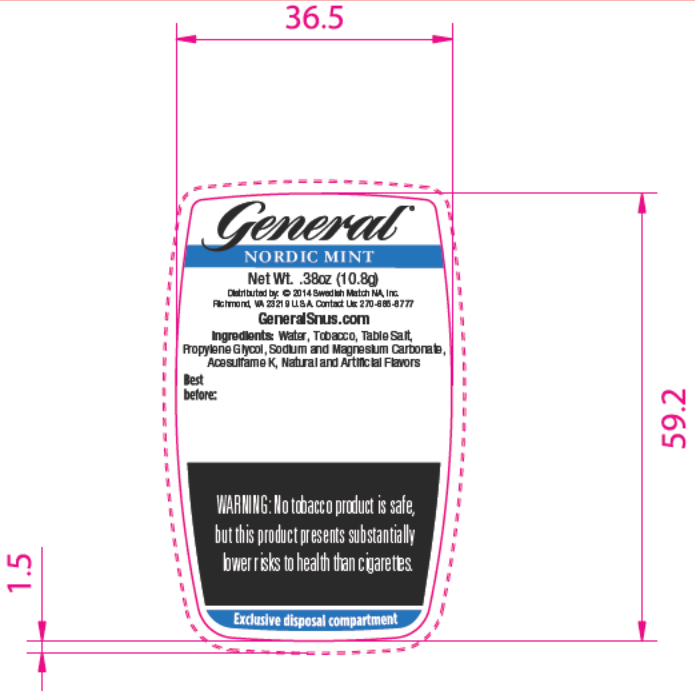
= Emboss

Warning is 30% of selling panel
Warning Text is 70% (12pt) of Warning Area

PMS 314 Mint Blue

Figure 4.2.8. General Nordic Mint Portion White Large (SKU 4875)

Warning is 30% of selling panel
Warning Text is 70% (13pt) of Warning Area



Warning is 30% of selling panel
Warning Text is 70% (9pt) of Warning Area

PMS 3005: Nordic Mint Blue

Figure 4.2.9. General Portion White Large (SKU 4881)

Warning is 30% of selling panel
Warning Text is 60% (13pt) of Warning Area

= Emboss

Warning is 30% of selling panel
Warning Text is 70% (12pt) of Warning Area

K=27 White Silver

Figure 4.2.10. General Wintergreen Portion White Large (SKU 4882)

Warning is 30% of selling panel
Warning Text is 60% (13pt) of Warning Area

= Emboss

Warning is 30% of selling panel
Warning Text is 70% (12pt) of Warning Area

PMS 341 Wintergreen

5. ENVIRONMENTAL ASSESSMENTS

5.1 General Loose (SKU 4852)

ENVIRONMENTAL ASSESSMENT
GENERAL LOOSE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000140

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Loose snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

3) **DATE**

June 6, 2014

4) **NAME OF APPLICANT/SUBMITTER**

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

5) **ADDRESS**

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

6) **DESCRIPTION OF PROPOSED ACTION**

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Loose snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the product label.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

7) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Loose
Stock-Keeping Unit ("SKU"): 4852
STN: SE0000140

8) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Loose snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of paraffin-coated cardboard cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is not expected to be any different than the currently marketed product. Consequently, no

adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

9) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

10) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

11) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

12) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.2 General Dry Mint Portion Original Mini (SKU 4800)

ENVIRONMENTAL ASSESSMENT
GENERAL DRY MINT PORTION ORIGINAL MINI
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000139

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Dry Mint Portion Original Mini snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Dry Mint Portion Original Mini snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Dry Mint Portion Original Mini
Stock-Keeping Unit ("SKU"): 4800
STN: SE0000139

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Dry Mint Portion Original Mini snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.3 General Portion Original Large (SKU 4880)

ENVIRONMENTAL ASSESSMENT
GENERAL PORTION ORIGINAL LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000143

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Portion Original Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Portion Original Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the product label,

and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Portion Original Large
Stock-Keeping Unit ("SKU"): 4880
STN: SE0000143

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Portion Original Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product . Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.4 General Classic Blend Portion White Large – 15 ct (SKU 4877)

ENVIRONMENTAL ASSESSMENT
GENERAL CLASSIC BLEND PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000138

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Classic Blend Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Classic Blend Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of Swedish snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Classic Blend Portion White Large
Stock-Keeping Unit ("SKU"): 4877
STN: SE0000138

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Classic Blend Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the United States. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing Application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of the snus product does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.5 General Classic Blend Portion White Large – 12 ct (SKU 4878)

ENVIRONMENTAL ASSESSMENT
GENERAL CLASSIC BLEND PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000138

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Classic Blend Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Classic Blend Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of Swedish snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Classic Blend Portion White Large
Stock-Keeping Unit ("SKU"): 4877
STN: SE0000138

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Classic Blend Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the United States. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing Application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of the snus product does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.6 General Mint Portion White Large (SKU 4352)

ENVIRONMENTAL ASSESSMENT
GENERAL MINT PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000141

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Mint Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Mint Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the product label,

and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Mint Portion White Large
Stock-Keeping Unit ("SKU"): 4352
STN: SE0000141

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Mint Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.7 General Nordic Mint Portion White Large – 15 ct (SKU 4876)

ENVIRONMENTAL ASSESSMENT
GENERAL NORDIC MINT PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000142

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Nordic Mint Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Nordic Mint Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Nordic Mint Portion White Large
Stock-Keeping Unit ("SKU"): 4876
STN: SE0000142

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Nordic Mint Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.8 General Nordic Mint Portion White Large – 12 ct (SKU 4875)

ENVIRONMENTAL ASSESSMENT
GENERAL NORDIC MINT PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000142

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Nordic Mint Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

11) DATE

June 6, 2014

12) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

13) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

14) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Nordic Mint Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

15) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Nordic Mint Portion White Large
Stock-Keeping Unit ("SKU"): 4876
STN: SE0000142

16) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Nordic Mint Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

17) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

18) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

19) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

20) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.9 General Portion White Large (SKU 4881)

ENVIRONMENTAL ASSESSMENT
GENERAL PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000144

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the product label,

and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Portion White Large
Stock-Keeping Unit ("SKU"): 4881
STN: SE0000144

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise lass than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

5.10 General Wintergreen Portion White Large (SKU 4882)

ENVIRONMENTAL ASSESSMENT
GENERAL WINTERGREEN PORTION WHITE LARGE
PROPOSED MODIFIED RISK TOBACCO PRODUCT
SUBMISSION TRACKING NUMBER ("STN"): SE0000145

This environmental assessment has been prepared in accordance with 21 C.F.R. §25.40 as part of a submission under Section 911(g) of the FDCA. The Agency action under consideration is the issuance of a modified risk tobacco product order for the General Wintergreen Portion White Large snus product manufactured by Swedish Match. As detailed below, Swedish Match believes that there is no environmental impact associated with FDA's potential decision to issue a modified risk tobacco product order under Section 911(g) of the FDCA in this instance.

1) DATE

June 6, 2014

2) NAME OF APPLICANT/SUBMITTER

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

3) ADDRESS

Two James Center
1021 East Cary Street
Suite 1600
Richmond, VA 23219

4) DESCRIPTION OF PROPOSED ACTION

a. Requested Action

Issuance of a modified risk tobacco product order under Section 911(g) of the FDCA.

b. Need for Action

Swedish Match proposes to amend the label of its General Wintergreen Portion White Large snus product, which is currently marketed in the United States. In particular, Swedish Match seeks certain product-specific modifications to the warning statements mandated by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, in order to better communicate to consumers the risks of snus as compared to other commercially marketed smokeless tobacco products. No other changes will be made to the

product label, and no aspect of the product other than the label will be altered.

c. Location of Use

The product will continue to be manufactured at Swedish Match's facilities in Sweden and imported by Swedish Match's factory in Owensboro, KY. The product will likewise continue to be sold to consumers at a variety of retail establishments, and consumed primarily in homes and automobiles. The new product will be widely distributed, as is the currently marketed product, and use of the new product will correspond with national population density, as do other smokeless tobacco and snus products. The modification of the product's label will not change any aspect of the location of the product's use.

d. Location of Disposal

Used tobacco and empty packaging, including that associated with the new product, are typically disposed of in community solid waste management systems, which may include landfills, incineration, and recycling. According to the U.S. Environmental Protection Agency's 2009 update regarding municipal solid waste in the United States, about 54.3% of municipal solid waste was land disposed, 11.9% was combusted, and 33.8% was recovered (recycled and composted). The types of environments present at and adjacent to these disposal locations will not differ for the new product. The modification of the product's label will not change any aspect of the product's disposal.

5) IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

Trade Name: General Wintergreen Portion White Large
Stock-Keeping Unit ("SKU"): 4882
STN: SE0000145

6) ENVIRONMENTAL ISSUES

a. Introduction of Products into the Environment

Amending the label of the General Wintergreen Portion White Large snus product is not expected to result in any new or additional adverse environmental impacts. The product with the amended labeling is expected to replace the currently-marketed snus product. Therefore, its manufacture, transport, use and disposal are not expected to contribute to any significant new or additional environmental impacts. Moreover, over the past few decades, the tobacco market as a whole has been contracting (rather than expanding) in the U.S. Thus any potential increase in the production, transport, use or disposal of the snus product with the revised product labeling is expected to result in a reduction in the sales, production, use and disposal of other tobacco products. As a result, there are not likely to be any added environmental impacts as a result of the labeling change.

i. *As a Result of Manufacture and Transport*

As discussed in the foregoing application, there are no extraordinary or unusual circumstances associated with the manufacture of this tobacco product compared to other commercially available tobacco products.

ii. *As a Result of Use*

The use of snus products does not introduce any materials into the environment, other than in the disposal of the used product. Moreover, the new product will contain the same ingredients as the currently marketed product, and will be used in the same manner as the currently marketed product. Therefore, the new product will not introduce any new materials into the environment.

iii. *As a Result of Disposal*

The new product and any associated waste will be disposed of in the same manner as the currently marketed product. Product containers (composed of plastic cans with plastic lids) are not intended for repeat use. Disposal by the ultimate consumer of canisters, used tobacco, and any other waste material will be by conventional rubbish disposal and, therefore, primarily by sanitary landfill or incineration. The proposed modification to the product label may result in an increase in product sales; (b) (4) However, this increase is expected to be offset by the withdrawal of currently marketed snus products and reduction in the use of other tobacco products. Moreover, the new product is expected to comprise less than 1% of the total tobacco sales in the United States, and waste from the product will make up a very small portion of total municipal solid waste. It will not significantly alter the emissions from properly operating municipal solid waste combustors. As a result, those municipal solid waste incinerators will continue to operate in compliance with applicable laws and regulations such as 40 C.F.R. Part 60, as well as relevant state and local laws.

b. Fate of Products Released into the Environment

The new product is expected to enter into the environment in extremely small quantities, if at all, as a result of the use and disposal of the product. Swedish Match does not anticipate that the fate of any materials from this product will be different from other snus products commercially available. Thus, no meaningful impacts are expected on air, water, and land resources or on the organisms that inhabit these media as a result of the proposed action.

c. Environmental Effects of Released Products

Only extremely small quantities of the ingredients of the new product, if any, are expected to be released into the environment through leaching and combustion, and this quantity is

not expected to be any different than the currently marketed product. Consequently, no adverse effects on organisms in the environment are expected.

d. Use of Resources and Energy

As is the case with other smokeless tobacco and snus products and their ingredients, the production, use, and disposal of the new product and its ingredients require the use of natural resources such as petroleum products and coal. However, the new product will not differ from the currently marketed product in this respect, especially given that production occurs in Sweden and is in all respects the same as for the currently marketed product.

7) MITIGATION MEASURES

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, mitigation measures need not be discussed.

8) ALTERNATIVES TO THE PROPOSED ACTION

Based on current information, Swedish Match has not identified any adverse environmental effects associated with the proposed action. Therefore, alternatives to the proposed action are not proposed.

9) LIST OF PREPARERS

Gerard J. Roerty, Jr.
Vice President, General Counsel & Secretary
Swedish Match North America Inc.

10) REFERENCES

U.S. Environmental Protection Agency, Municipal Solid Waste Generation, Recycling, and Disposal in the United States: Facts and Figures for 2009, EPA-530-F-010-021, December 2010, Washington, DC.

6. SUMMARY OF ALL RESEARCH FINDINGS

Introduction

Section 6 of this Application addresses the following five key areas of investigation identified in the MRTP Guidance:

6.1 Health Risks of the Tobacco Product

6.2 Effect on Tobacco Use Behavior among Current Users

6.3 Effect on Tobacco Use Initiation among Non-Users

6.4 Effect of Marketing on Consumer Understanding and Perceptions

6.5 Effect on the Population as a Whole

Each of the five key areas above begins with an overview of the evidence and is followed by a list of references. In addition, the discussion of each of the key areas has been divided into several subsections. For example, Section 6.1 Health Risks of the Tobacco Product, is followed by subsection 6.1.1. "Health Risks Associated with the Use of Snus as Compared to Using Cigarettes" and various other subsections.

The most extensive and most applicable evidence cited in Section 6 is from research conducted using Swedish Match snus. Most of this evidence, including several large epidemiology studies, comes from studies undertaken by and with the support of Swedish academic institutions and governmental authorities. This Swedish-based evidence—referred to as the Swedish Experience throughout this Application—has been widely cited by public health agencies and scientific institutions globally and has been the basis for hundreds of published articles and presentations.

The evidence comprising the Swedish Experience is supplemented by additional product-specific evidence collected by Swedish Match, including (i) a series of clinical trials initiated just prior to the passage of the Tobacco Control Act which were sponsored by the Company, and (ii) additional product-specific research undertaken following the issuance of the MRTP Guidance—most notably, premarket consumer perception study designed to assess the effect on consumer understanding and perceptions of marketing the Snus Products as MRTPs. These data are presented in Section 6.4 "Effect of Marketing on Consumer Understanding and Perception."

Additional product-specific evidence is derived from the results of modeling using the Dynamic Population Model ("DPM"). The DPM forecasts the public health impact of the proposed MRTPs by estimating changes in all-cause mortality for a hypothetical population of persons who have never used tobacco and who, as they age, may transition into and out of different tobacco exposure states, including current and former smoking or MRTP use. DPM modeling data are cited extensively in Section 6.5 "Effect on the Population as a Whole."

Another key component of this Application's product-specific evidence is GOTHIATEK®,

Swedish Match's proprietary quality standard which subjects all Swedish Match products to rigorous controls in order to maintain the highest quality throughout all stages of the manufacturing process from tobacco plant to consumer. GOTHIATEK® sets the standard for raw material quality requirements, manufacturing process requirements, consumer product information requirements, and maximum permitted levels of undesirable substances found naturally in the tobacco plant.

Evidence is also presented from studies undertaken by the Norwegian Institute for Alcohol and Drug Research (SIRUS) to evaluate public measures that were initiated in Norway during 2003-2008 to prevent the use of tobacco. From 2009 to 2013 SIRUS published several articles documenting the burgeoning "Norwegian Experience" with Swedish snus. The Norwegian Experience and the Swedish Experience share certain fundamental similarities, as both are well documented; both document the shift away from smoking to snus use by men, and the more recent increase in the percentage of women snus users; both report that, among ever-smokers, snus is the most preferred method for quitting; and in both countries Swedish Match's snus products have dominated the snus markets, making the epidemiological data product-specific for the Company's products (see Subsection 2.5.2.2.2 "Other relevant evidence").

However, a primary difference between the Swedish and Norwegian Experiences relates to when, and over what length of time, the switch from cigarettes to snus occurred. In Sweden, the switch occurred over three to four decades and was well documented, allowing for the collection of epidemiological information on health outcomes which resulted in the publication of numerous scientific articles demonstrating the reduction in individual risk. In Norway, the transition has been much more recent and sudden, which does not yet allow for epidemiological findings related to health risks among individual users or the whole population. Having benefitted from the Swedish epidemiological evidence and the accepted risk reduction that occurs with the switch from cigarettes to snus, Norwegian researchers have focused their research efforts on the role of snus in smoking cessation.

In Section 6.2 "Effect on Tobacco Use Behavior Among Current Users", some additional evidence is presented from US studies and surveys. These data are clearly not product-specific due to the low rate of snus use in the United States. Most of the relevant US studies considered the broad general category of STPs, which, in addition to Swedish snus, includes a broad range of tobacco products which are more commonly used in the United States, such as, moist and dry snuff, and chewing tobacco. These data are presented as complimentary background information and the individual studies are summarized in the ENVIRON TUB Report 2013 (attached as Appendix 6B).

Overview of Key Areas

6.1: Health Risks of the Tobacco Product

This section summarizes the evidence on the health risks associated with the use of Swedish Snus, as manufactured by Swedish Match, compared to smoking. The section emphasizes those diseases that contribute the most to the excess mortality observed among smokers. This selection was based on an analysis of risk data of smoking mortality in the United States. The

cited Swedish epidemiological evidence is primarily based on relative risk estimates from the analytical epidemiology studies of Swedish tobacco use in which risks among snus users and smokers are compared to a common reference population permitting direct comparisons of the risks associated with the two types of products. This means that some individual epidemiology studies that only permit indirect risk comparisons were not included. However, the ENVIRON Snus Monograph 2013 (attached as Appendix 6A) was based on a systematic review of the available literature and includes all published studies. Generally, the excluded studies support the conclusions in this section in that they also typically show no statistically significant risk increases among snus users in contrast to the risks estimated for smokers. The section also includes, as complementary information, results from some large cohorts and recent meta-analyses of individual studies of Swedish snus users and cigarette smokers that permit indirect risk comparisons.

In addition, Subsection 6.1.4 "Additional Health Risk Information," includes an analysis of Hazardous and Potentially Hazardous Constituents ("HPHCs"), which is drawn largely from information collected by the Company pursuant to the principles of GOTHIATEK®.

6.2: Effect on Tobacco Use Behavior among Current Users

Section 6.2 addresses the likelihood that current tobacco users will start using Swedish snus and the likelihood that the snus users will switch to or back to other tobacco products that present higher risk of tobacco-related harm or disease. This section also addresses considerations that are fundamental to the evaluation of the population benefit of the proposed MRTPs—namely, the issue of dual use and the likelihood that users who may otherwise quit using tobacco products will instead use Swedish snus.

This section relies primarily on product-specific evidence from the Swedish Experience that addresses the health risk to the individual as well as the benefit to the overall population. The Swedish evidence is complemented by usage data from the United States, the Norwegian Experience, and Swedish Match clinical trials. Youth behavior evidence is also presented, primarily drawn from the Swedish BROMS cohort, with supporting data from Norway.

6.3: Effect on Tobacco Use Initiation among Non-Users

Section 6.3 addresses the likelihood that non-users, particularly youth and young adults, will initiate use of Swedish snus. It summarizes the evidence pertaining to the likelihood that non-users who start using snus will switch to other tobacco products that present higher levels of individual risk, or that former users of tobacco products will re-initiate use.

This Section relies primarily on product-specific evidence from the Swedish Experience that addresses the health risk to the individual as well as the benefit to the overall population. Norwegian evidence is also cited, as are the Swedish Match clinical trials. Evidence relating to youth behavior is presented, primarily from the Swedish Experience and supporting evidence from Norway is also summarized.

6.4: Effect of Marketing on Consumer Understanding and Perceptions

Section 6.4 presents the results from Swedish Match's premarket consumer perception study

conducted in 2013-2014 to assess the effects on current smokers and non-smokers of the proposed modifications to the Snus Products' warning labels. The research assessed the effect of the proposed label changes on subjects' tobacco use behavior and their understanding and perception of health risks associated with the Snus Products as a result of exposure to test and control labels. This Section's product-specific research (conducted by Swedish Match) is complemented by class-specific research.

6.5: Effect on the Population as a Whole

Section 6.5 presents evidence derived from the results of modeling using the DPM. This model was developed by ENVIRON, primarily with funding from R. J. Reynolds Tobacco Company ("RJR"), but with additional financial support from Swedish Match. The DPM forecasts the public health impact of the proposed MRTPs by estimating changes in all-cause mortality for a hypothetical population of persons who have never used tobacco and who, as they age, may transition into and out of different tobacco exposure states, including current and former smoking or MRTP use. Background information and information relating to the development of the DPM are presented in this section and in Appendix 6F.

6.1 Health Risks of the Tobacco Product

The potential health effects of Swedish snus have been well studied, particularly in Sweden, where the product is widely used. Numerous studies, undertaken by independent and university-based researchers and institutions around the world over the past three decades, have resulted in a solid base of literature documenting the health effects of Swedish snus. This evidence is product-specific for Swedish Match's snus products given that (i) snus accounts for nearly all of the Swedish smokeless market and (ii) Swedish Match (and its predecessors in interest) have historically dominated the Scandinavian snus market.

ENVIRON was contracted by Swedish Match to produce a comprehensive summary of the existing literature on human health effects of Swedish snus based on a systematic literature search. This summary forms the main part of the ENVIRON Review of the Scientific Literature on Snus (Swedish Moist Snuff) (ENVIRON Snus Monograph 2013), which is appended to this application (Appendix 6A). It is mainly based on cohort studies, case-control studies (mostly population-based), systematic reviews, and meta-analyses although some of the information is based on cross-sectional, descriptive studies. The report also includes a rewiew of studies of the chemical properties of snus, biomarkers of snus, and non-clinical toxicological studies.

The ENVIRON Snus Monograph (2013) constitutes a systematic review of the literature on Swedish snus available through April 2013. The basic literature search strategy consisted of the following terms: "tobacco, smokeless" [MeSH Terms] OR chew tobacco* OR oral tobacco* OR snuff OR plug tobacco* OR spit* tobacco* OR smokeless tobacco* OR loose leaf tobacco* OR dip tobacco* OR dipping tobacco* OR snus OR Swedish snuff OR Swedish tobacco. Literature searching was conducted primarily using the National Library of Medicine's PubMed database. Targeted outcome terms were used in addition to the basic exposure terms listed above, for example, cancer or neoplasms, oral lesions, cardiovascular, stroke, etc. In addition to using PubMed, periodic literature searches using similar key words have been performed in Dialog® (a

commercial compilation of more than 650 databases), as well as in other databases such as Toxnet, an online toxicology database, and the World Wide Web, to identify any published reports that may have been missed. Following the identification of articles and abstracts (as available), they were reviewed by ENVIRON staff for potential relevance. Those studies that appeared relevant were retrieved and evaluated for inclusion. Once actual articles were obtained, the reference lists of these publications were "tree-searched" to identify other relevant studies or publications that may have been missed in the data base searches.

The ENVIRON Snus Monograph (2013) covers human health effects including: oral and dental effects, periodontal disease, oral and pharyngeal cancer, other head and neck cancers, esophageal cancer, stomach cancer, pancreatic cancer, lung cancer, kidney and bladder cancer, other cancers, CVD (including myocardial infarction and stroke), diabetes and impaired glucose tolerance, metabolic syndrome, gastroesophageal reflux, Chrohn's disease, ulcerative colitis, irritable bowel syndrome, pregnancy outcomes and reproductive effects, amyotrophic lateral sclerosis, complications after surgery, rheumatoid arthritis, sarcoidosis, multiple sclerosis, and plaque psoriasis.

For the purposes of this Application, in particular the proposed labeling changes that refer to the risk differential between cigarette smoking and use of snus, and the lack of convincing scientific evidence linking use of Swedish snus to clinically significant gum disease and tooth loss, this section will focus on the scientific literature that provide direct evidence on the difference in risk associated with smoking versus use of Swedish snus with emphasis on those diagnoses that account for most of the excess mortality observed among US smokers (indirect evidence from selected large cohorts and meta-analyses of individual studies are provided as supporting documentation). Consequently, it is based mainly on Appendix VI of the ENVIRON Snus Monograph (2013), and the sections of that report that pertain to oral and dental conditions. A more detailed review and analysis is also presented of the scientific evidence on the risk of pancreatic cancer among snus users, as the possibility of an increased risk has been widely debated in recent years.

Swedish Match describes below human studies evaluating the health effects of Swedish snus. These studies demonstrate that use of Swedish snus, as manufactured by Swedish Match, is associated with in a significant reduction in harm and the risk of tobacco-related disease as compared to smoking among individual tobacco users. These studies also illustrate the lack of convincing scientific evidence linking the use of Swedish snus to clinically significant gum disease, and tooth loss, and the weak and unconvincing evidence base for an association between use of snus and an increased risk of pancreatic cancer. Taken together, these studies permit a full assessment, using clinical risk endpoints, of the health risks of snus as compared to other consumer behaviors for other tobacco products on the market, most notably cigarettes.

6.1.1. Health Risks Associated with the Use of Snus as Compared to Using Cigarettes

6.1.1.1. Health Outcomes

This section of the Application summarizes the available data on the health risks associated with the use of Swedish snus compared to those from smoking, with emphasis on diagnoses that are most relevant to the proposed modified risk claims. The evidence was analyzed using the following three data sets:

1. Relative risk estimates from epidemiology studies of Swedish tobacco use in which snus and smoking are each compared to a reference population (usually non-users of tobacco products). In the following analyses of smoking related health outcomes, the results of numerous studies collectively provide evidence of much lower and typically no increased risks of smoking-related health endpoints from use of Swedish snus compared to the substantially increased risks from smoking.

2. Relative risk estimates from meta-analyses and large cohort studies of Swedish snus users and cigarette smokers, in which risk estimates were used to assess the relative risks for snus and for cigarettes, and to provide context to the data from the individual epidemiology studies. Although the relative risks and risk estimates from these large cohorts are not as directly comparable to each other, these data support the findings in the individual studies.

3. Risk data of smoking mortality in the United States were used to estimate potential excess mortality among smokers. The health outcomes included in this analysis, combined with nonmalignant respiratory diseases known to be caused by smoking, account for approximately 90% of all smoking-related deaths (Centers for Disease Control and Prevention (CDC) 2008).

The adverse health outcomes causally related to smoking were first confirmed in the 1960s, and have been well studied since that time (2010). These include lung and other cancers, noncancer pulmonary diseases such as emphysema and chronic obstructive pulmonary disease ("COPD"), CVD, and reproductive and developmental effects. The estimated disease mortality burden that smoking poses in the United States has been quantified using relative risk estimates from the American Cancer Society's Cancer Prevention Study II (CPS-II) data. These data are presented in (**Table 6-1**) (Centers for Disease Control and Prevention (CDC) 2008), ranked by the highest number of deaths among smokers attributed to each health outcome. More recently, the U.S. Food and Drug Administration revised the estimates of smoking-attributable mortality using updated relative risk assessments based on National Health Interview Survey data (Rostron 2012). In the updated analysis, the estimated attributable fractions of smoking-related deaths were very similar to those presented in the CDC (2008) analysis (see **Table 6-2**). However, because the updated analyses included fewer disease-specific categories, the original CDC (2008) estimates were used in the following analysis for all outcomes of interest except lung cancer, ischemic heart disease ("IHD"), other heart disease and stroke, for which the updated

Rostron (2012) estimates were available.

Table 6-1: Estimated Number of Outcome-Specific Deaths and Attributable Fraction among All Smokers, 2000-2004

Rank (by # of deaths)	Outcome	Smoking Deaths	Attributable Fraction*
1	**Lung Cancer**	125,522	32.0%
2	**IHD**	80,005	20.4%
3	COPD	78,988	20.1%
4	**Other heart disease**	21,004	5.3%
5	**Stroke**	15,922	4.1%
6	Bronchitis, Emphysema	13,927	3.5%
7	Pneumonia, influenza	10,423	2.7%
8	**Esophageal Cancer**	8,592	2.2%
9	**Aortic Aneurysm**	8,419	2.1%
10	**Pancreatic Cancer**	6,683	1.7%
11	Urinary Bladder Cancer	4,983	1.3%
12	**Oral Cancer**	4,893	1.2%
13	Kidney Cancer	3,043	0.8%
14	Laryngeal Cancer	3,009	0.8%
15	**Stomach Cancer**	2,484	0.6%
16	**Atherosclerosis**	1,893	0.5%
17	Other circulatory disease	1,254	0.3%
18	AML	1,192	0.3%
19	Cervical Cancer	447	0.1%

*Among a total estimate of 392,683 smoking-related deaths (males and females combined)

Bolded outcomes were those analyzed in the ENVIRON Snus Monograph (2013) appendix

Reference: CDC (2008) (Based on CPS-II data)

Table 6-2: Estimated Number of Outcome-Specific Deaths and Attributable Fraction (AF) among All Smokers, 2004			
Rank (by # of deaths)	**Outcome**	**Smoking Deaths**	**Attributable Fraction***
1	Lung Cancer	118,950	31.5%
2	COPD	91,045	24.1%
3	IHD	88,525	23.4%
4	Other heart disease	16,113	4.3%
5	Stroke	14,692	3.9%
6	Pneumonia, influenza	10,444	2.8%
*Among a total estimate of 377,521 smoking-related deaths (males and females combined) Reference: Rostron (FDA) (2012) (Based on NHIS data)			

The following analysis compares the relative risks for smoking-related adverse health outcomes among smokers and Swedish snus users in epidemiology studies that provide both of these estimates in a common study population, relative to non-tobacco users in the same population. The analysis examined health outcomes with the highest number of deaths attributable to smoking (i.e., lung cancer, CVD, and stroke), as well as several additional health outcomes provided in the studies.

The results presented in this section demonstrate that the use of Swedish snus presents a much lower risk, if any risk at all, of the tobacco-related diseases associated with smoking. The health outcomes included in this analysis, combined with nonmalignant respiratory diseases known to be caused by smoking, account for approximately 90% of all smoking-related deaths. Use of Swedish snus as an alternative to smoking is associated with a very large reduction in risk from CVD. In addition, there is no evidence of an association between Swedish snus and lung cancer or respiratory disease (i.e., COPD, bronchitis and emphysema, and pneumonia and influenza). Such risks are widely considered to be non-existent on mechanistic grounds because Swedish snus is a non-combusted tobacco product and, hence, does not involve the inhalation of firsthand or secondhand smoke.

6.1.1.2. Methodology: Study and Relative Risk Estimate Selection

This analysis used the pool of epidemiology studies of potential health risks among snus users identified in the literature search described in the Introduction and Appendix I of the ENVIRON Snus Monograph (2013). Relative risk estimates were extracted from studies that provided these estimates for snus users and cigarette smokers within the same study population. The overall

relative risk estimates, and those from sub-group analyses, including analyses of age- or dose (exposure)-groups, were plotted to provide a pictorial comparison of the relative risks for tobacco-related disease among users of snus and cigarettes (Figures A VI-1 – 10). A summary for each of the health outcomes that lists the selected relative risk estimates, as well as other relevant study details, is provided in Tables A VI-1 – 10 of the ENVIRON Snus Monograph (2013).

Lifelong non-tobacco users, the usual (and desirable) comparison group for each tobacco group, were not always available for each study analysis. Relative risk estimates that were not controlled for tobacco use in other categories (i.e., nonuse, smoking, or snus use), either by stratification or using other statistical methods, are listed and described in the ENVIRON Snus Monograph (2013), but are not plotted in the corresponding Figures. Relative risk estimates that are stratified by or adjusted for *current* tobacco use only, which may not account for past tobacco use, are included in the forest plots. When multiple relative risk estimates were available, the following order of preference was used to select the most valid comparisons:

- First, relative risk estimates in which a common reference group (e.g., never-users of tobacco) and common exposure groups (e.g., ever smokers vs. ever snus users) was provided;

- Second, relative risk estimates in which the exposures were defined similarly, such as ever users or current users (or whichever exposure groups were presented commonly for both smokers and snus users);

- Third, relative risk estimates from multivariate analyses in which potential confounders were included in the model were selected over relative risk estimates from uni-variate analyses, where possible and

- Finally, in dose-response analyses, the relative risk estimate for the highest tobacco use group was selected (for both snus and cigarette users).

This order of selection was followed if the preferred relative risk estimates were available; however, there were instances where more than one relative risk estimate was included (e.g., multivariate in addition to relative risk estimates stratified by tobacco use, dose and/or duration groups, gender, mortality and incidence, age groups, etc.). In situations where the preferred analyses were carried out for only one tobacco type (i.e., smoking but not for snus), relative risk estimates meeting the lower-priority criteria were selected for the plot so that the health risks of snus and cigarettes were more comparable. Relative risk estimates selected for each health outcome include both morbidity and mortality endpoints.

In addition to relative risks from the individual epidemiology studies, the summary data for each health outcome also include results of recently-published meta-analyses or large cohorts identified in the literature search described above. The results from the meta-analyses of snus studies may be overlapping (e.g., where meta-analyses were conducted on the same or similar set of studies). Boffetta et al. (2008) conducted a meta-analysis for four cancer outcomes

(esophageal, lung, oral and pancreatic). Boffetta and Straif (2009) conducted a meta-analysis of CVD and stroke. Lee and Hamling (2009b) published a meta-analysis of cancer outcomes. These data were also presented by Lee (2011), which also presented summary relative risk estimates for CVD and stroke. Lee (2007) presented a summary relative risk specifically for ischemic heart disease (IHD), myocardial infarction (MI) and stroke. Additional epidemiology studies of these outcomes were subsequently published by Hansson et al. (2009).

Several targeted literature searches were conducted for smoking-related morbidity and mortality using methods similar to those described earlier. Three meta-analyses for specific outcomes (i.e., diabetes, pancreatic cancer, and stroke) among smokers compared to nonsmokers were identified (Iodice et al. 2008; Shinton and Beevers 1989; Willi et al. 2007). The literature search also identified relative risk estimates for the specific health outcomes among smokers compared to nonsmokers from three large US cohorts and one large, international case control study. These are presented on the plots and include CPS-II (SAMMEC 2013; USDHHS 1989), the Kaiser Permanente cohort (Friedman et al. 1997), the U.S. Veterans cohort (McLaughlin et al. 1995) and the large INTERHEART case-control study of myocardial infarction (Teo et al. 2006).

Forest plots of relative risk estimates for each of nine health outcomes are presented in Figures A VI-1 – 10.

6.1.1.3. Results

The results of the risk analyses for each of the health outcomes that were analyzed for snus users and cigarette smokers are summarized below. Health outcomes that represent the highest attributable fraction of smoking-related deaths are presented first, followed by health outcomes that provide a smaller fraction, or for which no smoking-related attributable risk estimates were identified (e.g., diabetes).

The summary for each health outcome provides a brief description of the literature (e.g., the number and type of studies available), a summary of the relative risk estimates as selected for and presented in the Tables and Figures of Appendix VI of the ENVIRON Snus Monograph (2013), a discussion of the study qualities, and an overall conclusion for that outcome. The overall results and figures from that appendix are provided here.

Lung Cancer (Figure A VI-1)

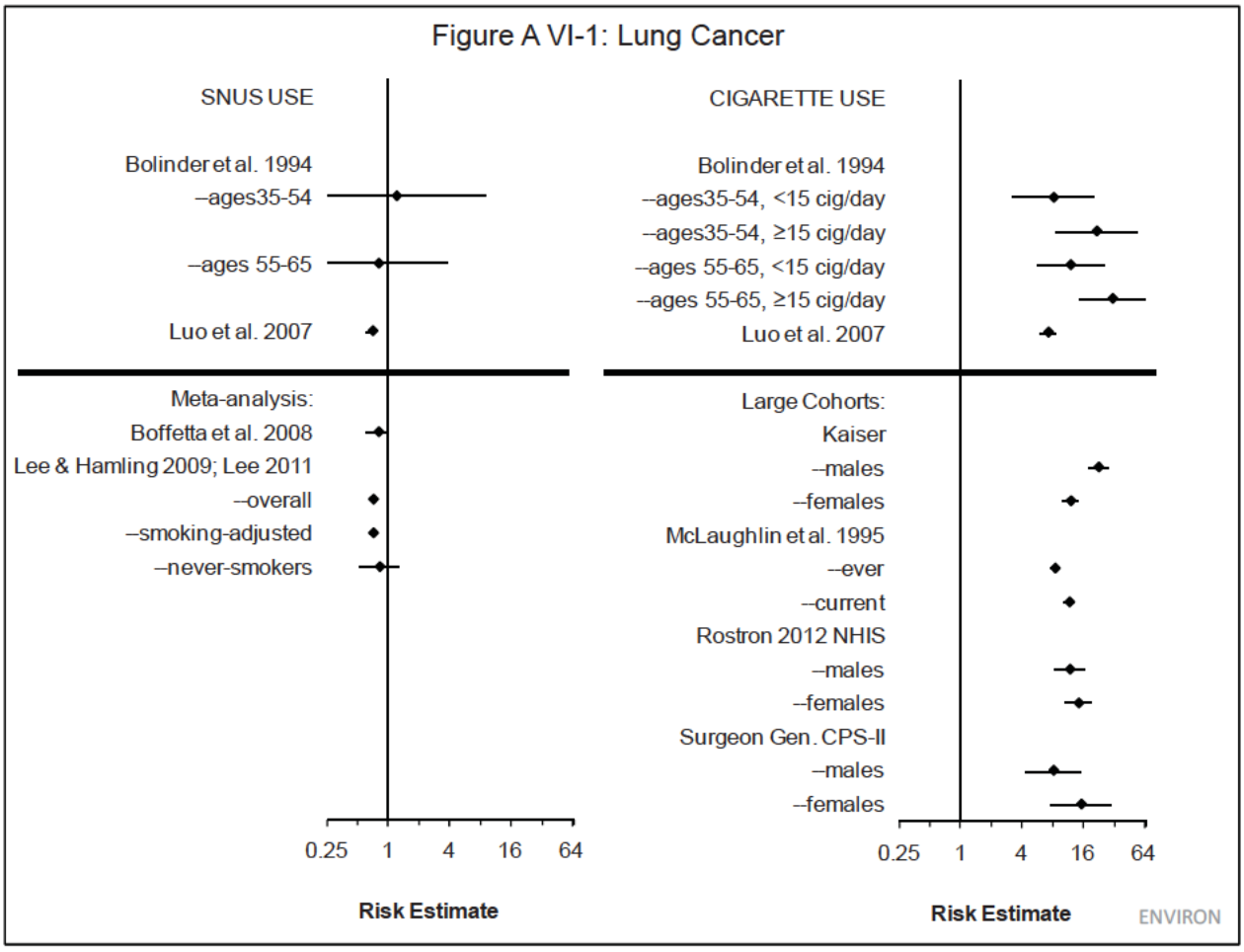
- Two Swedish cohort studies reported lung cancer risk estimates for both snus users and smokers in the same population, and two meta-analyses reported summary risk estimates from the Swedish cohort studies (Boffetta et al. 2008; Bolinder et al. 1994; Lee 2011; Luo et al. 2007).

- Neither the relative risks from the individual studies nor the summary estimates from the two meta-analyses were significantly increased among Swedish snus users. Almost all of the point estimates were below 1.0, and one study (Luo et al. 2007) reported a significantly reduced risk of lung cancer among snus users. As expected, the risk estimates among

smokers were all significantly increased, with risk estimates ranging from 7.2 to 30.6 in the individual studies (Bolinder et al. 1994; Luo et al. 2007) and from 8.1 to 22.3 among the large US cohorts (Friedman et al. 1997; McLaughlin et al. 1995; Rostron 2012; USDHHS 1989).

- The two available studies of Swedish snus users and smokers used a common reference group and comparable exposure groups for smokers and snus users (Bolinder et al. 1994; Luo et al. 2007).

- 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).



Cardiovascular Disease (CVD): (ischemic heart disease (IHD), coronary heart disease (CHD), myocardial infarction (MI) and Overall CVD) (Figure A VI-2)

- Six cohort studies (Bolinder et al. 1994; Haglund et al. 2007; Hansson et al. 2009; Janzon and Hedblad 2009; Johansson et al. 2005; Roosaar et al. 2008), four case-control studies (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Wennberg et al. 2007), and one cross-sectional study (Bolinder et al. 1992) reported relative cardiovascular risk estimates for both snus users and smokers in the same population. The study by Janzon and Hedblad (2009) was excluded from the analysis because this study did not provide a smoking relative risk estimate that was adjusted or controlled to exclude the potential effects of snus use. The cross-sectional study conducted by Bolinder et al. (1992) was not included in the plot because the later study by Bolinder et al. (1994) presented a prospective analysis of the same cohort.

- Among snus users, relative risk estimates for CVD included in this analysis were not significantly increased for the individual studies, with the exception of increased risks of IHD and overall CVD observed in the Swedish Construction Worker cohort study reported by Bolinder et al. (1994). Pooled risk estimates from meta- and pooled-analyses combining studies of snus users were generally consistent in showing no increased risk, except for a small, statistically significant increase in fatal MI reported by Boffetta and Straif (2009). The more recent meta-analysis (Lee 2011) and pooled analysis (Hansson et al. 2009) found no increased summary risk of any or fatal MI. Among smokers, all but one point estimate (for individuals smoking ≤10 cigarettes/day) (Huhtasaari et al. 1992), were significantly increased. This is consistent with the risk estimates from the large US CPS-II cohort and a case-control study of 52 countries (Teo et al. 2006). The relative risk estimates for CVD among Swedish smokers extracted from the individual studies generally ranged from 1.5 to 3.6.

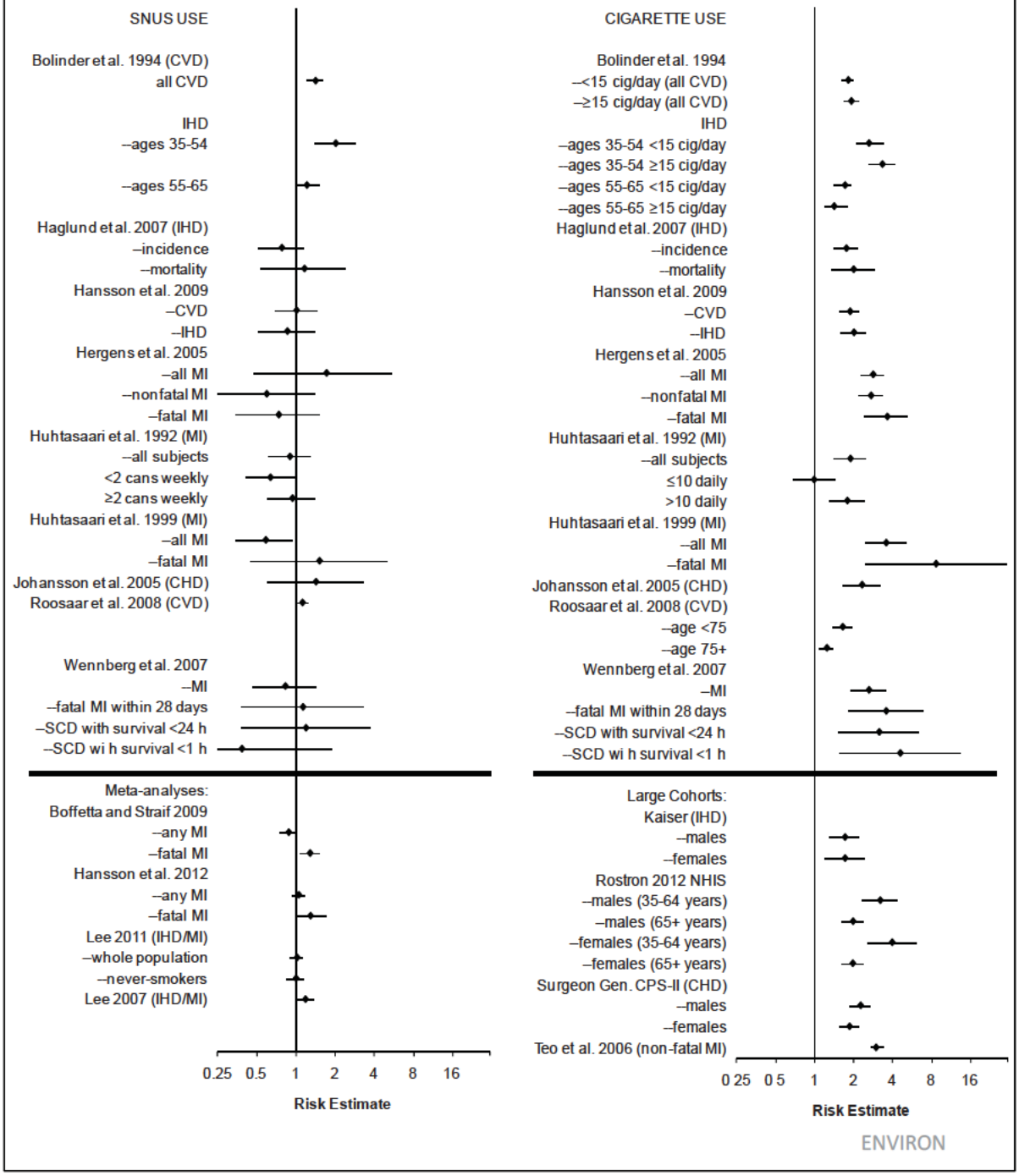
- Only Roosaar and colleagues (2008) did not use a common reference group for smokers and snus users. Control for confounders varied by study, but generally included several important risk factors for cardiovascular disease. Outcome definitions varied from study to study, though most include MI or IHD and include similar International Classification of Disease (ICD) code definitions, although the Bolinder et al. (1994) and Roosaar et al. (2008) studies included a broader spectrum of cardiovascular events not included in the other studies. Three of the studies used in the forest plots compared risk estimates based on different exposure groups (Bolinder et al. 1994; Johansson et al. 2005; Roosaar et al. 2008).

- 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. In particular, the study conducted by Hansson et al. (2009) of more than 16,000 participants within the Swedish Twin Registry provided convincing evidence that snus use (at any intensity) is not significantly associated with an increased risk of overall CVD or IHD, while an increased risk among smokers was observed as expected. Hansson et al. (2009) used similar exposure groups, and included tobacco use categories of exclusive snus users or smokers, and controlled for important potential confounders, such as age, sex, diabetes, blood pressure, and cholesterol levels. The summary risk estimate for IHD by Lee (2007)

did not include Hansson et al. (2009) which had not yet been published.

- Known differences in exposures may account for the observed difference in risk of CVD between snus users and cigarette smokers. Though snus users and smokers are both exposed to nicotine, which has known acute effects on the cardiovascular system, cigarette smokers are also exposed to other cardiovascular toxicants including carbon monoxide and fine particulate matter. Pope et al. (2009) concluded that relatively low levels of fine particulate exposure from secondhand cigarette smoke are sufficient to induce adverse biological responses that increase the risk of cardiovascular disease mortality.

Figure A VI-2: Cardiovascular Disease (IHD, CHD, MI and Overall CVD)



Stroke (Figure A VI-3)

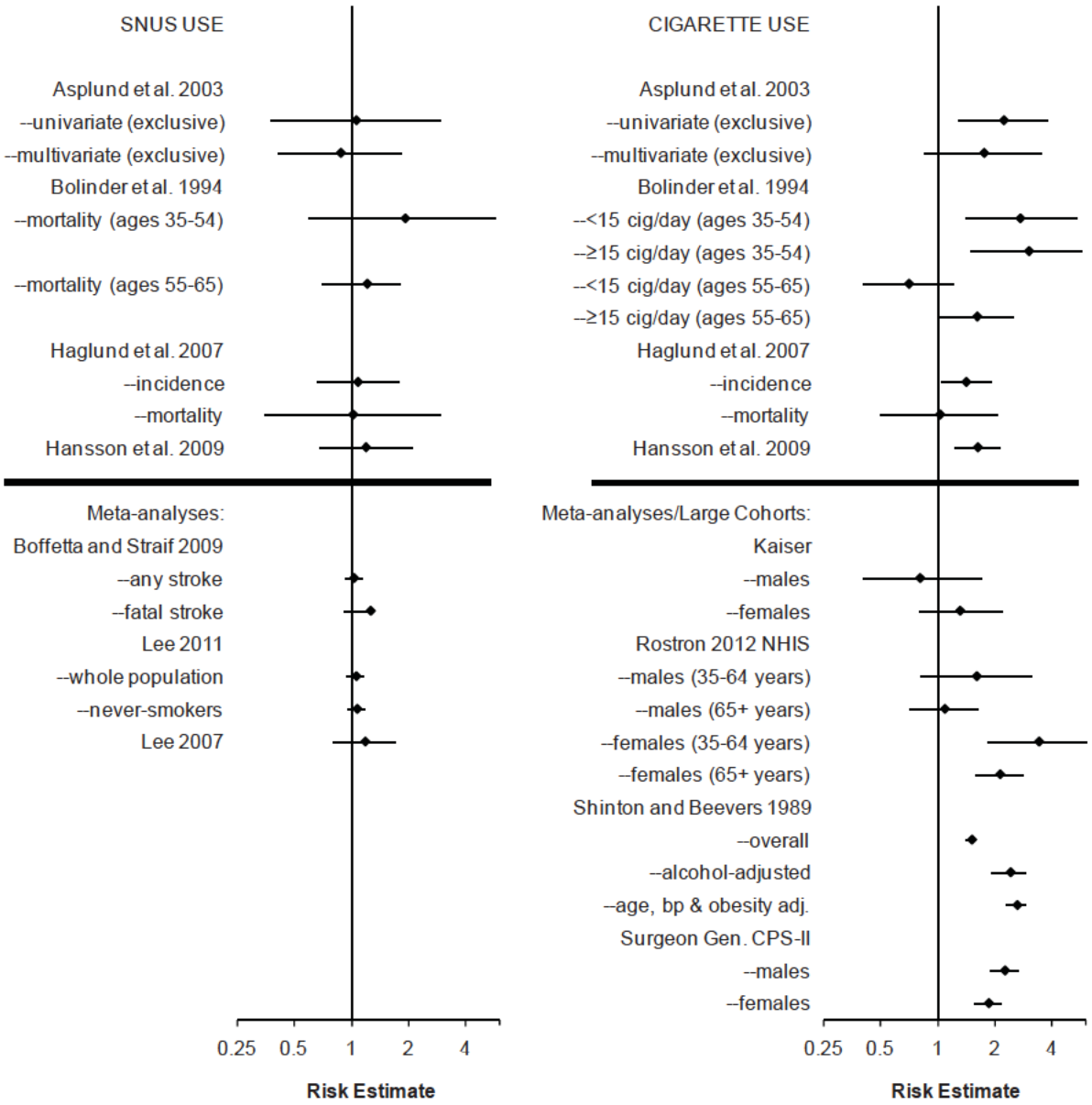
- Two case-control (Asplund et al. 2003; Koskinen and Blomstedt 2006) and four cohort studies (Bolinder et al. 1994; Haglund et al. 2007; Hansson et al. 2009; Janzon and Hedblad 2009) reported relative risk estimates for stroke among both snus users and smokers in the same population. One case-control study (Koskinen and Blomstedt 2006) and one cohort study (Janzon and Hedblad 2009) were excluded from the forest plots because the authors did not control for tobacco use among snus users, smokers, or both.

- Among snus users, stroke risk estimates from the individual studies and summary estimates from meta-analyses (Boffetta and Straif 2009; Lee 2007; Lee 2011) were not significantly increased. Among smokers, risk estimates from most of the individual studies were significantly increased and where increased, generally ranged from 1.4 to 3.0. Meta-analyses and large US cohorts were generally consistent with the results from the individual studies.

- All of the individual studies cited above except Bolinder et al. (1994) used a common reference group for smokers and snus users. Outcome definitions for stroke were also similar among the studies. The analyses in three of the four studies (Asplund et al. 2003; Bolinder et al. 1994; Hansson et al. 2009) controlled for high blood pressure or hypertension, an important risk factor for 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. Of the four studies (Asplund et al. 2003; Bolinder et al. 1994; Haglund et al. 2007; Hansson et al. 2009), which included two cohort studies of the Swedish Construction Workers and Swedish Twin Registry, none reported any significantly increased risk of stroke among snus users, while all four reported a significantly increased risk among smokers. Further, the Swedish Twin Registry (Hansson et al. 2009) provided relative risks that were adjusted for high blood pressure, a major potential confounder.

Figure A VI-3: Stroke



Respiratory Disease

- There is no known mechanism by which snus could cause nonmalignant respiratory disease. By contrast, nonmalignant respiratory disease is a major cause of smoking-related death. These diseases include chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, pneumonia, and influenza, which account for 103,338 (26.3%) smoking-related deaths annually (Centers for Disease Control and Prevention (CDC) 2008).

- No studies are available that investigated the relationship between the use of Swedish snus and any of these nonmalignant respiratory diseases, although one study investigated the effects of snus use and smoking on respiratory death in general. Roosaar and colleagues (2008) reported a significantly increased risk of respiratory death among smokers (RR = 1.7; 95% CI: 1.2-2.3) and snus users over the age of 80 years (RR = 1.8; 95% CI: 1.2-2.7). No increased risk of respiratory death among snus users was observed among those younger than age 80 (RR = 0.8; 95% CI: 0.4-1.6).

- Of the HPHCs in STPs which CTP has identified to date, none has been suggested to be linked to the development of chronic lung disease unless they are inhaled. Expert panels (Levy et al. 2004) and institutional reports (SCENIHR 2007) have not considered the possibility that use of STPs could be a significant risk factor for respiratory disease. Therefore, the significant excess risk of respiratory death among those over age 80 could be due to confounding by other factors or to exposure misclassification. Indeed, the SCENIHR working group stated that "there is no consistent evidence that any smokeless tobacco products cause any of these major respiratory diseases. Complete substitution of STPs for tobacco smoking would thus ultimately prevent nearly all deaths from respiratory disease currently caused by smoking" (SCENIHR 2008). 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.

COPD

- COPD is commonly defined as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases" (Pauwels et al. 2001). Diagnosis is largely confirmed by spirometry using the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC). The presence of an $FEV_1 < 80\%$ of the predicted value, in combination with an $FEV_1/ FVC < 70\%$, confirms the presence of airflow limitation that is not fully reversible (Pauwels et al. 2001).

- COPD is usually considered to have three components (USDHHS 1984): airway thickening and narrowing with expiratory airflow obstruction, chronic mucus hypersecretion resulting in chronic cough and phlegm production, and emphysema, an abnormal dilation of distal airspaces combined with destruction of alveolar walls (Rennard and Vestbo 2008). There is a strong relationship between combustible tobacco use (mainly cigarettes) and COPD

(USDHHS 1984). A major hypothesis is that oxidative stress is largely responsible as a major predisposing factor for the smoking-induced COPD response (Barnes 2014; Kirkham and Barnes 2013). An alternative (and much older) theory is that COPD is the result of an imbalance between pulmonary proteases and anti-proteases (Abboud and Vimalanathan 2008), including a genetic deficiency of α_1-antritrypsin (Stoller and Aboussouan 2012).

- The pathobiology of COPD encompasses multiple injurious processes including inflammation (excessive or inappropriate innate and adaptive immunity), cellular apoptosis, altered cellular and molecular alveolar maintenance program, abnormal cell repair, extracellular matrix destruction (protease and anti-protease imbalance), and oxidative stress (oxidant and antioxidant imbalance). These processes are triggered by urban and rural air pollutants and cigarette smoke and modified by cellular senescence and infection. A series of receptor-mediated signal transduction pathways are activated by reactive oxygen species and tobacco components, resulting in impairment of a variety of cell signaling and cytokine networks, subsequently leading to chronic airway responses with mucus production, airway remodeling, and alveolar destruction (Barnes 2014; Kirkham and Barnes 2013; Yoshida and Tuder 2007).

- It is widely accepted that COPD results from long term exposure to airborne irritants. Some of the non-smoking risk factors for COPD are well-known and include occupational exposures, air pollution, airway hyperresponsiveness, asthma, and certain genetic variations, although many questions, such as why only < 20% of smokers develop significant airway obstruction, remain (Mannino 2002). Probably the most important risk factors, other than smoking, are age (Hagstad et al. 2012; MacNee 2009; Tuder and Petrache 2012) and genetic predisposition (Barnes 2014; Castaldi et al. 2010; El-Zein et al. 2012; Kirkham and Barnes 2013; Zhou et al. 2013).

- An extensive review of the literature (PubMed, SCOPUS) indicates that there is essentially no relationship between COPD and use of STPs such as Swedish snus (Schivo et al. 2014), nor with use of various types of nicotine replacement therapy (NRT) (Jimenez-Ruiz et al. 1998). This absence of a relationship is probably due to the above-mentioned theory of oxidative stress of cigarette smoke (Kirkham and Barnes 2013; Stevenson et al. 2006) introduced directly into the lungs being a likely contributor to the causation of COPD. Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking and exacerbations, with oxidative stress persisting long after the cessation of cigarette smoking or exacerbation, due to the continued production of reactive oxygen species from endogenous sources (Kirkham and Barnes 2013). Clearly, no such oxidative stress (Sundar et al. 2013) in the lungs is involved in the oral use of Swedish snus or in various types of NRT. At the same time, systemic nicotine concentrations would also not appear to be relevant. Age seems to be the most important factor in the development of COPD in Swedish non-smokers (Hagstad et al. 2012).

- In sum, it is widely accepted that COPD results from long term exposure from airborne irritants such as tobacco smoke and air pollution (e.g., from certain occupational exposures

and cooking fumes), among individuals with a certain genetic predisposition, rather than systemic exposure to any of the HPHCs identified in snus. In fact, of the HPHCs identified by CTP in smokeless tobacco (including Swedish snus) none has been suggested to be linked to the development of COPD (unless they are inhaled). Expert panels (Levy et al. 2004) and institutional reports (SCENIHR 2008) have not considered the possibility that use of STPs could be a significant risk factor for COPD, or any other acute or chronic lung disease. 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.

Esophageal Cancer (Figure A VI-4)

- Two case-control studies (Lagergren et al. 2000; Lewin et al. 1998) and one cohort study (Zendehdel et al. 2008) reported esophageal cancer risk estimates for both Swedish snus users and smokers in the same population.

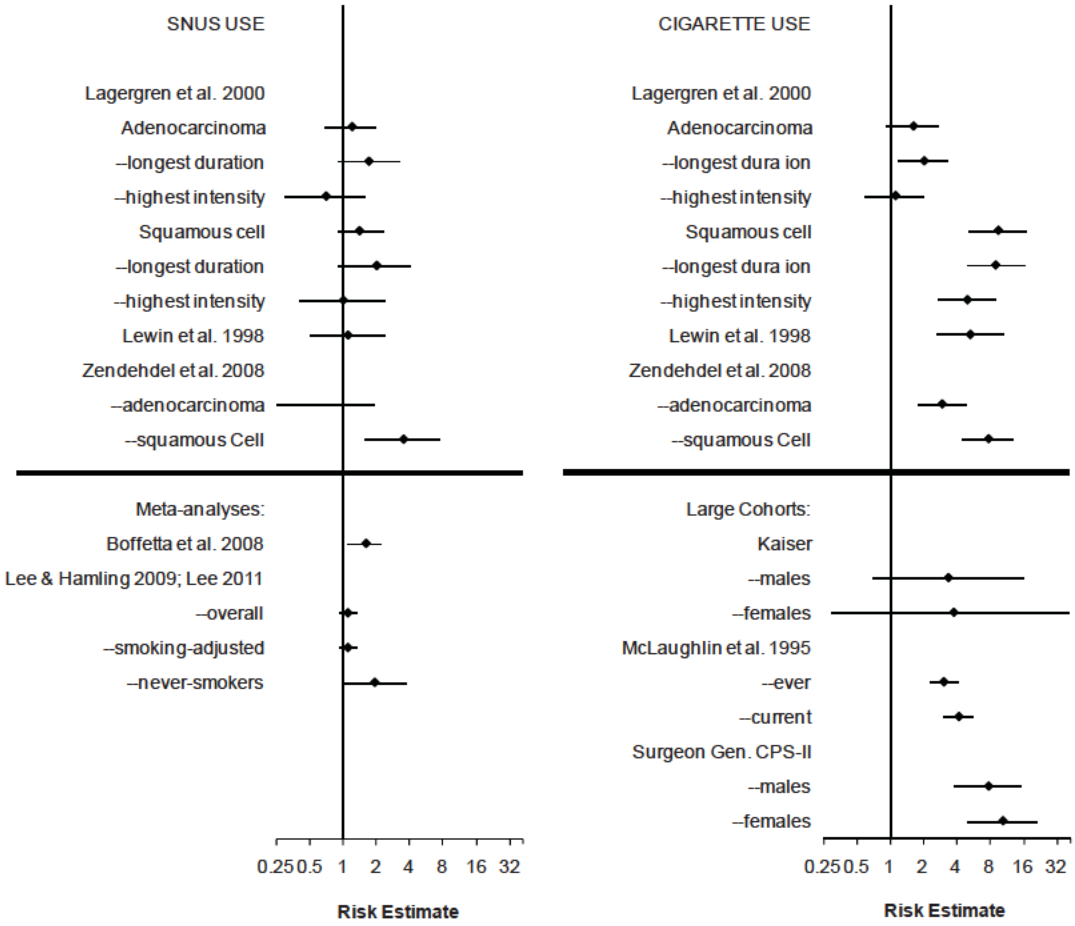
- Among snus users, two studies (Lagergren et al. 2000; Lewin et al. 1998) did not observe an association between snus use and esophageal cancer risk while one study (Zendehdel et al. 2008) reported a significant excess for one esophageal cancer subtype, squamous-cell carcinoma; (RR = 3.5; 95% CI: 1.6-7.6). Esophageal cancer risks were nearly universally increased for smokers in these studies, with the exception of adenocarcinoma among current smokers and high intensity smokers in the Lagergren et al. (2000) study. Point estimates for esophageal cancer risk among smokers ranged from 1.6 to 2.9 for adenocarcinoma and 7.6 to 9.3 for squamous cell carcinoma. Lewin et al. (1998) reported a relative risk estimate of 5.2 for smokers for all subtypes of esophageal cancer combined.

- Two meta-analyses of snuff users are consistent with the overall results for esophageal cancer among Swedish snus users: Lee and Hamling (2009b) and Lee (2011) reported no significant increase of esophageal cancer for all subtypes combined. In the only study that examined risk among never smokers, the relative risk estimate for esophageal cancer was borderline significant (RR = 1.92; 95% CI: 1.0-3.68; Zendehdel et al. 2008). Boffetta and colleagues (2008) reported a significantly increased summary estimate based on the higher squamous cell risk estimates from Lagergren et al. (2000) and Zendehdel et al. (2008), combined with the risk estimate for any subtype of esophageal cancer from Lewin et al. (1998). By comparison to snus, relative risks for esophageal cancer among smokers from the large cohorts were all significantly increased, and were generally consistent with relative risk estimates from the individual studies, ranging from 3.3 to 10.3 among current smokers.

- Only Zendehdel et al. (2008) used common reference groups for snus and smoking risk estimates (i.e., never-users of any tobacco). Lewin et al. (1998) reported the risk only for combined subtypes. The number of cases of esophageal cancer among snus users in the Zendehdel et al. (2008) study was small, especially for adenocarcinoma. This was the only study that did not control for potential confounding from alcohol.

- Overall, three of the four studies of esophageal cancer did not find an increased risk among Swedish snus users. The one study that found an increased risk did not control for alcohol (Zendehdel et al. 2008); a dose-response was suggested in another study (Lagergren et al. 2000). 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.

Figure A VI-4: Esophageal Cancer



Pancreatic Cancer (Figure A VI-5)

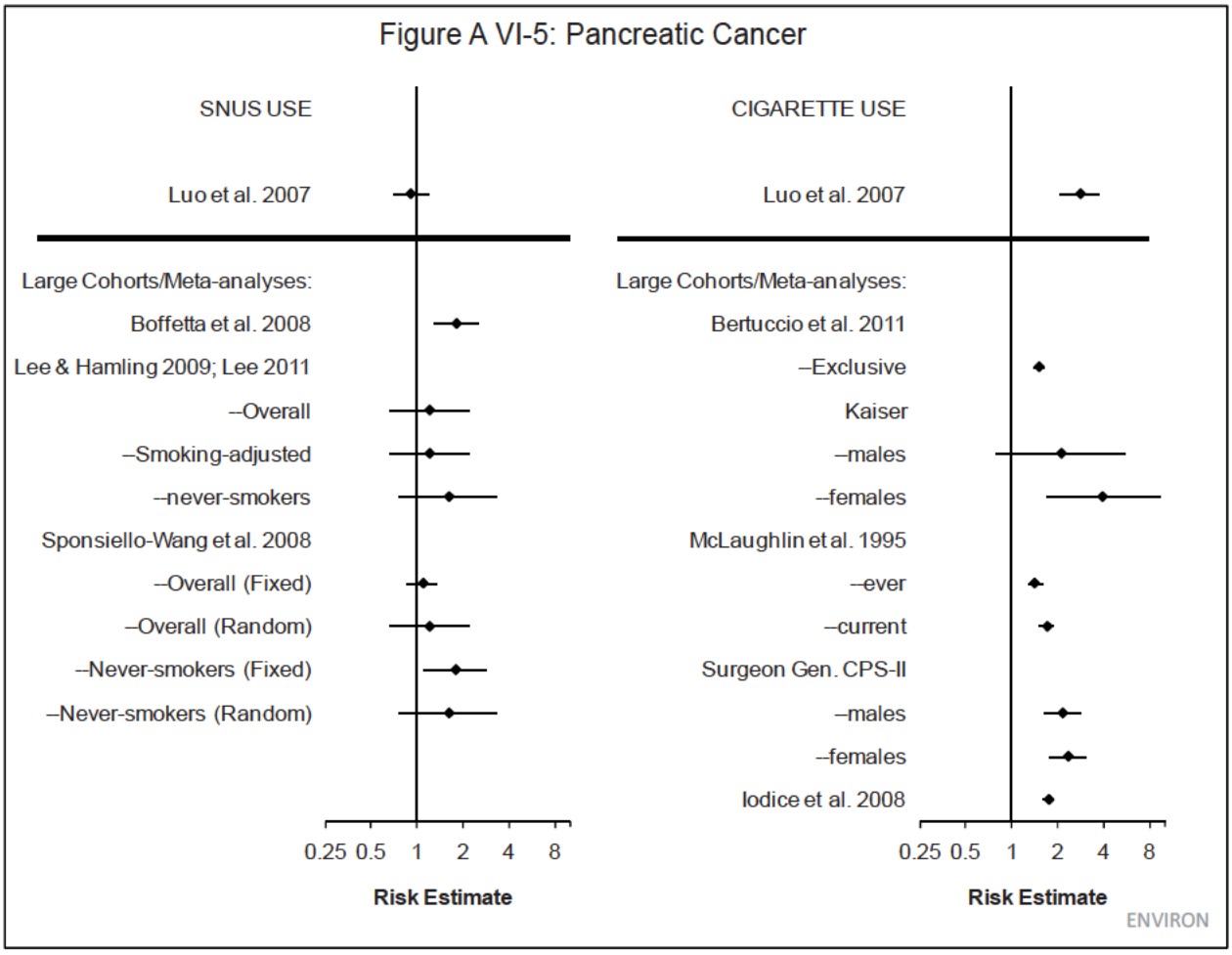
- Three reports (based on two separate cohorts) reported pancreatic cancer risk estimates for both snus users and smokers (Boffetta et al. 2005; Heuch et al. 1983; Luo et al. 2007). Of these, only the Luo et al. (2007) study was included in this analysis due to limitations in the analyses of the other two reports: Boffetta et al. (2005) did not provide an analysis among smokers that accounted for snus use, and Heuch et al. (1983), which was updated by the Boffetta et al. (2005) analysis, did not include confidence intervals in the multivariate

analysis, and the tobacco type used among participants of the study is unclear.

- In the one analysis within the study by Luo et al. (2007) which permitted a comparison of risks between snus users and smokers, the risk of pancreatic cancer among ever-users of snus (adjusted for smoking) was similar to never-users of any tobacco, while the risk among smokers (adjusted for snus use) was significantly increased (RR = 2.8; 95% CI: 2.1-3.7). Although the authors also reported the relative risk of pancreatic cancer among never-smoking snus users, they did not do a comparable analysis among smokers who were never-users of snus. The risk estimates used in the forest plot include those with common reference and exposure groups.

- Consistent with the known association between smoking and risk of pancreatic cancer, the relative risks of pancreatic cancer among smokers from the large US cohorts (Bertuccio et al. 2011; Friedman et al. 1997; Iodice et al. 2008; McLaughlin et al. 1995; USDHHS 1989) were elevated, and generally ranged from 1.4 to 2. Most of the point estimates from meta-analyses of snus users (Boffetta et al. 2008; Lee 2011; Lee and Hamling 2009b; Sponsiello-Wang et al. 2008) were generally around 1.0 with a few significant excesses observed, depending on the risk estimate selection criteria employed by the authors. For example, Boffetta et al. (2008) selected the higher relative risks from the Boffetta et al. (2005) and Luo et al. (2007) studies (smoking-adjusted from Boffetta et al. (2005) and the relative risk among never-smokers from Luo et al. (2007). Lee (2011) combined similar analyses and presented the smoking-adjusted and never-smoking summary estimates separately.

- 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 (Bertuccio et al. 2011; Boffetta et al. 2008; Friedman et al. 1997; Iodice et al. 2008; Lee 2011; Lee and Hamling 2009b; McLaughlin et al. 1995; Sponsiello-Wang et al. 2008; USDHHS 1989). Bertuccio et al (2011) recently performed a pooled-analysis of studies of cigarette and Western population smokeless tobacco users (though not Swedish snus) from eleven (11) international case-control studies. They reported an increased risk of pancreatic cancer among smokers (RR=1.5, 95% CI: 1.4-1.6), but found no increased risk of pancreatic cancer among smokeless tobacco users (RR = 0.62, 95% CI: 0.37-1.04). Although not specific to snus, this finding for smokeless tobacco suggests that it is unlikely that Swedish snus poses a risk for pancreatic cancer, particularly given that the smokeless tobacco products used by participants in these studies likely contained *similar or even higher* levels of tobacco-specific nitrosamines (TSNAs)—the principal component of tobacco thought to be associated with the development of pancreatic cancer—than Swedish snus. (Boffetta et al. 2008).



Oral Cancer (Figure A VI-6)

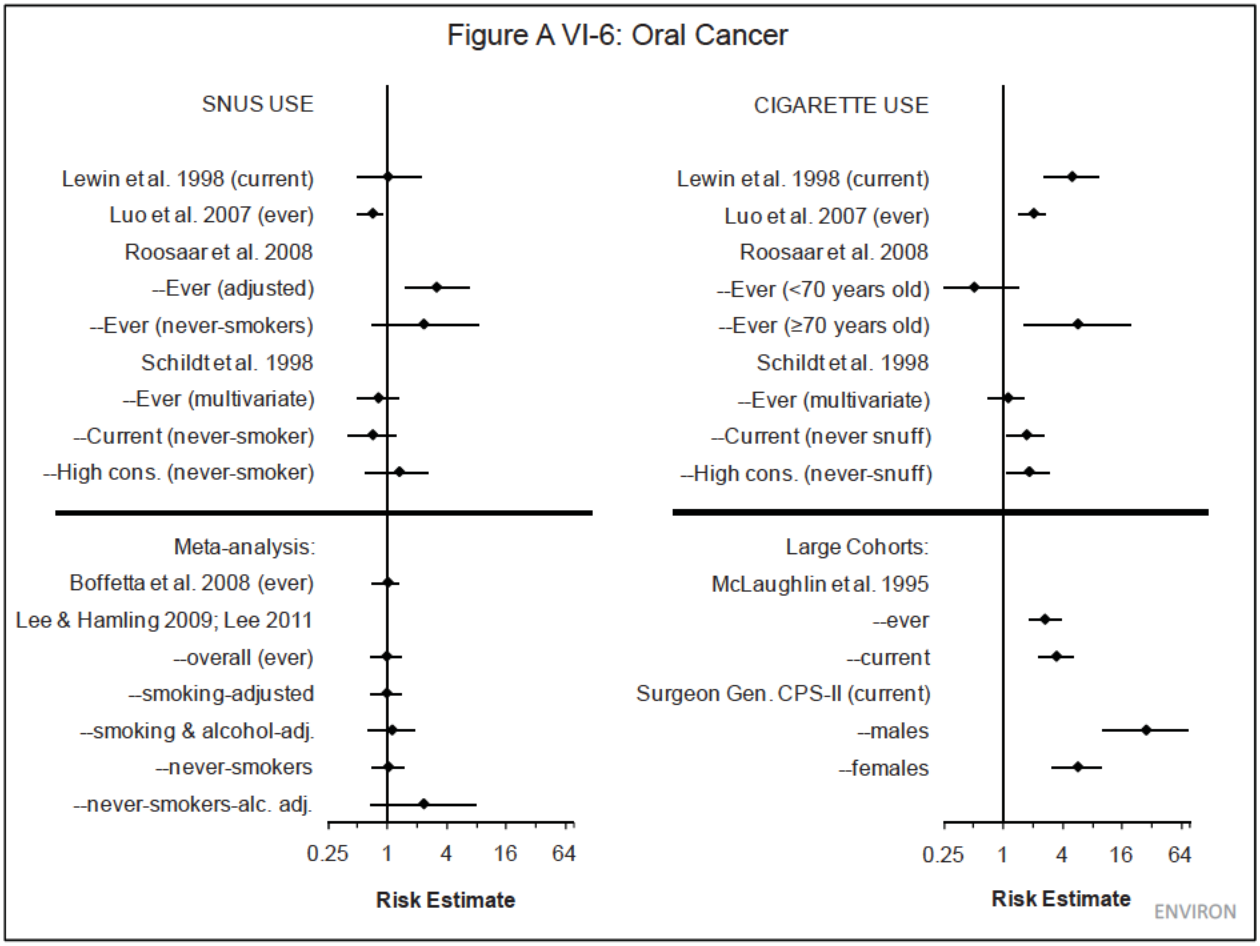
- Three case-control studies (Lewin et al. 1998; Rosenquist et al. 2005; Schildt et al. 1998) and two cohort studies (Luo et al. 2007; Roosaar et al. 2008) reported oral cancer risk estimates for both Swedish snus users and smokers in the same population. One case-control study (Rosenquist et al. 2005) was excluded from the forest plot because it is unclear whether the smoking estimates were adjusted for snuff use.

- Among snus users, risk estimates from the individual studies and summary estimates from meta-analyses were not significantly increased, with only one significant excess observed in a single study. Roosaar et al. (2008) observed an increased risk among ever-users of snus (adjusted for smoking), though this excess disappeared when analyzed among never-smokers. Among current or ever smokers, significantly increased risk of oral cancer was observed in most studies, ranging from 1.7 to 4.9, and all of the relative risk estimates from the large US cohorts (McLaughlin et al. 1995; USDHHS 1989) were significantly increased (ranging from 2.6 to 27).

- All of the studies except Luo et al. (2007) controlled for alcohol consumption, a known risk factor for oral cancer. Luo et al. (2007) was also the only study that used a common reference group for smokers and snus users. Most of the studies included in this analysis used comparable exposure groups, except for Roosaar et al. (2008), which stratified smokers by age, but did not provide a similar analysis for snus users. In addition, the ICD codes included in the definition of oral cancer varied by study.

- 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. This conclusion is based on evidence from various Swedish populations in four different case-control and cohort studies (Lewin et al. 1998; Luo et al. 2007; Roosaar et al. 2008; Schildt et al. 1998) (including the Swedish Construction Worker cohort, which was the only cohort not adjusted for alcohol consumption). In these same studies and in large US cohorts, the risk of oral cancer morbidity and mortality is consistently increased among the smokers, with risk estimates ranging from 1.7 to 27 (Lewin et al. 1998; Luo et al. 2007; McLaughlin et al. 1995; Roosaar et al. 2008; Schildt et al. 1998; USDHHS 1989).

Figure A VI-6: Oral Cancer



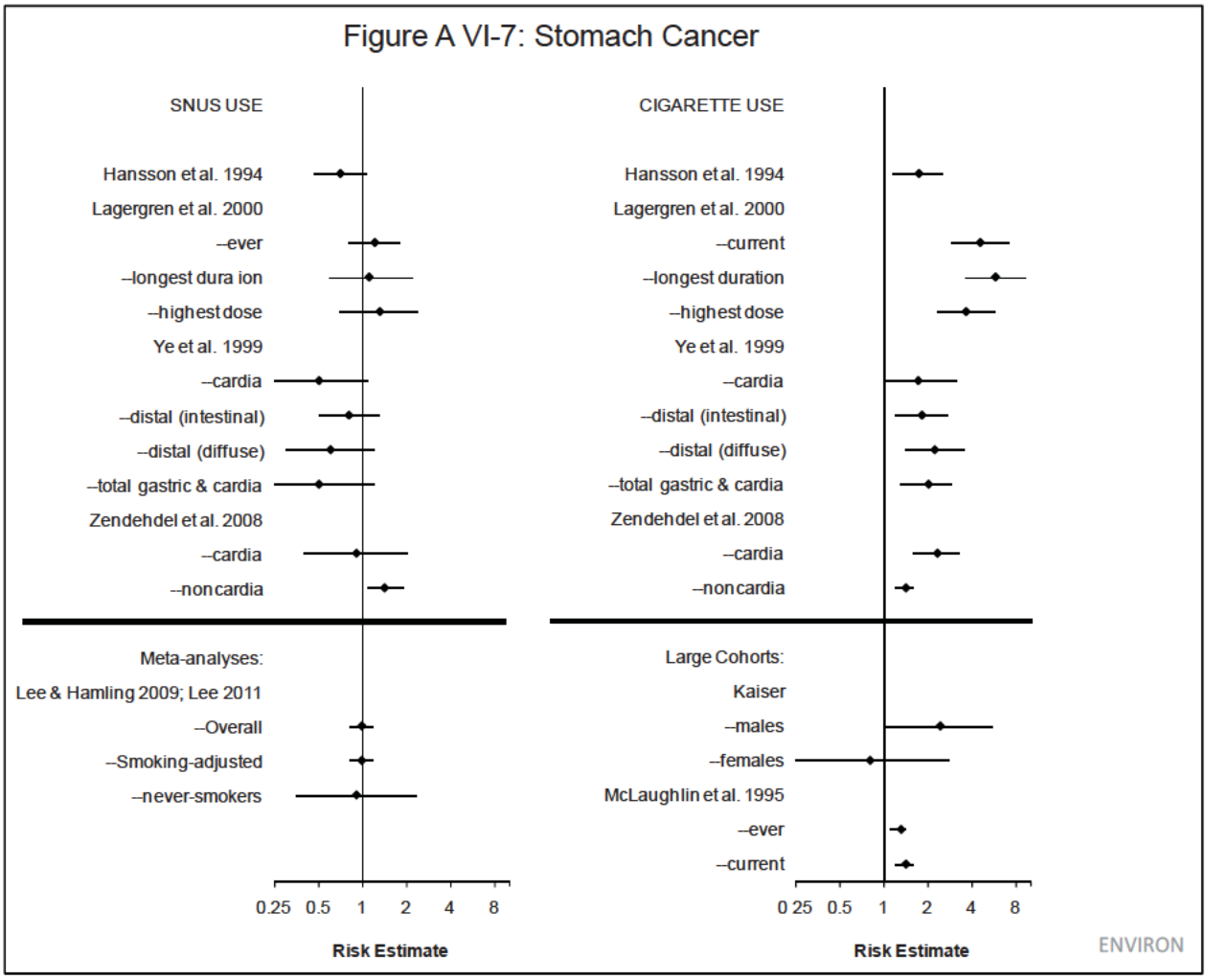
Stomach Cancer (Figure A VI-7)

- Three case-control studies (Hansson et al. 1994; Lagergren et al. 2000; Ye et al. 1999) and one cohort study (Zendehdel et al. 2008) reported risk estimates for both snus users and smokers in the same population.

- Among snus users, risk estimates from the individual studies (Hansson et al. 1994; Lagergren et al. 2000; Ye et al. 1999) and summary estimates from meta-analyses (Lee 2011; Lee and Hamling 2009b) were not increased, with the one exception of a significant excess observed for the non-cardia stomach cancer subtype (RR = 1.4; 95% CI: 1.1-1.9) (Zendehdel et al. 2008). Among smokers, almost all of the risk estimates among the individual studies were significantly increased (ranging from 1.4 to 2.3). Summary estimates from meta-analyses (Lee 2011; Lee and Hamling 2009b) and relative risks from large US cohorts (Friedman et al. 1997; McLaughlin et al. 1995) were consistent with the results from the individual studies among snus users and smokers, respectively.

- As described in Table A VI-7, which provides details for the individual studies, the comparability among studies was somewhat limited. The type of stomach cancers included in the four studies differed. Two of the four studies used common reference groups (Ye et al. 1999; Zendehdel et al. 2008), and only one study used comparable exposure groups (Ye et al. 1999).

- 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 (Lee 2011; Lee and Hamling 2009b).



Diabetes (Figure A VI-8)

- Two cross-sectional studies (Persson et al. 2000; Wandell et al. 2008), a third cross-sectional study with follow-up (Eliasson et al. 2004), and two cohort studies (Hilding et al. 2005; Ostenson et al. 2012) reported risk estimates for diabetes among snus users and smokers in the same population. One cohort study was excluded from the forest plot because it was unclear if other forms of tobacco use were controlled for among snus users and smokers (Hilding et al. 2005), however the same study population was examined in a more recent study (Ostenson et al. 2012).

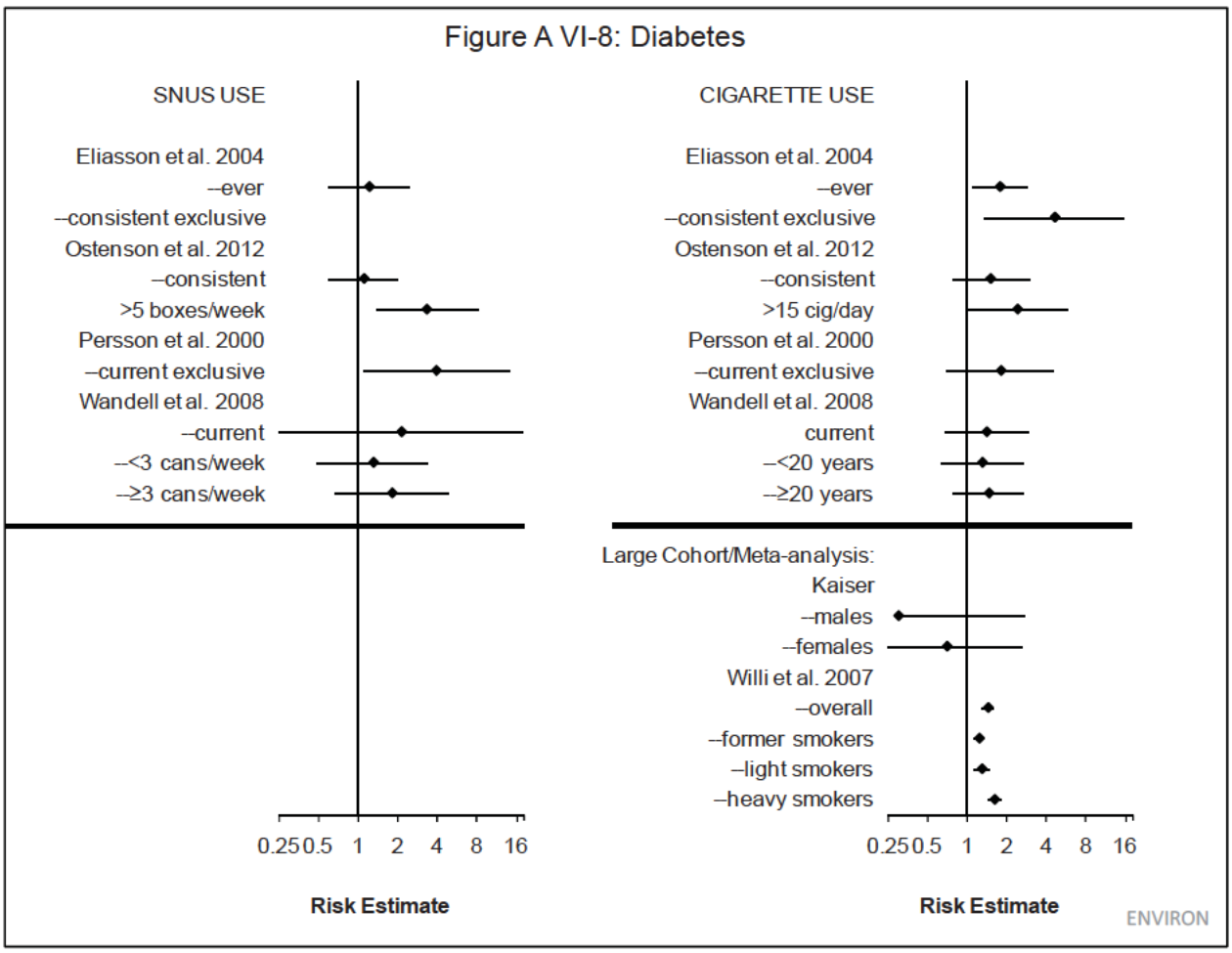
- Of the four studies included in the forest plot, one cross-sectional study (Persson et al. 2000) reported a significantly increased prevalence of diabetes among current exclusive snus users, and Ostenson et al. (2012) reported a significant association between high consumption (defined as >5 boxes of snus/week) and type 2 diabetes, but not among consistent snus users adjusted for smoking, or consistent exclusive snus use. Although this study adjusts for most of the important potential confounders with the exception of

any dietary variables, it presents many limitations, including the exclusion of diabetes cases discovered during follow-up, which may have differed with respect to tobacco use characteristics compared to cases ascertained at the final follow-up point. This and other study limitations are described in greater detail in Appendix III – M2 of the ENVIRON Snus Monograph (2013). For smokers, the cross-sectional study with follow-up (Eliasson et al. 2004) was the only study that reported an increased prevalence and incidence of diabetes (consistent with the meta-analysis among smokers by Willi et al. (2007)).

- Though few important potential confounders were accounted for, only Eliasson and colleagues (2004) reported risk estimates using a common reference group (i.e., never-users of tobacco) for snus users and smokers. However, all four studies reported risk estimates using comparably-defined tobacco exposure groups. Confidence intervals were imprecise for many of the risk estimates among snus users and smokers due to the small number of cases.

- No published meta-analyses that presented pooled estimates of diabetes risk among snus users were identified. However, a meta-analysis of smoking and diabetes was available, and reported a significantly increased risk of incident diabetes among active smokers (RR = 1.44; 95% CI: 1.31-1.58) (Willi et al. 2007). A US cohort study did not observe an increased risk of mortality due to diabetes among smokers (Friedman et al. 1997); however, the risk estimates had imprecise confidence intervals due to few observed cases (i.e., only three cases among women and one case among men were observed), and potential difficulties with identifying diabetes as a cause of death on death certificates (McEwen et al. 2006).

- Overall, it is unclear whether the risk of diabetes among snus users is different from those who do not use tobacco, although the only prospective analysis of the four studies that examined all incident cases of diabetes, conducted by Eliasson et al. (2004), observed no incident cases of diabetes among consistent exclusive snus users and an increased risk of diabetes among exclusive smokers who participated in the Northern Sweden MONICA cohort. A clear association between diabetes and smoking was also observed in a meta-analysis by Willi et al. (2007).



Metabolic Syndrome (Figure A VI-9)

- Two cross-sectional analyses (Gustafsson et al. 2011; Wandell et al. 2008) reported risk estimates for metabolic syndrome for both Swedish snus users and smokers in the same population. An additional cohort study (Norberg et al. 2006) was excluded from the forest plot because it appears that the authors did not control for tobacco use among snus users and smokers.

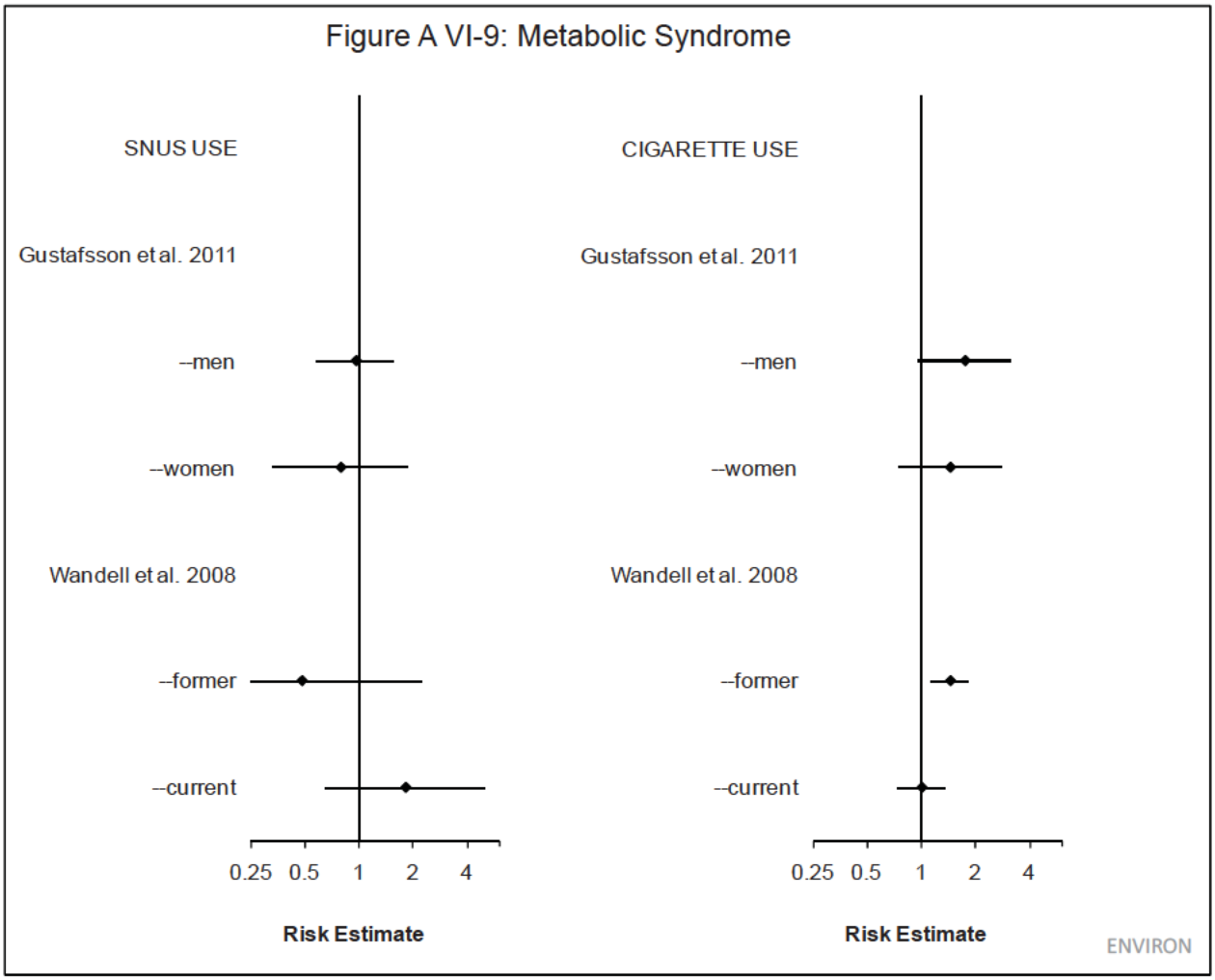
- None of the risk estimates among current snus users were significantly increased. A significant increase was observed for former smokers only.

- It is unclear which reference groups were used in the studies (Gustafsson et al. 2011; Wandell et al. 2008), though both use comparable exposure groups to determine risk of metabolic syndrome among snus users and smokers. Both studies used the International Diabetes Federation (IDF) criteria to define metabolic syndrome.

- The results of the limited number of studies available suggest that the prevalence of

metabolic syndrome is not significantly increased among snus users (Gustafsson et al. 2011; Wandell et al. 2008). An increased prevalence observed among former smokers may be related to weight gain following smoking cessation, and illustrates the importance of controlling for current and former smoking.

Figure A VI-9: Metabolic Syndrome



All-Cause Mortality (Figure A VI-10)

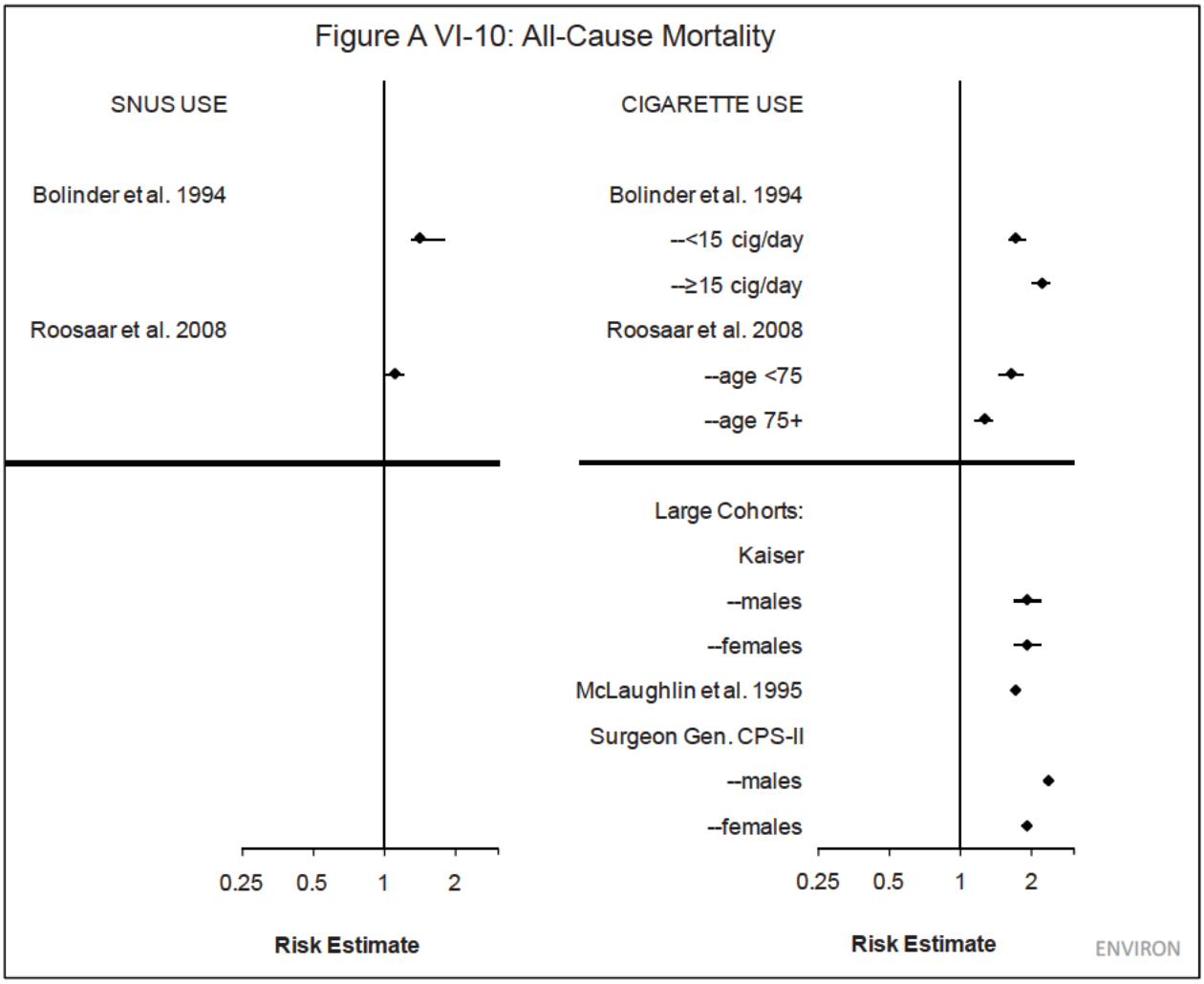
- Two cohort studies (Bolinder et al. 1994; Roosaar et al. 2008) reported risk estimates for all-cause mortality for both snus users and smokers in the same population.

- A significant increase in all-cause mortality was observed in these studies among smokers and snus users. For smokers, the relative risk point estimate for all-cause mortality in the individual studies (ranging from 1.2 to 2.2) was only slightly greater than that observed among snus users (ranging from 1.1 to 1.4). Mortality risks among smokers observed in the three large US cohorts (Friedman et al. 1997; McLaughlin et al. 1995; USDHHS 1989) were consistent with those observed in the two individual studies that reported smoking

relative risk estimates.

- Two head-to-head studies reported results for all-cause mortality. One (Bolinder et al. 1994) of the studies used a common reference group, and the authors of both studies used different exposure groups for the snus and smoking risk estimates. Few potential confounding factors were considered, with only one of the studies (Roosaar et al. 2008) controlling for alcohol consumption.

- The results for all-cause mortality from the two available studies (Bolinder et al. 1994; Roosaar et al. 2008) are inconsistent. The findings for the major smoking-related causes of death show significantly lower risks among Swedish snus users compared to smokers. Many health outcomes have been examined and updated for the Swedish Construction Worker cohort in several publications since the Bolinder et al. (1994) study was published, however, updated results for all-cause mortality have not been presented in any of these publications. 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. In particular, a significant excess risk of respiratory death among snus users over age 80 was also observed in this cohort even though there is no known mechanism by which snus could cause respiratory disease. Regarding all-cause mortality, Lee (2011) stated, "more evidence is clearly needed."



6.1.1.4. Discussion

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.

The twenty epidemiology studies that provided relative risk estimates for snus users and cigarette smokers in the same study populations were used to compare relative risks of major health outcomes to non-users of tobacco. In addition, risk estimates from meta-analyses that combine risk estimates of snus users and cigarette smokers and those from other large cohorts studies for smokers, were extracted and plotted to provide context for the results of the more-variable individual studies of snus users and smokers. Plots of the available relative risk estimates for

snus users and smokers show that relative to non-tobacco users, the expected increased risks among smokers were observed in the epidemiology studies conducted in Sweden and other Scandinavian countries. Among snus users, very few, if any, increased risks of these same health outcomes were observed, and they were not consistently increased among snus users compared to non-tobacco users.

Several limitations were identified that affect the comparability of the risk estimates both within individual studies and when comparing risk estimates across studies. First, as noted for each health outcome in the Summary Tables included in Appendix VI of the ENVIRON Snus Monograph (2013), there were several individual studies used in this analysis that did not use the same reference groups (ideally, non-tobacco users) to generate the risk estimates for snus and cigarette users. There were also several studies in which there were differences in the exposure group or subgroup analyses (e.g., where smokers but not snus users were stratified) preventing exact risk comparisons. For some comparisons, different inclusion criteria were applied to snus users and cigarette smokers (e.g., current snus users vs. ever smokers). In some studies, risk estimates stratified by exclusive tobacco use were reported for one tobacco user group, but not the other. Thus, risk estimates from multivariate analyses in which tobacco use (and possibly other potential confounders) was adjusted in the model were used in the plots. In other instances, the only comparable risk estimates available for analysis were from univariate, unadjusted analyses.

Again, as detailed in Appendix VI of the ENVIRON Snus Monograph (2013), between-study differences included different tobacco use definitions for snus and smoking (e.g., ever or current user, varying definitions of current use, such as daily or occasional, stratification by different dose groups, etc.). There were also differences in inclusion and exclusion criteria across disease outcomes (e.g., oral cancers including/excluding pharyngeal cancer, stroke and stomach cancer subtypes, and other differences in CVD outcomes). Studies differed in the consideration of and control for important confounders, and the quality of control for confounders. Some studies provided dose (risk/duration)-response analyses, whereas others did not. In addition, the studies and meta-analyses varied as to whether they considered morbidity versus mortality, both of which were included in the forest plots. Where cancer-related mortality is high, most cases of the outcome are captured. However, for outcomes such as oral cancer, diabetes, or cardiovascular disease, incident cases may be missed and risk estimates may be biased for these outcomes. In addition, the Swedish snus and smoking risk estimates from the individual studies are from Swedish and other Scandinavian populations, whereas the risk estimates from large cohorts provided for comparison are based mostly on US populations. Though there may be moderate differences in disease risks between populations, control for potential confounders in the multivariate analyses helps minimize potential population differences.

As detailed in the Summary Table for each of the health outcomes examined, the number of relevant studies of snus users that were excluded from the analysis because they lacked relative risk estimates for both snus users and smokers ranged from 0-2 studies depending on the outcome. The relative risk estimates for snus users from these excluded studies are, however, accounted for in the plots where they were included in the meta-analyses by (Boffetta et al. 2008;

Lee 2007; Lee 2011).

6.1.1.5. Harm Reduction Potential of Snus

As presented in **Table 6-1**, lung cancer, cardiovascular diseases (ischemic heart disease, other heart disease, atherosclerosis, aortic aneurysm), and stroke account for 252,765 (approximately 64% of smoking-related deaths) deaths annually due to smoking in the US (Centers for Disease Control and Prevention (CDC) 2008).

Though accounting for significantly fewer smoking-related deaths compared to some of the outcomes presented in Table 6-1, other outcomes were included in this chapter for a variety of reasons. Pancreatic cancer was included in this section due to ongoing controversy within the scientific community, though it accounts for only 1.7% of smoking-related deaths in the US annually. Although not confirmed as a smoking-related outcomes by the US Surgeon General (2010), diabetes and metabolic syndrome were also included due to the significant burden of morbidity in the population, and high interest as potentially tobacco-related outcomes within the scientific community. Oral cancer was included because it is commonly misperceived, by the general public and some within the scientific community, as an outcome related to Swedish snus, though numerous epidemiological studies and scientific reviews have now confirmed that no such association exists. In the CDC (2008) analysis, oral cancer accounted for 1.2% of smoking-related deaths annually in the US. Uncertainty about the possible relationship with snus remains for two other health outcomes presented in this section, notably esophageal cancer and stomach cancer, which account for 2.2% and 0.6% of annual smoking-related deaths, respectively. As with oral cancer, the results presented in this section generally suggest that the risk of stomach and esophageal cancer among snus users is no different than non-users of tobacco, and certainly much higher among smokers.

The health outcomes included in the foregoing analysis, when combined with nonmalignant respiratory diseases known to be caused by smoking, account for approximately 90% of smoking-related deaths. These data thus support the conclusion that use of Swedish snus as compared to cigarette smoking is associated with a very large reduction in overall risk of disease and death.

6.1.1.6. Non-Cancer Oral Effects

The ENVIRON Snus Monograph (2013) (pp. 117-135) presents a review of studies conducted to evaluate non-cancer oral effects in individuals that use snus. The following subsections are based on the data included in that review. This includes potential effects on anatomical sites such as the lips, buccal mucosa (i.e., the cheek membrane), gums (the gingivae), and teeth. Studies that have been conducted to evaluate the potential for snus to cause oral cancer are not included in this discussion, as these studies are reviewed in the previous sections.

Differences in physicochemical properties (e.g., pH, ingredient composition, particle size, humidity, and molality) of the various oral smokeless tobacco products, including snus, can affect the teeth and the oral mucosa (Andersson et al. 1995). Properties of snus potentially

related to effects on the oral cavity are presented in the discussion below. These potential effects of snus on the oral cavity can be divided into two general categories: dental effects including potential effects on teeth and gums, and oral mucosal effects, such as snuff dipper's lesion and potential precancer effects.

In examining any of the studies of potential noncancer oral effects, methodological considerations, such as study design, samples sizes, insufficient detail on product identification and exposure levels, lack of data control or comparison population (i.e., non-tobacco or non-snus users), varying definitions of the dental and oral conditions, and failure to control for important confounders (e.g., dietary and oral hygiene habits, and socioeconomic status), are important considerations in drawing conclusions. For example, in an investigation of individuals from Jönköping, Sweden, Hellqvist and colleagues (2009) reported that nonusers of snus visit the dentist more and brush their teeth more frequently than users, while Hirsch and colleagues (1991) reported that snus use is more common among groups with lower socioeconomic status. There are known associations between socioeconomic status and dietary and oral hygiene habits, or dental conditions such as periodontitis, as indicated by Julihn and colleagues (2008). Details of the available studies conducted to evaluate potential non-carcinogenic oral effects in snus users are provided below.

6.1.1.6.1. Dental Effects and Periodontal Disease

Several studies identified in the literature address the effects of snus on the teeth and the periodontal tissues. These effects can be generally divided into the following categories: (1) dental conditions (plaque, caries, tooth wear, and tooth loss); (2) gingivitis (inflammation of the gums); (3) gingival recession (receding gums); and (4) periodontal disease (periodontitis) (often preceded by gingivitis, an infection of the tissues surrounding and supporting the teeth and indicated by alveolar bone loss, pocket depth, attachment loss, bone height), though many outcomes are examined within the same study.

Dental Conditions

Eight cross-sectional studies examined the association between various dental conditions and snus use (Bergstrom et al. 2006; Ekfeldt et al. 1990; Hirsch et al. 1991; Hugoson et al. 2012; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004).

One study investigated the potential effects of snus (called snuff) use on tooth wear. The study by Ekfeldt and colleagues (1990) was designed to investigate factors associated with occlusal wear of the teeth in a population of 585 dentate Swedish adults ages 20-80 years. Snuff use was characterized simply with a "yes" or "no" response. The authors found that the following factors were significantly correlated with increased incisal and occlusal wear: number of existing teeth, age, sex, bruxism, use of snuff and saliva buffer capacity (pH), though use of snuff and saliva pH were found to be minor factors, accounting for less than 2% of the variance. The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

Hirsch and colleagues (1991) investigated tobacco use (including snus (called snuff) use) in a population of 2,145 Swedish teenagers (age 14-19 years), including 197 snuff dippers. This study found that snuff dippers had significantly higher numbers of decayed, missing, and filled teeth than did nonusers of tobacco. However, the authors acknowledge that a definitive conclusion cannot be made, given the lack of adjustment for dietary and oral hygiene habits.

Wickholm and colleagues (2004) compared the prevalence of periodontal disease in four groups of Swedish male and female adults (n=1,654), based on mutually exclusive lifetime tobacco use, nonusers of tobacco (n=549); exclusive cigarette smokers (972), exclusive snus users (54), and mixed users (99). Using standardized definitions, the authors examined the prevalence, across the tobacco groups, among participants with evidence of plaque, gingivitis, calculus, and gingival recession. The prevalence of having a higher score on the plaque index was not significantly different among the never tobacco users compared to any other tobacco group, including ever snuff users. For the calculus index, ever snuff users had a higher prevalence compared to never tobacco users, and was similar to the other tobacco-user groups. When comparing either the mean plaque index or calculus index among snus users and nonsnus users, the odds ratios were not statistically significant, as reanalyzed by Kallischnigg et al. (2008). The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

Rolandsson et al. (2005) examined 80 adolescent males between 16-25 years of age, including 40 snus (called snuff) users and 40 nonusers. Data were collected using a questionnaire on general and oral health, daily oral hygiene and tobacco habits and a clinical examination was carried out by two dental hygienists. There were no statistical differences between snuff users and nonusers regarding restored tooth surfaces, number of teeth, and presence of plaque. Rolandsson and colleagues (2005) found no significant differences in oral hygiene habits between snus users and nonusers of tobacco.

Bergström and colleagues (2006) examined the relationship between use of Swedish moist snuff and several potential oral effects, including plaque index. Participants were healthy men who were current, former, or never-users of snuff. Using a questionnaire, participants were classified as current (n=25), former (n=21), and never-users (n=38) of moist snuff. After controlling for age, there were no significant relationships, even among those with heavy snuff use (who used for 15 years or more) for any dental effect, including the mean plaque index. The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

A study by Monten and colleagues (2006) examined use of snus and oral health among adolescent 19 year old Swedish boys (33 snuff users, 70 controls). The study outcomes were plaque score, gingivitis, probing pocket depth, clinical attachment loss, alveolar bone level, and gingival recessions. There were no significant differences between boys who used snus but did not smoke and boys who had never used tobacco with any of the first 5 outcomes. With respect to the specific dental conditions, there were no significant differences in the mean number of teeth or proportion of sites showing plaque between boys who used snus but did not smoke and boys who had never used tobacco. The authors concluded that, in this population of Swedish adolescents, use of snus was not associated with the prevalence of periodontal disease

except for a significantly higher prevalence of gingival recessions. Monten and colleagues (2006) found no significant differences in oral hygiene habits between snus users and nonusers of tobacco.

Hugoson and Rolandsson (2011) examined the relationship between current snus use and periodontal health compared with non-tobacco users among three study populations ascertained in 1983, 1993 and 2003 in the city of Jonkoping, Sweden. After adjusting for age, gender and sociodemographic variables, there was no significant association between snus users and number of teeth, or plaque index relative to non-tobacco users.

Hugoson and colleagues (2012) also investigated the relationship between tobacco use and dental caries among three study populations ascertained in 1983, 1993 and 2003 in the city of Jonkoping, Sweden. A stratified random sample was invited to take part in a dental health exam, which included 130 participants who turned 20, 30, 40, 50, 60 & 70 in these years. 550, 552 and 523 attended the 1983, 1993 & 2003 exams, respectively. The participants were examined clinically and radiographically and decayed and filled tooth surfaces were recorded. The prevalence of decayed and filled tooth surfaces among snus users was significantly lower compared to non-users of tobacco during the years 1983 and 1993. There was no statistically significant difference in the year 2003. In an analysis adjusted for age, gender, education, employment, and marital status, a significant association between snus use and decayed and filled surfaces was not observed.

Gingivitis

Gingivitis is an early stage of periodontal disease, and is defined as an inflammatory condition in which the gums become swollen and bleed easily. At this stage, the disease is still reversible and can usually be eliminated by daily brushing and flossing. Of six cross-sectional studies that examined the prevalence of gingivitis, gingival index, or gingival bleeding among snus (called snuff) users, none reported a significant association with this dental effect (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004), with the exception of Modeer et al. (1980). The studies are described below.

Modeer and colleagues (1980) reported that 21.5% of 232 children ages 13-14 smoked (boys and girls) and 11% used snuff regularly (boys). Snuff usage was significantly correlated with gingival index after controlling for plague. The mean gingival index of snus users was 1.10 compared to 0.89 among nonusers (a gingival index of 2 or 3 is considered gingivitis). Furthermore, the evidence to support an association of snuff with gingivitis is limited by the inability to control for confounding variables in this study (the authors did not account for socioeconomic status, or dietary or oral hygiene habits).

Wickholm and colleagues (2004), discussed previously, compared the prevalence of periodontal disease in four groups of Swedish male and female adults and categorized tobacco groups based on exclusive tobacco use. When comparing the mean gingival index among snus users and nonsnus users, the odds ratio was not statistically significant, as reanalyzed by

Kallischnigg et al. (2008). As stated earlier, the authors did not account for socioeconomic status, or dietary or oral hygiene habits.

In the Rolandsson et al. (2005) study, which examined 80 adolescent males between 16-25 years of age, including 40 snuff users and 40 nonusers with similar oral hygiene habits, there were no statistical differences in the gingival index between snuff users and nonusers.

The study by Monten and colleagues (2006) reported that there were no significant differences in the proportion of sites showing full mouth gingivitis or for the subgroup of maxillary anterior tooth region between boys who used snus but did not smoke and boys who had never used tobacco. Both groups of boys were found to have similar oral hygiene habits. The authors concluded that, in this population of Swedish adolescents, use of snus was not associated with the prevalence of periodontal disease except for a significantly higher prevalence of gingival recessions.

Bergström and colleagues (2006) examined the relationship between use of Swedish moist snuff and several potential oral effects, including gingival bleeding on probing. Participants were healthy men who were current, former, or never-users of snuff. Using a questionnaire, participants were classified as current (n=25), former (n=21), and never-users (n=38) of moist snuff. After controlling for age, there were no significant relationships, even among those with heavy snuff use (who used for 15 years or more) for any dental effect, including the gingival bleeding on probing. The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

As described previously, Hugoson and Rolandsson (2011) examined the relationship between current snus use and periodontal health compared with non-tobacco users among three study populations ascertained in 1983, 1993 and 2003 in the city of Jonkoping, Sweden. After adjusting for age, gender and sociodemographic variables, there was no significant association between gingivitis relative to non-tobacco users.

Gingival Recession

There were four cross-sectional studies that specifically examined gingival recession (receding gums) in snus (called snuff) users.

Andersson and Axéll (1989) compared the prevalence of gingival recession among users of loose and portion-bag snus. They observed gingival recessions in 42/184 (23.5%) of the participants that used loose snuff compared to 2/68 (2.9%) of the participants that used portion-bag snuff. Loose snuff was significantly associated with gingival recession compared to the use of portion-bag snuff, while the authors provided no comparison of the effects of loose or portion-bag snuff use with non-use of tobacco.

Wickholm and colleagues (2004), discussed previously, compared the prevalence of periodontal disease in four groups of Swedish male and female adults and categorized tobacco groups based on exclusive tobacco use. When comparing the prevalence of gingival recessions

among snus users and nonsnus users, the odds ratio was not statistically significant, as reanalyzed by Kallischnigg et al. (2008). As stated earlier, the authors did not account for socioeconomic status, or dietary or oral hygiene habits.

The study by Monten and colleagues (2006) reported that the use of snus is associated with gingival recessions, but not a number of other periodontal conditions among adolescent 19 year old Swedish boys (33 snuff users, 70 controls). However, participants with gingival recessions had significantly increased odds of using snus (odds ratio (OR)=3.7; 95% confidence interval (CI): 1.40-9.87), after adjusting for plaque, gingivitis, and tooth-brushing. The authors concluded that, in this population of Swedish adolescents, use of snus was not associated with the prevalence of periodontal disease except for a significantly higher prevalence of gingival recessions.

As described previously, Hugoson and Rolandsson (2011) examined the relationship between current snus use and periodontal health compared with non-tobacco users among three study populations ascertained in 1983, 1993 and 2003 in the city of Jonkoping, Sweden. Compared to nonusers of tobacco, snus users exhibited a significantly lower percentage of sites with gingival recession ≥1 mm after adjusting for age, gender and sociodemographic variables.

Periodontal Disease

Periodontal disease is often preceded by gingivitis, and it is described as an infection of the tissues surrounding and supporting the teeth and is indicated by alveolar bone loss, pocket depth, attachment loss, and bone height. However, not all gingivitis progresses to periodontitis; later stages of periodontal disease (known as periodontitis) are irreversible. The most common symptom is bleeding gums, but loosening of the teeth, receding gums, abscesses in pockets between gums and the teeth, and necrotizing ulcerative gingivitis may be present as the disease progresses.

Six cross-sectional studies (Bergström et al. 2006; Hugoson and Rolandsson 2011; Julihn et al. 2008; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004) and one case-control study (Kallestal and Uhlin 1992) examined the relationship between the use of snus (called Swedish snuff) and periodontal disease. None of these seven studies reported a significant relationship between the use of snus and periodontal disease or indicators of periodontal disease.

Wickholm and colleagues (2004), discussed previously, compared the prevalence of periodontal disease in four groups of Swedish male and female adults and categorized tobacco groups based on exclusive tobacco use. All groups of tobacco users had a higher prevalence of periodontal disease than never-users of tobacco, and there was a significant association between smoking and periodontal disease (compared to never-smoking). The OR for former snuff use (n=31) was elevated after adjusting for age, gender, education and smoking and/or plaque, although was not statistically significant (OR=2.55, 95% CI 0.80, 6.80). The OR for periodontal disease among current snus users was not elevated (OR=0.66, 95% CI: 0.30-1.32), and there was no association with increasing can-years of snuff use was observed.

In the Rolandsson et al. (2005) study, which examined 80 adolescent males between 16-25 years of age, including 40 snuff users and 40 nonusers, there were no statistical differences between snuff users and nonusers regarding probing pocket depth. As stated previously, Rolandsson and colleagues (2005) found no significant differences in oral hygiene habits between snus users and nonusers of tobacco.

Bergström and colleagues (2006) examined the relationship between use of Swedish moist snuff and periodontal bone loss (as assessed by bone height) among healthy men who were current, former, or never-users of snuff. Following responses to the questionnaire, participants were classified as current (n=25), former (n=21), and never-users (n=38) of moist snuff. After controlling for age, there were no significant relationships, even among those with heavy snuff use (who used for 15 years or more). The user groups also did not differ with respect to other clinical characteristics (periodontal pocket depth or percentage of sites exhibiting gingival bleeding on probing). The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

The study by Monten and colleagues (2006) reported that there were no significant differences in probing pocket depth, clinical attachment loss or alveolar bone level between boys who used snus but did not smoke and boys who had never used tobacco. The authors concluded that, in this population of Swedish adolescents, use of snus was not associated with the prevalence of periodontal disease except for a significantly higher prevalence of gingival recessions. As stated previously, Monten and colleagues (2006) found no significant differences in oral hygiene habits between snus users and nonusers of tobacco.

A study was conducted by Julihn and colleagues (2008) to evaluate risk factors for incipient alveolar bone loss and subgingival calculus in 696 Swedish 19-year-olds (358 males, 328 females). The participants were from seven public dental clinics in suburban Stockholm that answered a questionnaire on general health, tobacco habits, oral hygiene habits, and their parents' socioeconomic background. The clinical and radiographic examination included registration of plaque, bleeding on probing, supra- and subgingival calculus, caries, and restorations. Incipient alveolar bone loss was recorded when the distance from the cemento-enamel junction to the alveolar crest was >2.0 mm. There were 80 participants that reported that they were daily snuff users and 26 of participants were evaluated for incipient alveolar bone loss. The adjusted odds ratio (OR) for incipient alveolar bone loss for snuff users was not statistically significant (OR=1.15, 95% CI: 0.7 – 1.89). The only risk factors that were statistically significantly correlated with incipient bone loss were subgingival calculus and proximal restoration ≥ 1. Odds ratios were adjusted for education level and occupational status of both parents of the participants.

Hugoson and Rolandsson (2011) examined the relationship between current snus use and periodontal health compared with non-tobacco users among three study populations ascertained in 1983, 1993 and 2003 in the city of Jonkoping, Sweden. After adjusting for age, gender and sociodemographic variables, there was no significant association between severity of periodontal disease, and frequency of probing pocket depth ≥ 4mm relative to non-tobacco users. The authors concluded that using snus did not seem to be a risk factor for periodontal

disease.

Finally, one case-control study of factors associated with buccal attachment was identified in which data on snuff users were collected (Kallestal and Uhlin 1992). The authors did not present any quantitative data on the relationship between STP use and loss of buccal attachment, but they stated that cases and controls did not differ in the use of STP. The authors did not account for socioeconomic status, or dietary or oral hygiene habits.

Summary and Discussion for Dental Effects and Periodontal Disease

- Dental Conditions: Of the eight cross-sectional studies of dental effects, two reported a significant association with the use of snus and dental caries and tooth loss (Hirsch et al. 1991) and tooth wear (Ekfeldt et al. 1990). Neither study accounted for the potential confounding effects of socioeconomic status, or dietary or oral hygiene habits. Several studies that did account for these potential confounding factors did not find a relationship between the use of snus and dental caries (Hugoson et al. 2012; Rolandsson et al. 2005) or for tooth loss (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005). None of the five studies that investigated the relationship between dental plaque and snus use reported a significant relationship between the two (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004). Three out of those five studies accounted for socioeconomic status, or dietary or oral hygiene habits (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005).

- Gingivitis: Of six cross-sectional studies of gingivitis, gingival index, or gingival bleeding, one reported a significant association between a higher gingival index and the use of snus (Modeer et al. 1980). The authors of this study did not report whether oral hygiene habits or sociodemographic variables differed between snus users and nonusers of tobacco. The mean gingival index of snus users was 1.10 compared to 0.89 among nonusers (a gingival index of 2 or 3 is considered gingivitis). Among the five studies that reported no association with gingivitis or other endpoints associated with gingivitis (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004), three of the five accounted for either oral hygiene habits and/or socioeconomic variables (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005).

- Gingival Recession: Of three cross-sectional studies that compared gingival recession among snus users and non-users of tobacco, one reported that participants with gingival recessions had significantly increased odds of using snus (Monten et al. 2006). The authors found no significant differences in oral hygiene habits between users and nonusers of snus. Of the two other studies, one found that the prevalence of gingival recession among snus users and nonusers was not significantly different (Wickholm et al. 2004), while the other reported a significantly lower percentage of sites with gingival recession $\geq$ 1 mm among snus users compared to nonusers (adjusted for sociodemographic variables) (Hugoson and Rolandsson 2011). A fourth study found that

loose snuff was significantly associated with gingival recession compared to the use of portion-bag snuff, while the authors provided no comparison of the effects of loose or portion-bag snuff use with non-use of tobacco (Andersson and Axell 1989).

- Periodontal Disease: None of the six cross-sectional studies nor the one case-control study (Kallestal and Uhlin 1992) reported a significant association between the use of snus and periodontal disease, or individual indicators of periodontal disease. Most studies, with only two exceptions (Bergstrom et al. 2006; Kallestal and Uhlin 1992), adjusted, or accounted for, socioeconomic status or oral hygiene habits. The five remaining studies accounted for either socioeconomic factors (Hugoson and Rolandsson 2011; Julihn et al. 2008; Wickholm et al. 2004) or oral hygiene habits (Monten et al. 2006; Rolandsson et al. 2005).

Lee (2011) presented a review of the available studies that examined dental-related outcomes. He concluded that a relationship of snus to periodontal and gingival diseases is not clearly established. Further, he stated that a possible relationship with tooth loss and dental caries is not established. His conclusions are consistent with an earlier review conducted by Kallischnigg and colleagues (2008). In that review, the authors evaluated the relationship between smokeless tobacco products and non-cancerous oral diseases in both Europe and the U.S. The authors concluded that the results from the Swedish studies reveal no clear relationship between snuff use and periodontitis or gingivitis. The authors described the evidence of an association between snuff use and gingival recession as limited, where several studies failed to compare to nonsnuff users; they noted, however, that one controlled study did observe a significant increase in gingival recession among male adolescent snuff users, and another study observed a higher prevalence of gingival recession among loose snuff users compared to portion-bag users.

6.1.1.6.2. Oral Mucosal Lesions

A specific, well-recognized mucosal reaction is associated with use of snus (called Swedish snuff) (Axell et al. 1976). It is characterized by thickening or discoloration of the oral mucosa (Axell 1987). Histologic changes observed in snuff-induced lesions (SILs) include hyperplasia of the epithelium with large, vacuolated cells, and a chevron type of keratinization. Numerous studies have observed that snus use is associated with this characteristic reaction in the oral mucosa (Andersson et al. 1989; Andersson et al. 1990; Andersson 1991; Andersson et al. 1994; Andersson et al. 1995; Andersson and Axell 1989; Andersson and Warfvinge 2003; Axell 1976; Axell et al. 1976; Axell 1987; Axell and Hedin 1982; Axell and Henricsson 1985; Axell 1993; Frithiof et al. 1983; Hirsch et al. 1982; Larsson et al. 1991; Martensson 1978; Mornstad et al. 1989; Rolandsson et al. 2005; Roosaar et al. 2006; Rosenquist et al. 2005; Salonen et al. 1990; Wallstrom et al. 2011). This type of lesion has been referred to by various names, including snuff dipper's lesion, snuff-induced leukoplakia, or snus-induced lesions. The lesion generally appears at the location in the mouth where the snus is held.

The published literature examining the relationship between the use of snus and oral mucosal lesions consists of approximately 20 cross-sectional studies (see Chapter 5 of the ENVIRON

Snus Monograph 2013). These studies do not provide quantitative estimates of the risk of oral mucosal lesions associated with use of snus. Furthermore, many of the available studies draw from the same population of snus users, which narrows the scope of available data. Eight studies described characteristics of oral mucosal lesions in the same population of snuff-using Swedish workers initially described by Andersson and Axell (1989). Six studies (Axell 1976; Axell et al. 1976; Axell 1987; Axell and Hedin 1982; Axell and Henricsson 1985; Mornstad et al. 1989) examined the prevalence of snuff use and the characteristics of oral mucosal lesions in a large population of Swedish adults initially described by Axell (1976).

Severity of Oral Mucosal Lesions

Most of the studies, graded clinical changes associated with oral mucosal lesions on a four-degree severity scale that was proposed by Axell and colleagues (1976) and is still in use today (e.g., Roosaar et al. 2006):

- Degree 1: A superficial lesion with a color similar to the surrounding mucosa, and with slight wrinkling. No obvious mucosal thickening.
- Degree 2: A superficial, whitish, or yellowish lesion with wrinkling. No obvious mucosal thickening.
- Degree 3: A whitish-yellowish to brown, wrinkled lesion with intervening furrows of normal mucosal color. Obvious thickening of the mucosa.
- Degree 4: A marked, white-yellowish to brown and heavily wrinkled lesion with intervening, deep, and reddened furrows and/or a heavy thickening of the mucosa.

The severity of oral mucosal lesions appears to be related to the daily duration, amount consumed, as well as the form of snuff used daily (i.e., loose snuff vs. portion-bag snuff). An association with characteristics of the snus product, such as higher pH and increased nicotine content, has also been suggested (Andersson and Warfvinge 2003; Mornstad et al. 1989; Wallstrom et al. 2011). The following section summarizes the findings related to these exposure factors and product characteristics.

Hirsch and colleagues (1982) found that patients with degree 3 (10.1 hours/day; 17.9 g/day on average) and 4 (10.6 hours/day; 22.3 g/day on average) lesions used snuff approximately twice as long per day as patients with degree 1 (5.2 hours/day; 6.8 g/day on average) and 2 (6.5 hours/day; 15.2 g/day on average) lesions. Statistically significant differences in consumption were only observed between degree 1 and degree 4 lesions. The study limitations include a relatively small sample size (50 participants), and potential confounding from alcohol use and smoking. Rolandsson et al. (2005), in a study of 40 male snuff users, ages 16-25 years old, also found that that the hours of daily snuff use had a statistically significant effect on the development of oral mucosal lesions. The mean daily duration of snuff use increased with severity among those with no (2.0 hours/day) lesions, degree 1 (7.2

hours/day), 2 (9.6 hours/day), and 3 (12.3 hours/day) lesions, with no degree 4 lesions observed. The amount of snuff used was not a significant predictor of snuff lesions. Mornstad and colleagues (1989) reported that the severity of the lesions among snuff users were positively correlated with age, years with the habit, amount of snuff consumed per day, and with the time with contact between snuff and the oral mucosa. Rosenquist and colleagues (2005) also reported that those who used snuff for more than 10 hours per day developed more pronounced lesions. However, Wallstrom and colleagues (2011), who conducted a small clinical follow-up study of 18 men without a history of smoking, did not find a significant correlation between the severity of the lesions and total exposure to loose snuff in terms of the years with the habit, daily hours of consumption and amount consumed on a daily basis. Participants had used snuff for an average duration of 14.7± 2.7 hours/day. Andersson and colleagues (1994) found no correlation between the degree of lesions with either total dose of nicotine or lifetime duration (the average duration of snus use was 14.5 years (loose) and 7.4 years (pouch)).

With regard to the form of snuff used, Andersson and colleagues (1989; 1994) concluded that use of snuff pouches is associated with less pronounced changes to the oral mucosa than loose snuff. The 1989 study was based on 14 matched pairs of loose and portion-bag users analyzed for histological changes related to the package form from a total of 252 biopsies obtained from snuff users. In the 1994 study, a total of 45 habitual snus users (men) were selected: 22 loose snus users and 23 portion-bag users (45 total snuff users who had participated in the Andersson and Axell 1989 study). In the latter study, for example, Andersson and colleagues (1994) observed less pronounced clinical changes in the oral mucosa in users of pouched snus compared with the changes in the mucosa of moist loose snus users. The snus pouch users showed predominantly Degree 1 and 2 lesions, while users of loose snus had more Degree 3 lesions. The authors reported that differences in severity of oral lesions among portion-bag and loose snuff users were not correlated to exposure and uptake of tobacco components such as nicotine, as measured in urine and saliva cotinine. The pH of the snus products was alkaline (7.9-8.6) and about 0.5 units higher in loose snus than in portion-bag snus. The authors suggested that the difference in tissue response between portion-bag users and loose snus users was probably due to the pH differences of the two types of products. The authors stated that this is further supported by the fact that users of chewing tobacco, which has considerably lower pH, exhibit only slight changes in the buccal mucosa.

Following that study, Andersson and colleagues (1995) then reported that they found no decisive pH differences between two different brands of snus, thus making the theory relating to the importance of pH value questionable. The only recorded difference between the brands was the nicotine content. Mornstad and colleagues (1989) noted that of three different brands of snus, more severe lesions were observed among the brand ("Ettan") with the highest pH (9.2). In a later study of subjects recruited from the same population as Andersson and colleagues (1989; 1994), Andersson and Warfvinge (2003) noted that even though snuff users had an alkaline salivary pH during and shortly after snuff use, mucosal changes were recorded only at the sites where the pinch of snuff was placed. The authors

noted that the amount of epithelial vacuolization was unchanged when only pH was lowered but decreased significantly when nicotine content was also lowered, and suggest that nicotine and pH may act synergistically as partial causes of snuff induced lesions. Wallstrom and colleagues (2011) also reported some evidence that suggests the potential influence nicotine may have on the oral mucosa. They found that 71% of subjects with oral lesions remaining after six months of abstinence from loose snuff had continued to use nicotine replacement therapy (gum) during that time, whereas only 18% of subjects without oral lesions remaining after six months used nicotine replacement therapy.

Rolandsson and colleagues (2005) also found that product type (loose snuff vs. portion-bag snuff) had a statistically significant effect on the development of snuff lesions. Out of the 18 snuff users in this study using loose snuff, 16 showed degree 2-3 snuff lesions, while only 8 of 22 portion-bag users showed degree 2 lesions (none showed degree 3 lesions).

Natural History and Reversibility of Snus Lesions

A prospective study by Roosaar and colleagues (2006) documented the natural course of snus-induced lesions (SILs) among 1,115 men over several decades. The total number of individuals initially examined was 16,144 (7,890 men and 8,254 women), and of those, 1,115 of the male participants had SIL; 183 were re-examined in 1993 (the investigators stated that because of limited resources, not all members of the original cohort could be included in the follow-up study). Among this subgroup, there was a strong and significant relationship between the current level of snus use (both number of hours used and number of g consumed per day) and the severity of the lesions.

With respect to histologic changes accompanying oral mucosal lesions, as opposed to describing oral mucosal lesions on a clinical scale (i.e., visible to the naked eye), oral mucosal lesions can also be described on a histologic, or microscopic, scale. Several of the studies summarized in Appendix B of the ENVIRON Snus Monograph (2013) identified the following types of histologic changes among users of snus:

- Increased variable degrees of non-specific inflammation;
- Increased thickness of the epithelial surface layer (epithelial hyperplasia) displaying large numbers of vacuolated cells;
- Increased mitotic rates; and
- Rarely dysplasia.

With respect to reversibility of oral mucosal lesions, there is evidence that snuff-induced oral mucosal lesions are reversible. In 20 of 29 snuff users (69%) followed by Larsson and colleagues (1991), histological data indicated that oral lesions were reversible in participants who had quit the use of snus. Frithiof and colleagues (1983) reported that snuff-induced mucosal lesions were almost entirely reversed 14 days after quitting the use of snus, even in

patients who had used snus for decades. Andersson and Warfvinge (2003) showed that clinical and histological changes became significantly less pronounced when heavy snuff users switched to snuff with lower pH and lower nicotine content.

In the long-term follow-up study conducted by Roosaar and colleagues (2006), SILs initially seen in 1973-1974 reversed if snus use was discontinued, and they also tended to regress among long-time users who did not change their snus habits. Of 176 users with grade 1-4 lesions in 1973-1974 who were reexamined in 1993-1995, the lesion had disappeared in 62/66 (94%) of those who stopped, and remained in 108/110 (98%) of those that continued to use snuff. The lesions reversed if snus use was discontinued, and they also tended to regress among long-time users who did not change their snus habits. During follow-up, 3 cases of oral cancer occurred (standardized incidence ratio=2.3, 95% CI: 0.5-6.7). None of the oral cancers occurred at the site of the original SIL and two occurred in individuals who were also daily smokers. The authors concluded that snus-induced lesions are probably no more than markers of current or recent snus consumption, and that oral cancers rarely occur at the site of such lesions. The authors speculated that the regression of SILs over time among men who had not decreased their snus use could reflect changes in commercially available snus over the years (e.g., the introduction of portion bags). These findings are important because they indicate that oral mucosal lesions are generally not dysplastic (i.e., characterized by irreversibility). According to Crissman and colleagues (1993), the presence of dysplasia is the single most important factor predicting risk for the subsequent development of invasive neoplasia.

Wallstrom and colleagues (2011), as described previously, also investigated the reversibility of SILs. They found that after six months of abstaining from snuff use, SILs did not resolve completely in 39% (n=7) of the 18 study participants. As mentioned previously, five of these seven subjects were still using nicotine replacement therapy on a daily basis (three chewing the gum and two placing it under the lip), while the two other participants were nicotine-free. However, the authors noted that the clinical changes among the participants who still exhibited SILs at six months were less severe and the area of the affected mucosa had diminished in size.

Leukoplakia

Leukoplakia is defined as a white patch or plaque of the oral mucosa that cannot be removed by scraping and that cannot be classified clinically or pathologically as any other definable lesion (Pindborg et al. 1997). The lesion can occur in all areas of the oral cavity, but is most common on the buccal mucosa. Leukoplakia represents 80% of potentially malignant oral lesions (Bouquot et al. 2006). The term “leukoplakia” describes a clinical condition; it has no specific histopathologic meaning and does not describe a microscopic finding. Furthermore, leukoplakia is a diagnosis of exclusion, used only when another condition cannot be diagnosed. The term is somewhat controversial and continues to undergo refinement (Neville and Day 2002). Lesions occurring in snus/snuff users are believed to represent a clinical entity that is distinct from leukoplakia.

In general, leukoplakia is believed to present a demonstrable, though extremely variable, risk of malignant transformation. Some clinical forms of leukoplakia are considered entirely benign, without malignant potential. Such benign lesions include frictional keratosis, chronic cheek-biting, and irritation due to dental restorations. Hairy leukoplakia, a clinical entity associated with human immunodeficiency virus (HIV), also does not appear to predispose to malignancy (Silverman, Jr. 1998). The malignant transformation rate for leukoplakia ranges from 1 to 28%, with an average of about 4% (Bouquot et al. 2006); leukoplakia also has the potential for spontaneous reversibility (Pindborg et al. 1997).

Confusion exists surrounding the use of the term leukoplakia, especially as related to the use of oral snuff. This is reflected in the various terms used to describe the condition in snuff users such as snuff dipper's lesion, oral leukoplakia, smokeless tobacco lesions, smokeless tobacco keratosis (Bouquot 1994; Greer 2006) and tobacco pouch keratosis (Neville and Day 2002). These differences in terminology, combined with the multiple number of classification systems used to grade the severity of these lesions, make direct comparison of studies difficult.

Bouquot (1994) made a distinction between leukoplakia and smokeless tobacco keratosis, defining the latter as a chronic white or gray translucent mucosal macule in an area of smokeless tobacco contact that cannot be scraped off. In contrast to leukoplakia, however, these lesions disappear with cessation of the STP use, as discussed below. In fact, Neville and Day (2002) argued against including the term "tobacco pouch keratosis" under the broad umbrella of leukoplakia, because tobacco pouch keratosis has a specific known cause and prognosis. Microscopically, these lesions show hyperkeratosis (thickening) of the mucosal epithelium. True dysplasia is uncommon, and if present, generally mild. Most tobacco pouch keratoses will reverse within a matter of weeks if the individual ceases using snuff. However, the potential for malignant transformation of smokeless tobacco keratosis is not known (Bouquot et al. 2006). Investigations using large numbers of tobacco chewers have found few, if any, keratotic lesions with serious dysplasias, although older and smaller investigations reported that as many as 16% of biopsied cases show at least mildly dysplastic cells (Stotts et al. 1992 and Bouquot et al. 1991 as cited by Bouquot et al. 2006).

Examination of patients with leukoplakia has provided some information into the likelihood of transformation and predictors of malignant transformation. Einhorn and Wersall (1967) evaluated 782 Swedish patients with a clinical diagnosis of leukoplakia; the participants included both tobacco users (smokers, snuff dippers) and nonusers of tobacco. Oral carcinoma developed in 2.4% of patients after 10 years, and in 4% of patients after 20 years. It was primarily the small group of cases of leukoplakia in persons not using tobacco that were responsible for the excess morbidity from oral carcinoma; among tobacco users with leukoplakia the figure was considerably lower. Another study of patients with dysplastic leukoplakia suggested that aneuploid status (having a chromosome number that is not an exact multiple of the normal number) was the most significant determinant of transformation to cancer, while tobacco use was a poor predictor of cancer (Greenspan and Jordan 2004; Sudbo et al. 2004).

The incidence of malignant transformation of leukoplakia is also reported to be related to any of the following factors: location on the floor of the mouth; non-homogeneous visible appearance, in particular an erythematous or verrucous component; dysplastic microscopic features; overgrowth with the fungus Candida albicans; alcohol abuse, particularly when co-incident with the use of cigarettes; and nutritional deficiencies of iron, folate or vitamin B12 (Dimitroulis and Avery 1998; Macigo et al. 1996; Silverman, Jr. 1998).

Dysplasia

The effect of snus on the occurrence of pre-carcinogenic conditions such as dysplasia has been investigated in a limited number of epidemiological studies. For a lesion to be a valid indicator of carcinogenic activity, the lesion must be shown to be composed of an abnormal population of cells that are precursors of neoplasms (Williams 1999). Relatively few oral cancers in western populations are preceded by a recognizable premalignant lesion (Dimitroulis and Avery 1998). Squamous epithelial dysplasia is considered a precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation and stratification short of carcinoma in situ (Pindborg et al. 1997). The general disturbance of the epithelium is designated dysplasia and the potential for developing invasive carcinoma increases with its severity (Pindborg et al. 1997).

Historically, the available literature has provided limited insight into the relationship between snuff use and dysplasia. Among 21 male users of Swedish snuff, 5 cases of mild epithelial dysplasia were observed (Frithiof et al. 1983). The authors noted that the premalignant significance of the dysplasia was questionable, and that the dysplasia may have been a reactive change due to inflammatory infiltration. Follow-up was not performed on these 5 cases of dysplasia, so it cannot be determined whether any of the dysplastic lesions became malignant (Frithiof 2000). Hirsch and colleagues (1982) observed slight dysplasia in 9 of 50 (18%) patients. In this study, patients with dysplasia used snuff for more years compared to patients with no dysplasia (23.9 years vs. 19.5 years).

Miscellaneous Oral Changes

One published investigation was identified that examined the use of snus (called snuff) and the induction of miscellaneous oral changes. Axell and Hedin (1982) examined whether the use of tobacco products, including snus, increased oral melanin pigmentation. According to Axell and Hedin (1982), oral melanin pigmentation is sometimes observed with rare pathological conditions such as Addison's disease or Peutz Jeghers' syndrome. Among 1,541 individuals examined, 42 were snus users. Prevalence of pigmentation in snuff dippers (4.7%) was not significantly higher than that among nonusers of tobacco (3.0%). In contrast, the prevalence of pigmentation in cigarette smokers (21.9%) and pipe smokers (16.8%) was significantly greater than in nonusers of tobacco. Axell and Hedin (1982) concluded that the use of snus did not significantly elevate the prevalence of oral melanin pigmentation.

Summary and Discussion of Oral Mucosal Effects

- Swedish snus causes 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.

- 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 pre-carcinogenic 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.

- A limitation in the available data is that the studies are largely descriptive in nature (e.g., cross-sectional), and some studies have important limitations including small sample sizes, and failure to control for important confounders.

Lee (2011) presented a review of the available studies that examined snus/snuff-induced lesions. He concluded that current snus users generally have "100% incidence, with severity clearly associated with daily time used and amount consumed." Further, he stated short-term quitting reduced severity, and that longer-term quitting results in the elimination of the lesion. His conclusions are consistent with an earlier review conducted by Kallischnigg and colleagues (2008). In that review, the authors evaluated the relationship between smokeless tobacco products and non-cancerous oral diseases in Europe and the U.S. The reviewers concluded that the available evidence confirms a strong association of current use of smokeless tobacco, particularly snuff, with prevalence of oral mucosal lesions. Among the 15 Scandinavian studies described in the review, the severity of the snuff induced lesions was associated with the length of time snuff was used and with the amount consumed per day. The severity was lower in users of portion-bag snuff than in users of loose snuff.

6.1.1.7. Discussion of Non-Cancer Oral Effects

Based on descriptive epidemiologic data, the following conclusions can be made about the use of snus and its effect on non-carcinogenic and pre-carcinogenic oral conditions:

- 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.

- 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.

- 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 pre-carcinogenic 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.

- A limitation in the available data is that the studies are largely descriptive in nature (e.g., cross-sectional), and some studies have important limitations including small sample sizes, and failure to control for important confounders.

6.1.1.8. Pancreatic Cancer

A possible relationship between use of snus and increased risk of pancreatic cancer has been widely publicized and debated in recent years. The hypothesis of an association originates from findings in two Scandinavian cohorts (Boffetta et al. 2005; Luo et al. 2007). The Boffetta report was based on a Norwegian cohort originally formed in the 1960s. The Luo study concerned individuals included in the Swedish Construction Worker Cohort formed in the 1970s and 1980s. The Norwegian data were not included in the analyses of individual studies presented in Section 6.1.1.3 (although both the Norwegian and Construction Worker Cohort data were included in all meta-analyses) due to several methodological shortcomings that precluded a reliable assessment of risk among both smokers and snus users. However, both the Boffetta and Luo reports suggested that use of smokeless tobacco was associated with an increased risk of pancreatic cancer in some subsets of the populations studied. But there are inconsistencies between the two reports with respect to the specific subgroups showing an increased risk. In fact, in a recent meta-analysis of the two studies (Lee 2011) the risk associated with use of snus was found to be not statistically significantly different from unity among all subjects with adjustment for smoking (RR 1.20, 95% CI: 0.66-2.20). This held true also for those classified as never smokers (RR 1.61, 95% CI: 0.77-3.34).

Cohort studies

The Norwegian cohort study by Boffetta et al. (2005) is an update of an earlier study (Heuch et al. 1983) which provided the first suggestion that the use of smokeless tobacco (including snus) might increase the risk of pancreatic cancer. In the updated cohort of more than 10,000 Norwegian men, the use of smokeless tobacco was associated with significant increases in risk of pancreatic cancer after adjustment for smoking: RR=1.67 (95% CI: 1.12-2.50) for ever use; RR=1.80 (95% CI: 1.04-3.09) for former use. There was a borderline, non-significant increase in risk of pancreatic cancer for current use: RR=1.60 (95% CI: 1.00-2.55). However, when risk was assessed by smoking status, a significant increase in risk was only seen among ever-users of smokeless tobacco who currently smoked (RR=1.86; 95% CI: 1.13-3.05). The authors concluded that this study provides evidence that STPs – including snus - may cause pancreatic cancer. It should be noted that, in contrast to Sweden where snus has always been the predominant form of smokeless tobacco accounting for approximately 99% of the smokeless market, other forms of STP were more common in Norway during the 1960s and 1970s, for example skrå (a form of chewing tobacco). The questionnaire used to collect exposure

information in the Norwegian study did not distinguish between different forms of STP so it is uncertain how much of the reported findings can be ascribed to Swedish snus.

Luo and colleagues (2007) investigated the relationship between the use of Swedish snus and several types of cancer among 279,897 male construction workers followed for 20 years. Among all cohort members (regardless of smoking or snus status), use of snus was not associated with increased risk of pancreatic cancer (RR=0.9; 95% CI: 0.7-1.2), when compared to never-users of tobacco. However, when analyses were restricted to the 125,576 men who were recorded as never having smoked, both ever-use of snus (RR=2.0; 96=5% CI: 1.2-3.3) and current use of snus (RR=2.1; 95% CI: 1.2-3.6) were associated with a statistically significantly increased risk of pancreatic cancer, after adjustment for age and body mass index ("BMI"). No adjustment was made for alcohol consumption as data are unavailable.

The authors suggested that there is a biologically plausible mechanism by which snus could increase the risk of pancreatic cancer, noting that rats treated with TSNAs in drinking water have been reported to develop pancreatic tumors. As noted previously, the Swedish construction worker cohort has many strengths (large size, long and almost complete follow-up), but this analysis also suffers from some weaknesses. The authors did not adjust the risk estimates for pancreatitis, a recognized risk factor for pancreatic cancer. It is also possible that exposure misclassification may contribute to uncertainty in the risk estimates; Luo and colleagues (2007) reported that a sensitivity analysis that accounted for possible changes in cigarette use affected the risk estimates "no more than trivially." Importantly, though, the authors did observe a difference in misclassification of smoking among participants who were recorded as nontobacco users at the initial visit compared to snus users when a sample of these participants was observed at follow-up visits. The authors reported that 12% of never-smoking snus users who did not report current or former smoking during their first visit, were later recorded during the second visit as having smoked while only 7% of those who reported never using tobacco during the first visit and later reported smoking.

Thus, to date there are two studies that suggest that use of snus could be associated with increased risk of pancreatic cancer among some groups of the population. However, there are inconsistencies between the studies with respect to the specific tobacco user subgroups at risk. Boffetta et al. (2005) found that the increased risk of pancreatic cancer was limited to STP users who were also smokers. In contrast, Luo and colleagues (2007) found that snus use was significantly increased only among a subgroup of men who had never smoked tobacco. It is not known why the two studies would have found that the increased risk was limited to two distinctly different subgroups.

The suggested relationship between snus and pancreatic cancer has been subject to a continuing debate in the scientific community (e.g., Boffetta et al. 2006; Colilla 2010; Lee and Hamling 2009a; Nilsson 2006; Ramström 2006; Rodu 2007; Rodu and Cole 2005; 2006). The Boffetta et al. (2005) study in particular has been the subject of much of this debate. Several methodological weaknesses of this study have been cited including:

- Failure to control for the possible confounding effect of alcohol;

- Failure to reassess tobacco habits after study enrollment (especially given that the follow-up was more than 30 years and tobacco habits may have changed);

- Evaluation of a different type of smokeless tobacco than snus (called "skra") that was commonly used in Norway until the early 1980s; thus, the results may not be relevant for snus;

- Limitations in the statistical methods used to adjust for smoking;

- Likely selection bias (in that the cohort had a much higher prevalence of smokeless use than the general population);

- Inability to assess dose-response; and

- Unconventional exposure groups (specifically, creating a reference group that combined never and occasional users).

In rebuttal, Boffetta and colleagues (2006) stated that their data show that alcohol is not a confounder of the association between snus use and pancreatic cancer in this cohort. They believe that snus and skrå contain comparable amounts of carcinogenic components and thus can be appropriately considered together (although analytical data to support this are unavailable). They do, however, agree that the small number of cases of pancreatic cancer among snus users who did not smoke is an important limitation of this study.

Studies of other STPs

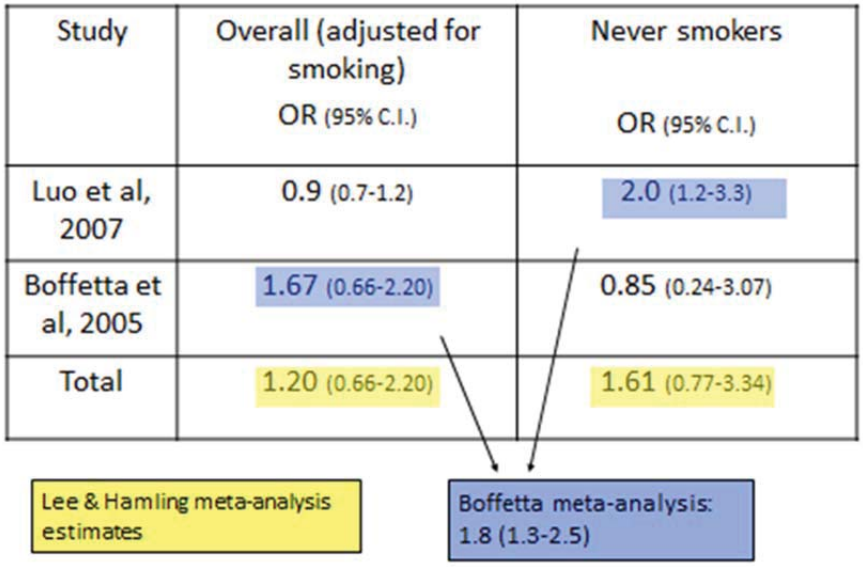
In a meta-analysis, Boffetta and colleagues (2008) combined the pancreatic risk estimates from use of a range of smokeless tobacco and snuff products using data from four US studies and the Luo et al. (2007) and Boffetta et al. (2005) studies. They reported a significant elevated summary risk for pancreatic cancer, and concluded that these studies suggest an increased risk of pancreatic cancer among snus users. The SCENIHR Working Group (2008) also reports that these two Scandinavian cohort studies identify the pancreas as a main target organ among smokeless tobacco users.

An additional meta-analysis conducted by Sponsiello-Wang and colleagues (2008) also examined the risk of pancreatic cancer from the use of smokeless tobacco in Europe and North America. These researchers conclude that although some subgroup analyses suggest a possible association, the risk estimates are heavily dependent on the contribution from one specific study (Luo et al. 2007) and stated that before a potential causal link can be established, further research should be conducted.

More recently, two additional meta-analyses that examined risk of pancreatic cancer risk among North American and European smokeless tobacco users (Lee and Hamling 2009b) or among snus users only (Lee 2011), reported no significantly elevated summary risk of pancreatic cancer among smokeless tobacco users using smoking adjusted risk estimates or those restricted to never smokers. The reason for the discrepancy between the results of the Lee & Hamling and

the Boffetta meta-analyses is that Boffetta et al (2008) selected the highest relative risk estimates from each study: the smoking-adjusted estimate from Boffetta et al. (2005) and the never-smokers estimate from Luo et al. (2007). Lee & Hamling (2009b) more appropriately combined estimates for all subjects in the two studies (with adjustment for smoking), and estimates for never-smokers (**Figure 6-1**).

Figure 6-1. Relative risk estimates for pancreatic cancer (with 95% confidence intervals) associated with use of snus in the Luo et al study (2007), and the Boffetta et al study (2005).



The Lee & Hamling meta-analysis from 2009, and Boffetta meta-analysis from 2008 published discrepant results regarding risk estimates for pancreatic cancer associated with snus use. Lee & Hamling provided an overall estimate (adjusted for smoking), and a separate estimate for never smokers, both estimates being statistically non-significant. In contrast, the Boffetta meta-analysis combined the highest risk estimate from each individual study, that is, the estimate for never smokers in the Luo et al study, and the overall estimate from the Boffetta et al study, arriving at a statistically significant meta-analysis result.

Case-control study of other STPs

Additional, related evidence on STP use and pancreatic cancer comes from a recent pooled analysis, in which data from 11 case-control studies of pancreatic cancer throughout North America, Europe (excluding Scandinavia), and Australia were pooled to examine tobacco use and risk of pancreatic cancer (Bertuccio et al. 2011). Data were available on smokeless tobacco

(snuff, chewing tobacco, or both) from 6 of the 11 studies. Though Swedish snuff was not used in any of the populations included in the analysis, these results are relevant with respect to Swedish snus since there is no potentially carcinogenic constituent that is particular to snus. In fact, smokeless tobacco traditionally used in North America and other western countries, if anything, probably contained more TSNAs than Swedish snus. TSNAs are thought to be the components of tobacco products that are likely associated with an increased risk of pancreatic cancer.

In the Bertuccio analysis, odds ratios were estimated and adjusted for major potential confounders available from the individual studies, including age, sex, education, race/ethnicity, BMI, history of diabetes, and total alcohol consumption. No increased risk of pancreatic cancer was observed among ever (OR=0.98, 95% CI: 0.75-1.3) or exclusive (OR= 0.62, 95% CI: 0.37-1.04) smokeless tobacco users. The authors state that their "results on smokeless tobacco use are in broad agreement" with the recently published meta-analysis of all published data by Sponsiello-Wang et al. (2008), and conclude that "while based on small numbers, no significant association emerged for … smokeless tobacco use." Additional strengths of this pooled analysis include the availability and use of data from individual studies, adequate control of important potential confounders for pancreatic cancer, and the confirmed association with cigarette smoking. The odds ratio for the association between smoking and pancreatic cancer (OR=1.50, 95% CI: 1.39-1.62), was of the same magnitude observed in other studies of this risk factor for pancreatic cancer (Friedman et al. 1997; McLaughlin et al. 1995) which can be used as an indicator of the adequacy of the tobacco-related exposure assessment and other methodologies of this study. Though not specific to Swedish snus, this pooled analysis contributes additional evidence that smokeless tobacco of any type commonly used in Europe and North America today is likely to confer less risk for pancreatic cancer than smoking, if an excess risk exists at all.

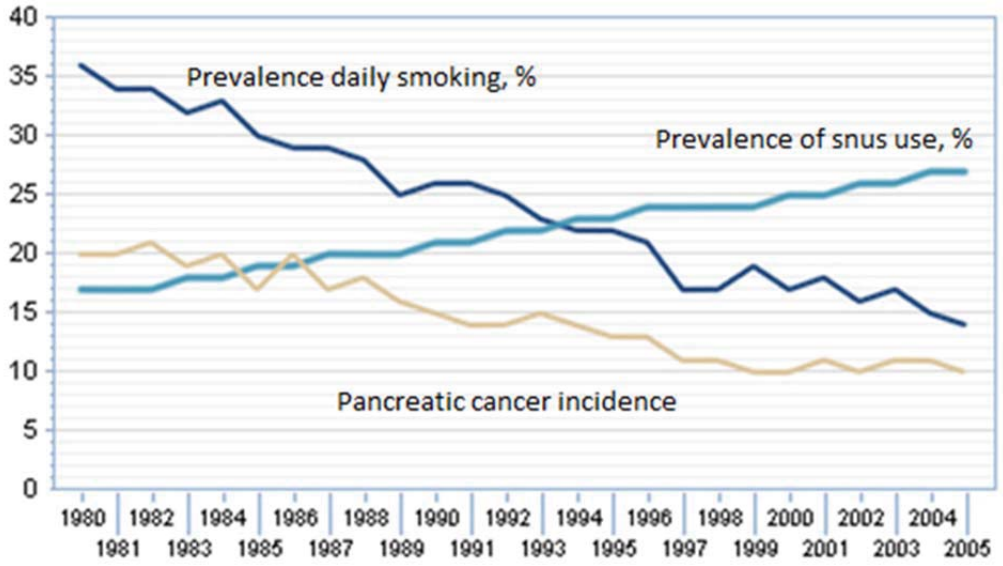
Ecologic data

An association between snus and pancreatic cancer is not supported by Swedish public health statistics. In a review of cancer mortality in European countries covering the years 2000-2004, it was found that Sweden had the lowest overall male cancer mortality (Sweden 125.8/105, European average 168.0/105), mainly as a result of lower rates for typically tobacco-related cancers (La Vecchia et al. 2009). In particular, pancreatic cancer mortality among Swedish males was lower than the European average.

In Sweden the incidence of pancreatic cancer among males decreased by half during 1980-2005 (**Figure 6-2**). During the same period, prevalence of snus use increased by about 50%. The decreased risk of pancreatic cancer parallels the decrease in smoking prevalence, but contrasts with the development in other European countries where mortality among males has remained fairly stable since 1975 (2009).

Thus, public health statistics do not suggest or support the existence of a significant risk factor for pancreatic cancer that is particular to Swedish males, such as snus.

Figure 6-2: Prevalence of daily smoking and snus use (daily and occasional) among Swedish males aged 16-84 years during 1980 through 2005 (data source: Swedish National Central Bureau of Statistics, Surveys of Living Conditions (ULF); Incidence of pancreatic cancer among Swedish men (all ages) per 100,000. Age standardization according to the Swedish population in 2000. (Source: Swedish Cancer Registry, National Board of Health)



Conclusions

The epidemiological evidence linking use of Swedish snus to an increased risk of pancreatic cancer remain weak and unconvincing, and are not supported by Swedish public health statistics.

6.1.1.9. Summary

The foregoing comprehensive review of the published scientific literature confirms the lack of serious adverse health effects associated with Swedish snus. Well-controlled epidemiological evidence indicates that use of Swedish snus is not associated with oral cancer or cancer of any part of the respiratory tract. Additional epidemiology studies have failed to demonstrate that Swedish snus is a significant risk factor for kidney, bladder, lung, skin, and hematopoietic cancers, and all cancers combined. One well-conducted analytic epidemiology study (Eliasson et al. 2004) found that use of Swedish snus was not associated with increased risk of diabetes, and the literature further indicates that use of Swedish snus is not associated with harmful gastrointestinal effects, including peptic ulcer, heartburn, Crohn's disease or ulcerative colitis.

Overall, there is very little evidence to suggest that current use levels of snus in Sweden are associated with any significant long-term health effects. Studies have reported that the use of Swedish snus is associated with a characteristic type of oral mucosal lesion which is localized to the area where the snus is placed (Andersson et al. 1989; Andersson et al. 1990; Andersson 1991;

Andersson et al. 1994; Andersson et al. 1995; Andersson and Axell 1989; Andersson and Warfvinge 2003; Axell 1976; Axell et al. 1976; Axell 1987; Axell and Hedin 1982; Axell and Henricsson 1985; Axell 1993; Frithiof et al. 1983; Hirsch et al. 1982; Larsson et al. 1991; Martensson 1978; Mornstad et al. 1989; Rolandsson et al. 2005; Roosaar et al. 2006; Rosenquist et al. 2005; Salonen et al. 1990; Wallstrom et al. 2011). However, the lesions are reversible following cessation of snus use and there is no clinical evidence to suggest that they progress into malignancies. Snus, like cigarettes, should not be used during pregnancy and nursing due to the risk of adverse outcomes. However, these adverse pregnancy outcomes are no worse for snus than with smoking, with the possible exception of the "protective effect" from smoking on pre-eclampsia.

6.1.2. Health Risks Associated with Switching to Snus from Cigarettes and Dual Use as Compared to Quitting Tobacco Entirely or Continued Smoking

6.1.2.1. Overview

This section of the Application summarizes the available data on the health risks associated with the use of Swedish snus as compared to other consumer behaviors, including:

- the changes in health risks to users who switch from using another tobacco product to using snus, including tobacco products within the same class of products;
- the health risks associated with switching to snus as compared to quitting the use of tobacco products; and
- the health risks associated with using snus in conjunction with other tobacco products.

This section provides information on the potential health risks of Swedish snus, using a subset of the studies that were reviewed in Chapter 5 of the ENVIRON Snus Monograph (2013). As is further explained below, the evidence from several different cohorts suggests that dual users do not face a higher disease risk than exclusive smokers, and that generally, the health risks among dual users appear to be similar to those observed among exclusive smokers. The health risks among those who switch to snus from cigarettes were clearly lower than those observed among individuals who continued to smoke cigarettes, and were generally comparable to, or had lower point estimates than, the risks estimates observed among those who quit tobacco entirely.

This section includes all studies that provided relative risk estimates for snus users who were also former smokers (switchers), and studies that provided relative risk estimates for any other varying categories of snus users in combination with smoking, such as dual users of snus and cigarettes. These studies allow the comparison of available risk estimates to examine potential differences in risks among switchers and dual users compared to non-tobacco users, individuals who quit tobacco entirely, and individuals that continue smoking cigarettes.

6.1.2.2. Methods

The available epidemiology studies summarized in the snus health effects review were examined for evidence of health effects among switchers and dual users; that is, studies that provided

relative risk estimates for snus users who were former smokers, and concurrent users of snus and cigarettes, respectively. Relative risk estimates for smokers who either quit tobacco entirely or continued smoking were also extracted from these studies using a methodology similar to that described in Appendix VI of the ENVIRON Snus Monograph (2013), specifically those studies in which relative risks were presented for the various types of tobacco users within the same study population using a common referent group (ideally, non-tobacco users). The health outcomes considered include the same smoking-related outcomes as those included in Appendix VI. Among the available studies of switchers, the outcomes evaluated included oral cancer, metabolic syndrome, diabetes, and various cardiovascular outcomes including overall cardiovascular disease, myocardial infarction (MI), ischemic heart disease, sudden cardiac death, coronary heart disease and stroke. These same outcomes were available for dual users, along with pancreatic, lung, stomach, and esophageal cancers.

In addition to the smoking-related outcomes included in the summary table, below, this section addresses several additional health outcomes that were studied among smokers, snus users, and dual users or switchers in order to ascertain whether combined use might present unique health risks for disease other than those considered to be smoking-related. These include several additional cancer types, neurologic diseases, gastric conditions, and potential effects on body weight.

6.1.2.3. Results

The health risks of (i) quitting smoking without a substitute, (ii) switching to snus from cigarettes, (iii) using snus and cigarettes concurrently, and (iv) continued smoking are presented in **Table 6-3** and described below. Note that all cited studies are product-specific as they examined the use of Swedish snus, even though the product may have been referred to by alternate names (e.g., oral snuff).

In this table, results for dual users are bolded, and results for switchers (i.e., former smokers who switched to snus) are italicized. The table is followed by a more detailed discussion of results by health outcome.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco

Study Info	Outcome	Results	Definition of Former Smoking Status & Dual Use Details
Boffetta et al. (2005) Cohort study	Lung Cancer Never-smokers/ever snus users **Current smokers/ever snus**	Relative Risk (95% CI) 1.00 (reference) **0.68 (0.51-0.90)****	Use of cigarettes and snus may not have been concurrent.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
Two sources: General Norwegian population (1960 census) and relatives of Norwegian migrants to the US (1964-1967 questionnaire). All risk estimates adjusted for age, sex and smoking (smoking estimates are among snuff users).	**users** Never-users Ever snus user Current snus users <u>Pancreatic Cancer</u> Never-smokers/ever snus users **Current smokers/ever snus users** Never-users Ever snus user Current snus users	 1.00 (reference) 0.80 (0.61-1.05) 0.80 (0.58-1.11) 1.00 (reference) **1.86 (1.13-3.05)*** 1.00 (reference) 1.67 (1.12-2.50)* 1.60 (1.00-2.55)	
Bertuccio et al. (2011) Pooled-analysis of 11 case-control studies (international) Adjusted for center, race, sex, age, education, history of diabetes, body mass index and total alcohol consumption.	<u>Pancreatic Cancer</u> Never tobacco users Ever smokeless tobacco user Exclusive smokeless tobacco user **Smokeless tobacco users and cigarette** Cigarette-only smokers	<u>Odds Ratio (95% CI)</u> 1.00 (reference) 0.98 (0.75-1.27) 0.62 (0.37-1.04) **1.36 (0.94-1.96)** 1.50 (1.39-1.62)*	Use of cigarettes and smokeless tobacco may not have been concurrent.
Haglund et al. (2007) Cohort study Swedish population	<u>IHD (incidence)</u> No tobacco Smoke Snuff	<u>IRR or MRR (95% CI)</u> 1.00 (reference) 1.74 (1.41–2.14)* 0.77 (0.51–1.15)	Dual users were concurrent users of both cigarettes and snus.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
1988 – 1989 through 2003 All risk estimates adjusted for age, sex (men only), socioeconomic status, residential area, self-reported health, number of longstanding illnesses, and physical activity. Tobacco use categories were exclusive (but may include former smokers/snuff users). ICD9: 410-414; ICD10: I20-I25 (IHD)	**Smoke and snuff** <u>IHD (mortality)</u> No tobacco Smoke Snuff **Smoke and snuff** <u>Stroke (incidence)</u> No tobacco Smoke Snuff **Smoke and snuff** <u>Stroke (mortality)</u> No tobacco Smoke Snuff **Smoke and snuff**	**1.64 (0.96–2.79)** 1.00 (reference) 1.98 (1.35–2.91)* 1.15 (0.54–2.41) **1.69 (0.52–5.46)** 1.00 (reference) 1.40 (1.03–1.91)* 1.07 (0.65–1.77) **1.98 (1.00–3.95)** 1.00 (reference) 1.02 (0.50–2.05) 1.01 (0.35–2.92) **4.30 (1.22–15.1)***	
Hansson et al. (2009) Cohort Study Swedish Twin Registry All risk estimates adjusted for age, sex, diabetes, high blood pressure, and high cholesterol. All CVD; ICD10: I20-I21, I24-	<u>Ischemic Heart Disease</u> Never smoking/never snus Former smoking/never snus *Former smoking/current snus* Current smoking/never snus Never smoking/current snus **Current smoking/current snus** <u>All CVD</u>	<u>Relative Risk (95% CI)</u> 1.00 (reference) 1.34 (1.10-1.64)* *1.22 (0.82-1.74)* 1.99 (1.59-2.50)* 0.85 (0.51-1.41) **1.50 (0.73-3.08)**	Information on tobacco use was ascertained through the question 'Have you ever smoked or used snus?'. Subjects stated whether they were never, former or current snus users and/or smokers, including regular and occasional use, such as 'now and

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
I25 [excluding I25.2] IHD: MI or coronary revascularization procedures Stroke: ICD10: I60-I61, I63-I64, G45; ICD9: 430-431, 433-436	Never smoking/never snus Former smoking/never snus *Former smoking/current snus* Current smoking/never snus Never smoking/current snus **Current smoking/current snus** <u>Stroke</u> Never smoking/never snus Former smoking/never snus *Former smoking/current snus* Current smoking/never snus Never smoking/current snus **Current smoking/current snus**	1.00 (reference) 1.17 (1.00-1.38) *1.04 (0.78-1.39)* 1.86 (1.56-2.22)* 1.00 (0.69-1.46) **1.51 (0.86-2.65)** 1.00 (reference) 1.01 (0.78-1.30) *0.77 (0.46-1.29)* 1.61 (1.22-2.13)* 1.18 (0.67-2.08) **1.45 (0.58-3.62)**	then' or 'at parties'. Dual users were concurrent users of both cigarettes and snus.
Hergens et al. (2005) Case-control Study Residents of Stockholm County All risk estimates adjusted for age, sex, hospital catchment area, diabetes, hyperlipidemia, hypertension, overweight, physical inactivity, and job strain. Myocardial Infarction (MI)	<u>All Cases of MI</u> Never snuff/never smoking Never snuff/ former smoking *Current snuff/former smoking* Never snuff/current smoking Current snuff/never smoking **Current snuff/current smoking** <u>Nonfatal MI</u> Never snuff/never smoking Never snuff/ former smoking *Current snuff/former smoking* Never snuff/current smoking	<u>Odds Ratio (95% CI)</u> 1.00 (reference) 1.30 (1.10-1.60)* *1.60 (1.10-2.20)** 2.80 (2.30-3.40)* 0.73 (0.35–1.5) **2.30 (1.6–3.4)*** 1.00 (reference) 1.20 (0.98-1.50) *1.60 (1.10-2.20)**	Subjects who at enrollment had been using snuff within the last 2 years were classified as current snuff users. Subjects who had stopped smoking more than 1 year before were classified as former smokers and those who had smoked within the past year were classified as current smokers.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
	Current snuff/never smoking **Current snuff/current smoking** <u>Fatal MI within 28 days</u> Never snuff/never smoking Never snuff/ former smoking *Current snuff/former smoking* Never snuff/current smoking Current snuff/never smoking **Current snuff/current smoking**	2.70 (2.20-3.30)* 0.59 (0.25-1.4) **2.10 (1.4-3.1)*** 1.00 (reference) 1.70 (1.60-2.60)* *1.50 (0.69-3.20)* 3.60 (2.40-5.20)* 1.70 (0.48-5.5) **3.80 (1.9-7.5)***	Dual users were concurrent users of both cigarettes and snus. Among controls, dual users smoked slightly fewer cigarettes than those who exclusively smoked (16.4 vs. 18.6 cigs/day). Similar for former smokers. This was also true for the former smokers (18.4 cigarettes per day with snuff use and 20.6 cigarettes per day without snuff).
Huhtasaari et al. (1999) Case-control study Northern Sweden MONICA project: Norrbotten and Vasterbotten provinces. 1991 – 1993 Multivariate estimates adjusted for age (matched) and sex (men only), hypertension, diabetes, high cholesterol, family history of early cardiac death, low education level, and marital status. Tobacco use categories were exclusive (but may include	<u>MI</u> Never users of tobacco Current snuff/no smoking Current smoking/no snuff Former smoker/never snuff **Current concomitant user**	<u>Odds Ratio (95% CI)</u> 1.00 (reference) 0.96 (0.65–1.41) 3.65 (2.67–4.99)* 1.05 (0.77–1.43) **2.66 (1.24–5.71)***	Dual users were daily, concurrent users of both cigarettes and snus.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
former smokers/snuff users). ICD:410-414 (MI)			
Johansson et al. (2005) Cohort study Random sample from Swedish population: SALLS survey All risk estimates adjusted for age, sex (men only), BMI, physical activity, diabetes, and hypertension. Risk estimates did not change much when socioeconomic status was considered. ICD9: 410-414; ICD10: I20-I25 (CHD event)	<u>Coronary Heart Disease</u> Never-smoker Former smoker *Daily snuffer/former smoker* Daily smoker Daily snuffer/never-smoker **Daily snuffer and smoker**	<u>Hazard Ratio (95% CI)</u> 1.00 (reference) 1.47 (1.07-2.03)* *1.18 (0.67-2.06)* 2.30 (1.66-3.19)* 1.41 (0.61–3.28) **2.73 (1.35–5.53)***	No definition of former smokers given. Dual users were daily, concurrent users of both cigarettes and snus.
Schildt et al. (1998) Case-control study 4 Northernmost counties of Sweden Matched for gender, age and county.	<u>Oral Cancer</u> Never snuff/never smoker Never snuff/ex-smoker *Active snuff/ex-smoker* Never snuff/active smoker Active snuff/never-smoker **Active snuff/active smoker**	<u>Odds Ratio (95% CI)</u> 1.0 (reference) 0.9 (0.6-1.4) *0.6 (0.3-1.3)* 1.7 (1.1-2.6)* 0.7 (0.4–1.2) **1.2 (0.6–2.4)**	An ex-smoker or ex-snuff user was defined as a person who had quit the habit at least 1 year before the diagnosis; for controls, the corresponding year was the year of diagnosis for the respective case. Subjects who had stopped smoking or stopped using moist snuff within the year before diagnosis were coded as

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
			current users of tobacco. Dual users were concurrent users of both cigarettes and snus.
Wandell et al. (2008) Cross-sectional study Men living in Stockholm county, Sweden Risk estimates adjusted for age (all 60), sex (men only), BMI, waist circumference, employment, educational level, living in an apartment, physical activity, alcohol intake. Metabolic syndrome definition: International Diabetes Federation (IDF).	<u>Diabetes</u> Reference not provided Never snuff/ex-smoker *Current snuff/ex-smoker* Never snuff/current smoker Never smoker/current snuff **Current smokers and snuffers** <u>Metabolic Syndrome</u> Reference not provided Never snuff/ex-smoker *Current snuff/ex-smoker* Never snuff/current smoker Never smoker/current snuff **Current smokers and snuffers**	<u>Odds Ratio (95% CI)</u> ---- 1.41 (0.76-2.60) *1.71 (0.67-4.35)* 1.40 (0.68-2.89) 2.12 (0.25-17.71) **2.48 (0.52-11.82)** ---- 1.44 (1.14-1.83)* *1.18 (0.76-1.83)* 1.00 (0.74-1.35) 1.81 (0.65-5.02) **0.85 (0.36-2.02)**	No definition of former smokers given. Dual users were daily, concurrent users of both cigarettes and snus.
Wennberg et al. (2007) Prospective incident case-referent study (Nested case-control study) Nested in northern Sweden MONICA cohort: Norrbotten and Vasterbotten provinces.	<u>MI</u> Never used tobacco Former smoker/never snuff *Former smoker/current snuff* Current smoker/no current snuff Never smoked/current snuff **Current smoker/current snuff**	<u>Odds Ratio (95% CI)</u> 1.00 (reference) 1.18 (0.82-1.70) *1.25 (0.80-1.96)* 2.60 (1.91-3.54)* 0.82 (0.46–1.43) **2.14 (1.28–3.60)***	No definition of former smokers given. Dual users were daily, concurrent users of both cigarettes and snus.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
All risk estimates adjusted for age, sex, BMI, leisure time physical activity, educational level and cholesterol level. Tobacco use categories were exclusive, but current smoking category may have included some past snuff users. ICD9: 410-414, 429.2; ICD10: I20-I25 (MI, fatal MI, Sudden cardiac death (SCD))	<u>Fatal MI within 28 days</u> Never used tobacco Former smoker/never snuff *Former smoker/current snuff* Current smoker/no current snuff Never smoked/current snuff **Current smoker/current snuff** <u>SCD with survival <24 h</u> Never used tobacco Former smoker/never snuff *Former smoker/current snuff* Current smoker/no current snuff Never smoked/current snuff **Current smoker/current snuff** <u>SCD with survival <1 h</u> Never used tobacco Former smoker/never snuff *Former smoker/current snuff* Current smoker/no current snuff Never smoked/current snuff **Current smoker/current snuff**	 1.00 (reference) 1.02 (0.45-2.31) *1.24 (0.44-3.53)* 3.53 (1.83-6.84)* 1.12 (0.38-3.29) **1.11 (0.34-3.69)** 1.00 (reference) 0.74 (0.28-1.97) *1.39 (0.44-4.42)* 3.12 (1.53-6.33)* 1.18 (0.38-3.70) **0.75 (0.17-3.28)** 1.00 (reference) 0.35 (0.07-1.78) *2.67 (0.52-13.80)* 4.54 (1.55-13.25)* 0.38 (0.08-1.89) **0.13 (0.01-2.10)**	
Ye et al. (1999) Case-control (population-based)	<u>Stomach Cancer</u> Never-smokers/never-users Never-smokers/ever-users	<u>Odds Ratio (95% CI)</u> 1.0 (reference) 0.5 (0.2-1.2)	Use of cigarettes and snus may not have been concurrent. Dual users smoked

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
Swedish population (5 counties) 1989-1995 Risk estimates for snuff use were adjusted for age, residence area, BMI, socio-economic status, and smoking. Odds ratios among smokers and exclusive tobacco groups were adjusted for age, gender, residence area, BMI, SES, use of smokeless tobacco, and use of beer, wine and liquor. Gastric cancer	Ex-smokers/never-users Ex-smokers/ever-users Current smokers/never-users **Current smokers/ever-users**	1.2 (0.9-1.8) 1.2 (0.8-1.9) 2.0 (1.3-2.9)* **1.0 (0.5-1.8)**	less and for a shorter duration than smokers who did not (ever) use snuff.
Zendehdel et al. (2008) Cohort study Swedish Construction Worker cohort 1971 – 1993 and followed through 2004 All risk estimates adjusted for attained age and BMI.	<u>Esophageal Adenocarcinoma</u> Ever-smokers/non snus users **Ever-smokers/snus use** Never-users of any tobacco User of snus only Smoker only <u>Esophageal squamous cell carcinoma</u> Ever-smokers/non snus users **Ever-smokers/snus use** Never-users of any tobacco User of snus only Smoker only	<u>Relative Risk (95% CI)</u> 1.0 (reference) **1.0 (0.6-1.5)** 1.0 (reference) 0.2 (0.0-1.9) 2.9 (1.8-4.8)* 1.0 (reference) **0.8 (0.6-1.2)** 1.0 (reference) 3.5 (1.6-7.6)* 7.6 (4.5-12.7)*	Use of cigarettes and snus may not have been concurrent.

Table 6-3: Health Risks of Dual Use, Switching to Snus from Cigarettes vs. Quitting Tobacco, Continued Smoking, and Non-use of Tobacco			
Study Info	**Outcome**	**Results**	**Definition of Former Smoking Status & Dual Use Details**
	Stomach cancer-cardia		
	Ever-smokers/non snus users	1.0 (reference)	
	Ever-smokers/snus use	**0.9 (0.7-1.3)**	
	Never-users of any tobacco	1.0 (reference)	
	User of snus only	0.9 (0.4-2.0)	
	Smoker only	2.3 (1.6-3.3)*	
	Stomach cancer-noncardia		
	Ever-smokers/non snus users	1.0 (reference)	
	Ever-smokers/snus use	**1.0 (0.9-1.2)**	
	Never-users of any tobacco		
	User of snus only	1.0 (reference)	
	Smoker only	1.4 (1.1-1.9)*	
		1.4 (1.2-1.6)*	

* denotes statistically significant increase in risk

** denotes statistically significant decrease in risk

Bold: dual use category

Italics: switching category

6.1.2.3.1. Switching

Oral Cancer

One case-control study reported risk estimates of oral cancer among former smoking snus users, along with risk estimates among former smokers who quit tobacco entirely and those who were current smokers (Schildt et al. 1998). The risk of oral cancer among ex-smokers was not increased, including ex-smokers who were active snus users. The risk among active smokers who had never used snus was significantly increased. This study observed that, among those who switched from cigarettes to snus, no increased risk of oral cancer was observed compared to those who were active smokers.

Diabetes and Metabolic Syndrome

One cross-sectional study reported risk estimates of diabetes and metabolic syndrome among former smoking snus users, former smokers who quit tobacco entirely, and those who were current smokers (Wandell et al. 2008). None of the risk estimates were significantly elevated for either outcome except for a significantly increased risk of metabolic syndrome among ex-smokers who quit tobacco entirely (i.e., did not switch to snus).

Stroke

One cohort study reported risk estimates of stroke among former smoking snus users, former smokers who quit tobacco entirely, and those who are current smokers (Hansson et al. 2009). The risk of stroke among former smokers, whether they had quit tobacco use altogether or had switched to snus was not significantly elevated. In contrast, the risk of stroke among active smokers who had never used snus was significantly increased (RR 1.61, 95% C. I.: 1.22-2.13).

Cardiovascular Disease

Two cohort (Hansson et al. 2009; Johansson et al. 2005) and two case-control (Hergens et al. 2005; Wennberg et al. 2007) studies reported risk estimates of all cardiovascular disease, MI, ischemic heart disease, sudden cardiac death, or coronary heart disease among former smoking snus users, former smokers who quit tobacco entirely, and current smokers. Three of the four studies did not find a significantly increased risk for the various CVD-related outcomes examined, including ischemic heart disease, all cardiovascular disease, coronary heart disease, MI (overall or fatal within 28 days) or sudden cardiac death (<24 hours and <1 hour) among former smoking snus users. The fourth study by Hergens and colleagues (2005), examined MI (all, fatal, nonfatal), and reported significantly increased risks of any MI, and non-fatal MI among former smoking snus users, but no significantly increased risk of fatal MI. These risks were either lower than or not significantly different from those observed among smokers, where the risks of the various CVD outcomes were consistently significantly increased among current smokers in all of the studies.

6.1.2.3.2. Dual Use

Epidemiology Studies

Dual use of multiple tobacco products plays an important part in understanding the role of the various tobacco products in tobacco use initiation and cessation. It is therefore important to understand the differences and changes in health risks for individuals who transition from one kind of tobacco use to another. In Scandinavia, and particularly in Sweden, individuals who have ever used snus are more likely to have ever smoked than people who never used snus. However, it is less clear from the literature whether people who are current snus users are more likely to also be current smokers. If they are more likely to be dual users it is difficult to assess the frequency and duration of use of both tobacco products, as the study designs employed often do not allow for an understanding of the temporality necessary to discern patterns of use. It is also difficult to assess the number of cigarettes and amount of smokeless tobacco used. There is evidence to suggest that smokers who use snus smoke fewer cigarettes per day (or per other specified period) than smokers who are not dual users. However, it is often not possible to

understand the temporal sequence of product initiation, since few of these studies measured frequency and intensity of tobacco use.

Diabetes and Metabolic Syndrome: One cross-sectional study reported risk estimates of diabetes and metabolic syndrome among concurrent users of snus (called snuff) and cigarettes (Wandell et al. 2008). None of the risk estimates were significantly elevated among participants who were current smokers and current snus users for either outcome; however, a significantly increased risk of metabolic syndrome was observed among ex-smokers.

Esophageal Cancer: One cohort study investigated the potential effects of dual use on esophageal cancer among snus users who were ever users of cigarettes (Zendehdel et al. 2008), although the use of snus and cigarettes may not have been concurrent among the study participants, and no information was provided on the amount of tobacco consumed by type. Among these dual users, the risks of esophageal adenocarcinoma and squamous cell carcinoma were not increased compared to ever smokers/non snus users, while the risks of both cancer subtypes were significantly elevated among exclusive smokers when compared to never tobacco users.

Lung Cancer: One cohort study investigated the potential risk of dual use on lung cancer among ever snus users who were current smokers (Boffetta et al. 2005). Although the use of snus and cigarettes may not have been concurrent among the study participants, and no information was provided on the amount of tobacco consumed by type, the risk of lung cancer was significantly lower among dual users. A risk estimate for exclusive smokers was not available for comparison with that of dual users.

Oral Cancer: One case-control study investigated the potential effects of dual use on oral cancer among concurrent users of snus (called snuff) and cigarettes (Schildt et al. 1998). Though no information is given on the amount of snus or cigarettes consumed by dual users, the risk of oral cancer among dual users was not significantly increased, while the risk among current smokers was significantly increased. The risk among snus users was near unity, suggesting no increased risk from snus use.

Pancreatic Cancer: One cohort study of Swedish snus users investigated the potential effects of dual use on pancreatic cancer among ever snus users who were current smokers (Boffetta et al. 2005). The risk of pancreatic cancer was significantly increased among dual users, though the use of snus and cigarettes may not have been concurrent among the study participants, and no information was provided on the amount of tobacco consumed by type. A risk estimate for exclusive smokers was not available for comparison with dual users.

Although there is limited snus-specific data, additional evidence was provided by a recent pooled-analysis of 11 studies of cigarette and Western population smokeless tobacco users (Bertuccio et al. 2011). In this study, dual users and exclusive smokeless tobacco users did not face a significantly increased risk of pancreatic cancer, whereas the risk of pancreatic cancer was significantly increased among smokers. Given that the smokeless tobacco used by participants in these studies likely contained higher levels of TSNAs, the principal component of tobacco

thought to be associated with the development of pancreatic cancer, as compared to Swedish snus, (Boffetta et al. 2008), it is unlikely that Swedish snus poses a risk for pancreatic cancer.

Stomach Cancer: One cohort study (Zendehdel et al. 2008) and one case-control study (Ye et al. 1999) reported risk estimates of stomach cancer among dual users of snus and cigarettes. The cohort study investigated the potential effects of dual use on stomach cancer among snus users who were ever users of cigarettes. Though the use of snus and cigarettes may not have been concurrent among the study participants, and no information was provided on the amount of tobacco consumed by type, the risks of cardia and non-cardia stomach cancer were not increased among dual users, while the risks of both cancer subtypes were significantly elevated among exclusive smokers (Zendehdel et al. 2008).

The case-control study investigated the potential effects of dual use on stomach cancer among smokers who were ever users of snus (called snuff) (Ye et al. 1999). Though the use of snus and cigarettes may not have been concurrent among the study participants, the risk of stomach cancer was not increased among dual users, while the risk of stomach cancer was significantly elevated among exclusive smokers. The authors reported that dual users smoked less and for a shorter duration than smokers who did not or did not ever use snus.

Stroke: Two cohort studies reported risk estimates for stroke among concurrent users of snus and cigarettes (Haglund et al. 2007; Hansson et al. 2009). Hansson and colleagues (2009) found that dual users did not face a significantly increased risk of stroke, while the risk of stroke was significantly increased among current exclusive smokers. Haglund and colleagues (2007) found that the risk of incident stroke was elevated and of borderline significance among dual users, and that fatal stroke was also elevated, and statistically significant, based on three cases available for analysis. The risk of fatal stroke was not significantly elevated among cigarette smokers. Neither study provided information on the amount of tobacco consumed by type.

Cardiovascular Disease: Three cohort (Haglund et al. 2007; Hansson et al. 2009; Johansson et al. 2005) and three case-control (Hergens et al. 2005; Huhtasaari et al. 1999; Wennberg et al. 2007) studies reported risk estimates of all cardiovascular disease, MI, ischemic heart disease, sudden cardiac death, or coronary heart disease among concurrent users of snus and cigarettes. Haglund and colleagues (2007) reported no significantly increased risk of IHD incidence or mortality among dual users, while the risk among smokers was significantly elevated for both. Hansson and colleagues (2009) also reported that the risk of IHD and all cases of CVD was not significantly increased among dual users, while the risks among smokers for both of these outcomes were significantly elevated. Johansson and colleagues (2005) reported a significantly increased risk of coronary heart disease among dual users, which was lower than the risk observed among exclusive smokers. Hergens and colleagues (2005) reported a significantly increased risk of all cases of MI, nonfatal MI, and fatal MI within 28 days among dual users. These risks were generally comparable to those observed among smokers. Huhtasaari and colleagues (1999) reported a significantly increased risk of MI among dual users, though this risk was lower than that observed among current exclusive smokers. Wennberg and colleagues (2007) reported a significantly increased risk of MI among dual users, but increased risks were not observed for fatal MI within 28 days, sudden cardiac death (SCD) with survival <24 hours,

and SCD with survival <1 hour, while the risks among smokers for all of these outcomes were significantly elevated.

None of the studies of CVD provided information on the amount of tobacco consumed with the exception of Hergens et al. (2005). Hergens and colleagues (2005) reported that, among controls, dual users smoked slightly fewer cigarettes than those who exclusively smoked cigarettes (16.4 vs. 18.6 cigarettes/day). The authors reported that this was also true for the former smokers (18.4 cigarettes/day with snus (called snuff) use and 20.6 cigarettes/day without snus. Overall, the risks of the various cardiovascular outcomes among dual users were either not increased, lower than that observed among smokers, or comparable to the risk observed among smokers. In no instance was the risk of CVD outcomes among dual users higher than that observed among smokers who did not use snus.

Other Outcomes: The results from studies of outcomes other than those presented in **Table 6-3** of dual snus/cigarette users were also investigated in order to ascertain whether combined use might present unique health risks for disease other than those considered smoking-related. Similar to the results provided in Appendix VI of the ENVIRON Snus Monograph (2013), dual users either did not face any risk or faced a risk not significantly different from exclusive smokers for outcomes which included various types of skin and blood cancers, ALS, multiple sclerosis, sarcoidosis, rheumatoid arthritis, and rectal, and anal cancers (Carlens et al. 2010; Fang et al. 2006; Fernberg et al. 2006; Fernberg et al. 2007; Nordenvall et al. 2011; Odenbro et al. 2005; Odenbro et al. 2007).

A few studies found that dual users faced a significantly increased risk where exclusive smokers did not, including one cancer study that reported a significantly increased risk of colon cancer for dual users but not among exclusive smokers (Nordenvall et al. 2011). The confidence intervals overlapped, however, and exclusive snus use was not associated with this outcome. Details regarding cigarette and snus consumption, and potential lifestyle differences among different tobacco user groups were not provided. Similar results were observed in one study of ulcerative colitis and Crohn's disease (Persson et al. 1993), where the risks of these outcomes were significantly increased among dual users, but not among smokers. Another study presented risk estimates that were similar, and significantly increased among both smokers and dual users for these conditions (Carlens et al. 2010). All of the participants in the Carlens et al. (2010) and Persson et al. (1993) studies may not have used snus and cigarettes concurrently. Though the confidence intervals overlapped, Aro and colleagues (2010) reported risk estimates that were significantly increased among dual users but not among current smokers for some, but not all of the gastric conditions investigated in that study. Dual users in this study were the highest consumers of alcohol. Potentially confounding lifestyle habits were not investigated in the other studies that observed significantly increased risks of gastric conditions among dual users.

Several studies investigated the potential effects of concurrent dual use on BMI, body weight or incident weight gain. Aro et al. (2010) observed that the mean BMI of dual users was similar to never-users of tobacco, while the mean BMI among current smokers was significantly greater than never-users of tobacco. Engstrom and colleagues (2010) did not find an increased prevalence of being underweight, but did report a significantly increased prevalence of being

overweight or obese among dual using men, whereas the risks were not significantly increased among exclusive smokers (though the confidence intervals did overlap). A significantly increased prevalence of overweight or obesity was not observed among women who were dual users. Hansson and colleagues (2011) and Rodu and colleagues (2004) reported a significantly increased risk of incident weight gain and becoming overweight, respectively, among dual users, while the risk was not significantly elevated among smokers. Hansson et al. (2011) did not report a significantly increased risk of becoming obese among dual users.

6.1.2.4. Discussion

The relative risk estimates of specific smoking-related health outcomes were examined among switchers (i.e., former smokers who were current snus users) and dual users (i.e., individuals who use both snus and smoke cigarettes). Among switchers, risks of the health outcomes examined (oral cancer, metabolic syndrome, diabetes, stroke and various cardiovascular outcomes) were either not statistically significantly increased, or were lower than those observed among current smokers, with the exception of an increased risk of MI and non-fatal MI in one case-control study (Hergens et al. 2005). The risk of non-fatal MI among switchers was not significantly different from, and the risk of all cases of MI in this study was lower than, that observed among current smokers. The risks of MI, CHD, IHD, overall CVD or SCD were not significantly increased among switchers in two cohort studies (Hansson et al. 2009; Johansson et al. 2005) and one other case-control study (Wennberg et al. 2007). The relative risk estimates for all outcomes among switchers were either similar to or had lower point estimates than that of former smokers who quit tobacco entirely, with the exception of non-fatal MI reported by Hergens et al. (2005).

These conclusions for Swedish snus differ from those reported by Henley and colleagues (2007) who investigated the potential health effects of switching from cigarettes to smokeless tobacco in the US American Cancer Society Cancer Prevention Study II cohort. The authors reported that men who switched from smoking cigarettes to using smokeless tobacco (using data that were collected at baseline only) had a higher rate of death from all causes, lung cancer, coronary heart disease, and stroke than those who had never used tobacco or those who were former cigarette smokers that quit using tobacco entirely, following adjustment for several potential confounders. The authors noted that switchers, compared to those who quit tobacco entirely, were less educated, more often employed in blue-collar occupations, and had a less healthy diet. Because information on tobacco use was collected only at baseline and not updated during follow-up, it is possible that men who quit smoking before enrollment, but resumed during the follow-up period, and those who initiated or discontinued using STPs after enrollment, could have been misclassified. In fact, a subset of the cohort whose smoking status was updated after 10 years, had low overall rate of recidivism, but that rate was statistically significantly higher among switchers (3.0%) than among those who quit using tobacco entirely (1.4%). Limitations of the study include lack of information on intensity of smoking, and the possibility that addiction may have influenced both smoking behavior and use of smokeless tobacco. Former smokers who switched may have been more addicted on average and may have smoked more than those who quit tobacco entirely.

Twelve (12) studies (Bertuccio et al. 2011; Boffetta et al. 2005; Haglund et al. 2007; Hansson et

al. 2009; Hergens et al. 2005; Huhtasaari et al. 1999; Johansson et al. 2005; Schildt et al. 1998; Wandell et al. 2008; Wennberg et al. 2007; Ye et al. 1999; Zendehdel et al. 2008) provide relative risk estimates for dual users of snus and cigarettes. Most of these studies reported relative risk estimates for dual users of snus and cigarettes that were not significantly increased or were similar to those observed among exclusive smokers. The health outcomes for which none of the relative risk estimates were significantly increased for dual users included esophageal cancer, lung cancer, oral cancer, stomach cancer, diabetes, and metabolic syndrome. Among the studies that reported significantly increased health risks among dual users, these risks were similar to, or had lower point estimates than, those observed among exclusive smokers, with the exception of one sub-analysis of fatal stroke (Haglund et al. 2007). In that study, although the point estimate of the relative risk for dual users was higher, the confidence intervals overlapped with the relative risk among exclusive smokers. Details regarding cigarette and snus consumption were not reported in this study, and there were only three cases of fatal stroke. With the exception of fatal stroke, the relative risk estimates for dual users among the studies of the other outcomes, which included pancreatic cancer, and the various cardiovascular outcomes, were either not significantly increased, or were comparable to the risk observed among smokers.

Only two of the twelve studies of dual users provided qualitative or quantitative information on consumption of individual tobacco types among dual users (Hergens et al. 2005; Ye et al. 1999). In both of these studies, the authors reported that dual users of snus and cigarettes smoked slightly less compared to exclusive smokers, and Ye et al. (1999) reported that they smoked for a shorter duration. The authors of at least one US study have reported that dual STP and cigarette users in that study population (the NHANES I follow-up study) smoked more than exclusive smokers (Accortt et al. 2002). The studies where the amount of tobacco consumption by type is not provided, do not indicate how smoking intensity may affect the interpretation of the reported risk estimates.

Although eight of the twelve studies reported relative risk estimates among concurrent users of snus and cigarettes (those who used both tobacco types at the same time, typically daily), four of the studies reported relative risk estimates among dual users who were either ever users of snus, cigarettes, or both (Bertuccio et al. 2011; Boffetta et al. 2005; Ye et al. 1999; Zendehdel et al. 2008). Thus, it is likely that not all of the participants were concurrent users of both tobacco types when they developed a disease.

It is also possible that the lifestyles, especially unhealthy habits such as risky alcohol consumption, binge drinking, low fruit and vegetable consumption, and a sedentary lifestyle known to affect disease risk, may differ significantly among the various tobacco groups, and may not be accounted for in the studies. Several individual studies have found that unhealthy lifestyle habits are more prevalent among dual users of tobacco compared to exclusive tobacco user groups, and non-tobacco users. Engstrom and colleagues (2010) reported that unhealthy lifestyle was strongly associated with dual use among Swedish men and women. Bombard and colleagues (2009) reported that lifetime poly-tobacco users in Canada were more likely to use drugs and alcohol. Klesges and colleagues (2011) reported that US Air Force recruits, who were dual users, had a higher prevalence of heavier alcohol consumption, more risk-taking behaviors,

and were more likely to be surrounded by smokers. Johansson and colleagues (2005) reported that the highest percentage of "no physical activity" was observed among daily smokers and dual users in a Swedish population. The highest percentage of overweight and obesity was also found among dual users in this study. Aro and colleagues (2010) found that the high alcohol consumption (>100 g/week) was highest among dual users in a Northern Swedish study population.

Dual use of cigarettes and nicotine replacement therapy (NRT) products has also been reported. Hughes and colleagues (2005) investigated the potential off-label use of a nicotine inhaler that had recently been prescribed to US smokers in a prospective study. Off-label use included using the inhaler and cigarettes concurrently or using the inhaler for non-cessation reasons. The authors reported that many smokers used the inhaler and cigarettes concurrently on the same day (43-55%) at some time during the six month follow-up period but found that this behavior did not persist in most individuals. Repeated concurrent use (weekly concurrent use for at least a month) was reported by only 7-12% of participants. The participants did not appear to become dependent on the inhaler (only 1.4% self-reported the DSM-IV or ICD-10 criteria for dependence, but a clinician who interviewed them did not believe any were dependent). The authors concluded that although concurrent use of NRT and cigarettes occurs in some users, harm from and dependence on NRT is rare.

Despite the potential limitations of the studies of dual users of Swedish snus and cigarettes, the evidence from several different cohorts suggests that dual users do not face a higher disease risk than exclusive smokers, and that generally, the health risks among dual users appear to be similar to those observed among exclusive smokers. A number of smoking-related diseases were examined, including various cardiovascular outcomes, smoking-related cancers as well as other non-smoking-related diseases. Thus, no unique or multiplicative health risks were identified among dual users of tobacco. These conclusions are consistent with that reached by Frost-Pineda and colleagues (2010), who reviewed the available literature on the health effects of dual use from US and European epidemiology studies. Those authors concluded that "the evidence is sufficient and clear that there are no unique health risks (either qualitative or quantitative) associated with dual use of cigarettes and smokeless tobacco products, which are not anticipated or observed from single use of these products for the major health effects associated with smoking and smokeless tobacco. Some data indicate that the risks of dual use are lower than those of exclusive smoking." These conclusions are also consistent with the results of a meta-analysis published by Lee (2013b), and are described in more detail in Section 6.1.2.5.

In this review, the health risks among those who switch to snus from cigarettes were clearly lower than those observed among individuals who continued to smoke cigarettes, and were generally comparable to, or had lower point estimates than the risks estimates observed among those who quit tobacco entirely. These conclusions are consistent with those reached by Lee (2013c), who reviewed the health effects of switching among the same studies of smoking-related outcomes included in this analysis. Lee (2013c) compared risk estimates of switchers with quitters and continuing smokers quantitatively and, where appropriate, provided combined summary estimates of switching vs. continued smoking (0.55; 95% CI: 0.45-0.68) and quitting

(1.02; 95% CI: 0.83-1.26). Lee (2013c) concluded that "the findings consistently demonstrate that switching from cigarettes to snus is associated with a clearly lower risk of CVD and cancer than is continuing to smoke. The risk in switchers is no different than that in smokers who quit smoking." Though the outcomes described among switchers in this section do not include all of the smoking-related outcomes described above, the results for those outcomes, where data on switchers were unavailable, are likely to be similar to those presented here, given the consistently lower risks among snus users compared to smokers presented therein.

6.1.2.5. Meta-Analysis of Dual Use

6.1.2.5.1. Overview

A review and meta-analysis of dual use of cigarettes and snus was recently published by Lee (2013b). The content of that manuscript is presented below, through section 6.1.2.5.5.

In the last decade, there has been increasing interest in snus as a possible safer alternative to smoking. Various reviews (e.g. Boffetta et al. 2008; Broadstock 2007; Kallischnigg et al. 2008; Lee 2007; Lee and Hamling 2009b; SCENIHR 2008; Weitkunat et al. 2007) have considered possible health effects, with oral and pancreatic cancer, oral disease, and cardiovascular disease (CVD) receiving particular attention. A recent summary, with meta-analyses, of the epidemiological evidence relating snus to health (Lee 2011) found no statistically significant association with cancer of any site or with heart disease or stroke, and concluded that any possible risk from snus, if it exists, is much less than that from smoking. It also noted that "snuff dipper's lesion" (Axell et al. 1976) does not predict oral cancer. Though that summary considered a wide range of possible health effects, and found no reliable evidence that snus increases initiation of smoking or discourages quitting, it did not evaluate health effects associated specifically with dual use of cigarettes and snus.

Since that time, evidence directly relating dual use to various health endpoints has been analyzed. Other aspects of dual use have also been investigated, including comparison of cigarette and snus consumption in single and dual users, and a summary of data on the frequency of dual use and on various aspects of the interrelationship of snus use and smoking, such as with which tobacco product dual users tend to start. Transitions to dual use and from dual use are also considered in order to gain insight into whether snus use affects initiation or cessation of smoking.

6.1.2.5.2. Materials and Methods

6.1.2.5.2.1. Health Effects

Searches were conducted for studies relating to snus use and cancer, circulatory disease, respiratory and digestive disease, all-cause mortality, pregnancy and reproductive effects, psychiatric and neurodegenerative disorders, musculoskeletal disorders and other conditions, and general health, all of which are considered in the review of snus and health by (Lee 2011). Additional publications were obtained by updating the literature search to February 2013, using the same search criteria used in 2011. All of these publications were examined to assess whether

they presented results allowing comparison of risk in those who smoked and used snus ("dual users"), those who smoked but did not use snus ("smoking only"), those who used snus but did not smoke ("snus only"), and those who neither smoked nor used snus ("neither"). Smoking and snus use were based on current or on lifetime habits.

Comparisons were made separately for ever and never smokers, of health risks for ever and never snus use, and separately for current and non-current smokers of health risks for current and non-current snus use. For each comparison, standard methods (Gardner and Altman 1989) were used to estimate the relative risk ("RR") or odds ratio ("OR") and 95% confidence interval ("CI") for snus only vs. neither, for dual use vs. smoking only, and for their interaction, i.e. the ratio of these two RR/OR estimates. The interaction tests whether the proportional increase in risk associated with snus is greater in smokers than in non-smokers (or whether the proportional increase in risk associated with smokers is greater in snus users than that associated with smoking in non-users of snus). Thus, the interaction tests whether there is any special hazard associated with dual use.

Where, as is usually the situation, a study provides a set of covariate-adjusted RR/ORs (with 95% CIs) for a complex two-way table of smoking by snus use (e.g. never/current/former smoking × never/current/former snus), the required RR/OR estimates were derived from the set using standard methods (Hamling et al. 2008). Where covariate-adjusted RRs were not provided, unadjusted were estimates calculated directly from the given numbers of cases and controls. In some cases, the required RRs/ORs were derived from estimates for ever snus use given separately for never smokers and for the whole population. Where appropriate, meta-analyses of estimates were derived using standard methods (Fleiss and GROSS 1991).

6.1.2.5.2.2. Other Aspects of Dual Use

The aim of this analysis was to gain insight into seven questions: 1) What is the cigarette consumption of dual users compared to smokers of cigarettes only? 2) what is the snus consumption of dual users compared to users of snus only? 3) what is the frequency of dual use? 4) are current snus users more likely to smoke than current non-users of snus? 5) are those who have ever used snus more likely ever to have smoked than never users of snus? 6) are snus users more likely to initiate smoking than non-users? and 7) are smokers who also use snus more likely to quit smoking than smokers who do not use snus? The analysis considered publications cited in the earlier review (Lee 2011), additional publications from updated literature searches, and references cited in the recently updated Scandinavian chapters of International Smoking Statistics (Forey et al. 2006).

For cross-sectional studies relating snus to smoking, ORs (with 95% CIs) relevant to questions 4 and 5 were derived from the numbers of subjects who were dual users, smoking only, snus only, or neither. RRs (with 95% CIs) relevant to question 6 were derived from cohort studies, using the numbers of non-smokers at baseline and the numbers subsequently initiating, separated by snus use at baseline. For cohort studies relating snus use at baseline to subsequent quitting, RRs (with 95% CIs) relevant to question 7 were derived from cohort studies using the numbers of smokers at baseline and the numbers subsequently quitting. As many of the results relating to questions 3

to 7 were presented earlier (Lee 2011), selected results are presented here for more recent, larger and more nationally representative surveys.

6.1.2.5.3. Results

6.1.2.5.3.1. Health Effects

The literature search identified 21 relevant publications, for which study details are presented in **Table 6-4.** Four publications relate to the Swedish Construction Workers study, three (Carlens et al. 2010; Nordenvall et al. 2011; Zendehdel et al. 2008) concerning occurrence of various conditions seen during the more than 20 years follow-up, the other (Nordenvall et al. 2013) concerning survival among those with incident cancer seen after baseline. Another four publications (Gunnerbeck et al. 2011; Wikstrom et al. 2010a; Wikstrom et al. 2010b; Wikstrom et al. 2010c) are based on the Swedish Medical Birth Register. The remaining thirteen publications describe separate studies, four prospective cohort studies (Haglund et al. 2007; Hansson et al. 2009; Johansson et al. 2005; Roosaar et al. 2008), eight case-control studies (Hedstrom et al. 2009; Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Persson et al. 1993; Schildt et al. 1998; Wennberg et al. 2007; Ye et al. 1999)(one nested within a prospective study), and one cross-sectional study (Aro et al. 2010). All of the studies were conducted in Sweden and, apart from publications based on the Swedish Medical Birth Register, the snus users considered were either all or virtually all men.

Table 6-5 summarizes results for cardiovascular disease, with the main results presented in the body of the table and results for subgroups (e.g. for fatal and non-fatal cases separately) given in the footnotes. None of the RR/ORs presented show a significant ($p<0.05$) increased risk associated with snus use, either in non-smokers or smokers, or a significant interaction associated with dual use. Seven results evaluate current use for ischaemic heart disease (IHD), coronary heart disease (CHD) or acute myocardial infarction (AMI) The meta-analysis of these results gives non-significant estimates of 0.95 (0.83-1.09) for snus only vs. neither, 0.82 (0.67-1.01) for dual use vs. smoking only, and 0.85 (0.68-1.05) for the interaction, with no evidence of between-study heterogeneity. Results for ever use for IHD, CHD or AMI, and results for stroke and for all CVD are less numerous, but similarly do not suggest any effect of dual use.

Table 6-6 similarly summarizes results for cancer. Of the fifteen interaction estimates shown, four are non-significantly above 1.0, two are equal to 1.0, and nine are less than 1.0, significantly ($p<0.05$) so in five cases. The significant negative interactions for squamous cell oesophageal cancer and for non-cardia stomach cancer seen in the Construction Workers Study (Zendehdel et al. 2008) arise from significant increases associated with snus use in never smokers but not in ever smokers. As noted elsewhere (Lee 2011), the overall evidence on effects of snus suggests no relationship with stomach cancer and, at most, suggestive evidence of a possible effect on oesophageal cancer. The negative interactions for smoking-related cancer and for mortality from any cancer (Roosaar et al. 2008) and on time from diagnosis to death from cancer of the same primary site (Nordenvall et al. 2013) again arise from increases associated with snus seen in never smokers that are not seen in smokers. Table 6-4 also includes results for respiratory mortality, for total non-cancer mortality, and for overall cancer, which also show no evidence of

a positive interaction.

Table 6-7 summarizes results for nine conditions related to pregnancy and birth from a series of papers (Gunnerbeck et al. 2011; Wikstrom et al. 2010a; Wikstrom et al. 2010b; Wikstrom et al. 2010c) based on the Swedish Medical Register. For three conditions (pre-eclampsia, diabetes, antenatal bleeding) there is no evidence of an effect or an interaction of snus use, in either exsmokers or smokers. For five conditions (very preterm birth, preterm birth, stillbirths, small for gestational age, neonatal apnea), there is a significant ($p<0.05$) association with snus use in non-smokers, but not in smokers, and the interaction is non-significantly negative. The only condition showing a significant positive interaction is gestational hypertension, where an association with snus use is evident in smokers, but not in non-smokers.

Table 6-8 summarizes results for chronic inflammatory diseases. There is no consistent evidence of an effect of snus on any of the five diseases considered in either never or ever smokers, and no significant positive interaction. A significant ($p<0.05$) negative interaction for multiple sclerosis was seen in one study (Carlens et al. 2010), due to an increased risk in never smokers but not in ever smokers, was not seen in the other study with relevant data (Hedstrom et al. 2009).

One further study (Aro et al. 2010) presented detailed results for gastrointestinal morbidity, allowing calculation of interactions, both for ever/never use and for current/noncurrent use, for a range of endpoints, including reflux symptoms, dyspepsia, irritable bowel syndrome, epigastric pain, abdominal pain, oesophagitis, and *H Pylori* infection. Of eighteen interactions calculated (details not shown), eight were greater than 1.0 and 10 were less than 1.0, with only one significant at $p<0.05$. This was for irritable bowel syndrome, where an association with current snus use was evident in current smokers (OR 2.90, 95% CI 1.10-7.62) but not in non-smokers (0.75, 0.43-1.30) with the interaction OR estimated as 3.89 (1.28-11.86). This interaction was not seen (0.76, 0.35-1.66) in analyses based on ever/never use.

ii. Consumption of cigarettes and snus in single and dual users

Table 6-9 presents 12 comparisons from 10 studies of cigarette consumption in dual users and in those who smoke but do not use snus (Aro et al. 2010; Carlens et al. 2010; Eliasson et al. 1995; Rodu et al. 2002; Wennmalm et al. 1991). All show reduced cigarette consumption in dual users, the mean ratio being 0.74 (SE 0.15). Table 6-9 also presents six comparisons of snus use in dual users and in those who use snus but do not smoke (Aro et al. 2010; Carlens et al. 2010; Eliasson et al. 1995; Gilljam and Galanti 2003; Hansson et al. 2009; Hergens et al. 2005; Janzon and Hedblad 2009; Lund and McNeill 2013; Rodu et al. 2002; Sundbeck et al. 2009; Wennmalm et al. 1991). With the exception of one small study (Wennmalm et al. 1991) of military conscripts, all show reduced snus use in dual users, the mean ratio being 0.80 (SE 0.15).

Two of those studies also compared cotinine levels, as a marker of total nicotine uptake, in dual users and single users. In one study (Eliasson et al. 1995), mean plasma cotinine levels in dual users, 308 ng/ml, were higher than in those who only smoked, 242 ng/ml, but lower than in those who only used snus, 351 ng/ml ($p<0.01$ for difference between groups). In the other

(Wennmalm et al. 1991) a different pattern was seen, with median urinary cotinine higher in dual users, 1773 ng/ml, than in either those who only smoked, 1560 ng/ml, or those who only used snus, 1210 ng/ml (with no significant difference between groups).

iii. Frequency of dual use and the interrelationship of snus use and smoking

Table 6-10 presents data from selected recent surveys on current smoking and current snus use (Aaro et al. 2008; Engstrom et al. 2010; Helleve et al. 2010; Larsen et al. 2013; Liefman 2013; Lindstrom 2007; Lund et al. 2007; Nilsson et al. 2009; Norberg et al. 2011; Overland et al. 2010; Raisamo et al. 2011; Statens Folkhalsoinstitut (Swedish National Institute of Public Health) 2012; Statistiska Centralbyrån (SCB Statistics Sweden) 2013). These data, and more extensive data in **Table 6-8** of the earlier review (Lee 2011), demonstrate that, in Swedish adults, the prevalence of dual use is quite low, with rates reducing with age, and lower in women than men. It is also evident that there is no strong association between snus use and smoking. In Norwegian adults, the prevalence of dual use is lower still, and smokers are less likely to use snus than non-smokers. In Swedish adolescents, however, the prevalence of dual use may be higher, though dependent on the definitions used, and there is a consistent tendency for smokers to be much more likely than non-smokers to use snus. Odds ratios ranging from about 4 to 15 can be estimated from many other Swedish studies of adolescents (Lee 2011).

For ever smoking and ever snus use, the situation is rather different. **Table 6-11** presents data from the VIP survey (Norberg et al. 2011). This and additional data presented in **Table 6-8** of the earlier review (Lee 2011), demonstrate that the frequency of dual ever use is much higher than the frequency of dual current use. Also, those who have ever smoked are much more likely than those who have never smoked to have ever used snus, a tendency which is even more strongly seen in adolescents.

The observations of a much higher prevalence of dual use and a much stronger association between the habits, when estimated based on ever use rather than current use, is consistent with some people avoiding tobacco, and many of the rest trying both products, eventually settling for one.

TABLE 6-4. Study details for publications providing relevant evidence on health effects

Reference	Source Table	Study Design (size)[a]	Timing[b]	Sex[c]	Age (years)	Data on ST use[d]	Endpoint[e]
Huhtasaari et al. (1992)	I	CCP (585)	1989-1991	M	35-64	C	AMI
Persson et al. (1993)	1,2	CCP (63,82)[f]	1984-1997	M	15-79	E	CD, UC

Reference	Source Table	Study Design (size)[a]	Timing[b]	Sex[c]	Age (years)	Data on ST use[d]	Endpoint[e]
Schildt et al. (1998)	III	CCP (410)	1980-1989	M,F	Mean 69.6 (M) Mean 72.3 (F)	C,E	Oral cancer
Huhtasaari et al. (1999)	1	CCP (687)	1991-1993	M	25-64	C	AMI
Ye et al. (1999)	VII	CCP (375)	1989-1995	M,F	40-79	E	Gastric cancer
Hergens et al. (2005)	3	CCP (1432)	1992-1994	M	45-70	C,E	AMI
Johansson et al. (2005)	3	PC (3120)	1988-1989, 12 years	M	30-74	C	CHD
Haglund et al. (2007)	III,IV	PC (5002)	1988-1989, 14-16 years	M	16-74	C	IHD, stroke
Wennberg et al. (2007)	2,3	NCC (525)	1985-1999	M	30-74	C	AMI
Roosaar et al. (2008)	II	PC (9976)	1973-1974, 28-29 years	M	15+	E	All cancer, oral cancer, all deaths, respiratory deaths
Zendehdel et al. (2008)	III,IV	PC (336381)	1971-1993, Mean 22.2 years	M	Mean 34.7	E	Gastroesophageal cancer

Reference	Source Table	Study Design (size)[a]	Timing[b]	Sex[c]	Age (years)	Data on ST use[d]	Endpoint[e]
Hansson et al. (2009)	2	PC (16642)	1998-2002, 4.9 years	M	40+	C,E	CVD, IHD, stroke
Hedstrom et al. (2009)	4	CCP (902)	2005-2008	M,F	16-70	E	MS
Aro et al. (2010)	2-6	CS (1001)[g]	1998-2001	M,F	18-80	C,E	Gastrointestinal morbidity
Carlens et al. (2010)	4	PC (277777)	1978-1993, Mean 20 years	M	Mean 36	E	RA, UC, CD, sarcoidosis, MS
Wikstrom et al. (2010c)	1	CS (605203)[h]	1999-2006	F	Childbearing age	C	GH, pre-eclampsia
Wikstrom et al. (2010b)	1	CS (610879)[h]	1999-2006	F	Childbearing age	C	Stillbirths, complications of pregnancy
Wikstrom et al. (2010a)	2	CS (610199)[h]	1999-2006	F	Childbearing age	C	Preterm birth
Gunnerbeck et al. (2011)	1	CS (609551)[h]	1999-2006	F	Childbearing age	C	Preterm birth, SGA, neonatal apnea
Nordenvall et al. (2011)	2	PC (336381)	1971-1992, Mean 24 years	M	Mean 35	E	Colon cancer, rectal cancer, anal cancer
Nordenvall et al. (2013)	2	PC (40230)[i]	1971-1992, To 2007[i]	M	Mean 67 at cancer diagnosis	E	Cancer, other causes

Reference	Source Table	Study Design (size)[a]	Timing[b]	Sex[c]	Age (years)	Data on ST use[d]	Endpoint[e]

[a] CCP = case-control study with population controls, CS = cross-sectional study, NCC = nested case-control study, PC = prospective cohort study. Numbers in brackets are of cases for case-control study, and of at risk for prospective cohort studies

[b] The timing of the initial interviews is given, and then the length of follow-up for prospective cohort studies

[c] F = female, M = male

[d] C = data available for current use, E = data available for ever use

[e] AMI = acute myocardial infarction, CD = Crohn's disease, CHD = coronary heart disease, CVD = cardiovascular disease, GH = gestational hypertension, IHD = ischaemic heart disease, MS = multiple sclerosis, RA = rheumatoid arthritis, SGA = small for gestational age, UC = ulcerative colitis

[f] 63 cases of Crohn's disease, 82 of ulcerative colitis

[g] The 1001 subjects underwent an oesophagogastroduodenoscopy

[h] Births

[i] The study concerned survival of 40230 men with incident cancer among 336381 workers interviewed initially in 1971-1992

TABLE 6-5. Dual use and cardiovascular disease[a]

Disease	Source	RR/OR (95% CI)				Interaction[b]
		Current or ever use	Cases in dual users	Snus only vs. neither	Dual users vs. smoking only	
IHD, CHD or AMI						
IHD incidence	Hansson et al. (2009)	Ever	101	0.92 (0.61-1.39)	0.95 (0.74-1.22)	1.03 (0.64-1.67)
AMI cases[c]	Hergens et al. (2005)	Ever	203	0.87 (0.48-1.55)	0.99 (0.80-1.22)	1.14 (0.62-2.13)[d]
IHD incidence	Haglund et al. (2007)	Current	15	0.77 (0.51-1.15)	0.94 (0.56-1.59)	1.22 (0.63-2.37)[e]
IHD incidence	Hansson et al. (2009)	Current	9	0.90 (0.67-1.21)	0.75 (0.36-1.55)	0.83 (0.38-1.82)
AMI cases[c]	Hergens et al. (2005)	Current	66	1.21 (0.89-1.63)	0.80 (0.55-1.16)	0.66 (0.41-1.07)[f]
AMI cases[c]	Huhtasaari et al. (1992)	Current	32	0.79 (0.54-1.13)	0.68 (0.40-1.17)	0.87 (0.45-1.67)[g]
AMI cases[c]	Huhtasaari et al. (1999)	Current	20	0.96 (0.65-1.41)	0.73 (0.34-1.57)	0.76 (0.32-1.80)
CHD incidence	Johansson et al. (2005)	Current	10[h]	0.99 (0.63-1.56)	1.19 (0.60-2.37)	1.20 (0.52-2.73)
AMI cases[c]	Wennberg et al. (2007)	Current	30	1.00 (0.71-1.43)	0.82 (0.48-1.40)	0.82 (0.43-1.55)[i]
Total[j]	7 studies	Current	182	0.95 (0.83-1.09)	0.82 (0.67-1.01)	0.85 (0.68-1.05)
Stroke						
Stroke incidence	Hansson et al. (2009)	Ever	43	1.24 (0.78-1.97)	0.83 (0.59-1.16)	0.67 (0.38-1.19)
Stroke cases[c]	Haglund et al. (2007)	Current	9	1.07 (0.65-1.77)	1.41 (0.71-2.83)	1.32 (0.56-3.11)[k]
Stroke incidence	Hansson et al. (2009)	Current	5	0.89 (0.61-1.31)	0.90 (0.36-2.27)	1.01 (0.37-2.73)

Disease	Source	RR/OR (95% CI)				Interaction[b]
		Current or ever use	Cases in dual users	Snus only vs. neither	Dual users vs. smoking only	
All CVD						
CVD incidence	Hansson et al. (2009)	Ever	138	1.07 (0.79-1.45)	0.91 (0.75-1.11)	0.85 (0.59-1.22)
CVD incidence	Hansson et al. (2009)	Current	14	0.93 (0.74-1.17)	0.81 (0.46-1.43)	0.87 (0.47-1.60)

[a] All RR/OR estimates are for males. All estimates are adjusted for age and other risk factors except for two studies (Huhtasaari et al. 1992; Huhtasaari et al. 1999), where the estimates are unadjusted

[b] The interaction RR, the ratio of RRs associated with snus use in smokers and in non-smokers, was used to test for special effects of dual use: Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

[c] Fatal and non-fatal cases

[d] Interaction 1.24 (0.62-2.46) for non-fatal AMI and 0.50 (0.16-1.58) for fatal AMI

[e] Interaction 0.74 (0.19-2.97) for IHD mortality

[f] Interaction 0.60 (0.36-0.99) for non-fatal AMI and 0.89 (0.36-2.18) for fatal AMI

[g] Interaction 0.82 (0.34-1.98) for age 35-54 and 0.70 (0.23-2.10) for age 55-64

[h] Estimated

[i] Interaction 0.25 (0.06-1.03) for fatal AMI in 28 days and 0.16 (0.03-0.89) for sudden cardiac death with survival less than 24 hours

[j] Results of fixed-effects meta-analysis are shown, there being no significant heterogeneity between studies

[k] Interaction 4.17 (0.78-22.36) for stroke mortality

TABLE 6-6. Dual use and cancer, respiratory and all cause mortality[a]

Disease	Source	RR/OR (95% CI)			Interaction[b]
		Cases in dual users	Snus only vs. neither	Dual users vs. smoking only	
Oral cancer – squamous cell	Schildt et al. (1998)	10	0.86 (0.51-1.44)	0.40 (0.17-0.93)	0.47 (0.17-1.26)
Oral cancer – squamous cell	Schildt et al. (1998)	39	1.20 (0.67-2.15)	0.73 (0.45-1.19)	0.61 (0.29-1.30)
Oropharyngeal cancer	Roosaar et al. (2008)	6	2.30 (0.70-8.30)	3.66 (1.45-9.24)	1.59 (0.34-7.46)
Oesophageal cancer – adenocarcinoma	Zendehdel et al. (2008)	26	0.20 (0.02-1.90)	1.00 (0.60-1.50)	5.00 (0.50-49.74)
Oesophageal cancer – squamous cell	Zendehdel et al. (2008)	40	3.50 (1.60-7.60)	0.80 (0.60-1.20)	0.23 (0.10-0.54)
Gastric cancer	Ye et al. (1999)	72	0.50 (0.20-1.22)	0.80 (0.57-1.13)	1.60 (0.61-4.18)
Stomach cancer – cardia	Zendehdel et al. (2008)	50	0.90 (0.40-2.20)	0.90 (0.70-1.30)	1.00 (0.42-1.37)
Stomach cancer – non cardia	Zendehdel et al. (2008)	185	1.40 (1.10-1.90)	1.00 (0.90-1.20)	0.71 (0.52-0.97)
Colon cancer[c]	Nordenvall et al. (2011)	440	1.08 (0.91-1.29)	1.08 (0.97-1.21)	1.00 (0.82-1.24)

Rectal cancer	Nordenvall et al. (2011)	319	1.05 (0.85-1.31)	1.04 (0.92-1.19)	0.99 (0.77-1.28)
Anal cancer	Nordenvall et al. (2011)	14	0.61 (0.07-5.07)	1.44 (0.74-2.81)	2.37 (0.25-22.28)
Smoking-related cancer – incidence[d]	Roosaar et al. (2008)	32	1.60 (1.10-2.50)	0.79 (0.54-1.16)	0.50 (0.28-0.87)
Any cancer – incidence	Roosaar et al. (2008)	99	1.10 (0.90-1.40)	0.94 (0.78-1.12)	0.85 (0.64-1.13)
Any cancer – mortality	Roosaar et al. (2008)	NA[e]	1.28 (0.96-1.69)	0.80 (0.62-1.04)	0.63 (0.43-0.92)
Any cancer – survival[f]	Nordenvall et al. (2013)	2122	1.15 (1.05-1.26)	0.94 (0.89-0.99)	0.82 (0.74-0.91)
Respiratory mortality - age <80	Roosaar et al. (2008)	NA[e]	0.80 (0.20-3.00)	0.80 (0.36-1.79)	1.00 (0.21-4.84)
Respiratory mortality - age 80+	Roosaar et al. (2008)	NA[e]	2.00 (1.20-3.40)	1.53 (0.86-2.92)	0.77 (0.33-1.75)
Non-cancer mortality[g]	Nordenvall et al. (2013)	1579	1.12 (1.01-1.25)	1.02 (0.97-1.08)	0.91 (0.81-1.03)
Any cause – survival[h]	Nordenvall et al. (2013)	3859	1.13 (1.05-1.20)	0.97 (0.93-1.00)	0.86 (0.79-0.92)
Total mortality	Roosaar et al. (2008)	NA[e]	1.23 (1.09-1.40)	0.97 (0.85-1.11)	0.79 (0.66-0.95)

[a] All RR/OR estimates are for males, and are for ever use, except for one study (Schildt et al. 1998), where the estimates are for sexes combined and current use. All estimates are adjusted for age and other risk factors

[b] The interaction RR, the ratio of RRs associated with snus use in smokers and in non-smokers, was used to test for special effects of dual use: Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

[c] Interactions 1.18 (0.86-1.63) for cancer of right colon and 0.91 (0.65-1.27) for cancer of left

colon

[d] As defined by Levitz et al. (2004); it includes oral, pharyngeal, oesophageal, gastric, pancreatic, laryngeal and pulmonary cancer as well as cancer of the kidney, bladder and other urinary organs

[e] NA = not available

[f] Death from cancer at the same site as the primary cancer – analysis is based on follow-up of incident cancer cases

[g] Death from causes other than cancer or from cancer of a site other than the primary cancer – analysis is based on follow-up of incident cancer cases

[h] Analysis is based on follow-up of incident cancer cases

TABLE 6-7. Dual use and conditions related to pregnancy and birth[a]

Disease	Source	Cases in dual users	RR/OR 95% CI Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
Very preterm birth	Wikstrom et al. (2010a)	4	1.34 (1.03-1.74)	0.84 (0.31-2.23)	0.63 (0.23-1.72)
Preterm birth	Wikstrom et al. (2010a)	24	1.24 (1.12-1.37)	0.94 (0.64-1.40)	0.76 (0.51-1.14)
Pre-eclampsia	Wikstrom et al. (2010c)	13	1.11 (0.97-1.28)	1.20 (0.65-2.20)	1.08 (0.58-2.01)
Gestational hypertension	Wikstrom et al. (2010c)	7	0.89 (0.68-1.15)	2.72 (1.30-5.69)	3.06 (1.40-6.69)
Stillbirths	Wikstrom et al. (2010b)	4	1.91 (1.40-2.62)	1.67 (0.62-4.49)	0.87 (0.31-2.47)
Diabetes	Wikstrom et al. (2010b)	7	0.93 (0.76-1.14)	0.88 (0.42-0.84)	0.95 (0.44-2.04)
Antenatal bleeding	Wikstrom et al. (2010b)	5	1.21 (0.98-1.48)	0.66 (0.27-1.58)	0.55 (0.22-1.34)
Small for gestational age	Wikstrom et al. (2010b)	23	1.18 (1.01-1.38)	1.12 (0.75-1.67)	0.95 (0.62-1.46)
Neonatal apnea	Gunnerbeck et al. (2011)	0	1.96 (1.30-2.96)	0.00	0.00

[a] RR/ORs for pre-eclampsia, gestational hypertension, stillbirths and neonatal apnea are adjusted for age and other characteristics. Others are unadjusted and are calculated based on rates (%) to 1 decimal place, so are subject to some inaccuracy. All estimates are for current use

[b] The interaction RR, the ratio of RRs associated with snus use in smokers and in non-smokers, was used to test for special effects of dual use: Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

TABLE 6-8. Dual use and chronic inflammatory disease[a]

Disease	Source	Cases in dual users	RR/OR 95% CI Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
Rheumatoid arthritis	Carlens et al. (2010)	141	1.20 (0.80-1.80)	0.87 (0.71-1.06)	0.72 (0.46-1.14)
Sarcoidosis	Carlens et al. (2010)	41	1.10 (0.80-1.50)	1.00 (0.70-1.42)	0.91 (0.57-1.46)
Ulcerative colitis	Carlens et al. (2010)	191	1.00 (0.80-1.20)	1.17 (0.98-1.39)	1.17 (0.89-1.52)
Ulcerative colitis	Persson et al. (1993)	15	1.10 (0.40-3.10)	3.25 (1.23-8.56)	2.95 (0.72-12.09)
Crohn's disease	Carlens et al. (2010)	108	1.00 (0.80-1.40)	0.93 (0.75-1.16)	0.93 (0.65-1.33)
Crohn's disease	Persson et al. (1993)	11	0.90 (0.30-3.10)	2.65 (0.94-7.47)	2.94 (0.62-14.02)
Multiple sclerosis	Carlens et al. (2010)	37	1.80 (1.10-2.90)	0.76 (0.51-1.12)	0.42 (0.23-0.79)
Multiple sclerosis	Hedstrom et al. (2009)	87	0.40 (0.03-5.34)	0.40 (0.19-0.82)	1.00 (0.07-13.34)

[a] All RR/OR estimates are for males, and for ever use, except for one study (Hedstrom et al. 2009) where they are for sexes combined, and snus use is current/non-current. All estimates are adjusted at least for age

[b] The interaction RR, the ratio of RRs associated with snus use in smokers and in non-smokers, was used to test for special effects of dual use: Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

TABLE 6-9. Consumption of cigarettes and snus in single and dual users[a]

						Cigarettes per day		Snus use		
Source	Sex	Age (yrs)	Year	No. of dual users	Current or ever use	Smoking only	Dual use	Snus only	Dual use	Units
Aro et al. (2010)	M+F	20+	1998-2001	22	C	11.5	6.2	3.2	2.2	cans/wk
Carlens et al. (2010)[b]	M	Mean 36	1978-1993	43425	E	12	9	22	16	g/day
Eliasson et al. (1995)	M	25-64	1990	38	C	16.5 (0.6)	10.1 (1.1)	3.2 (0.2)	2.5 (0.2)	cans/wk
Gilljam and Galanti (2003)	M	25-55	2000	84	C	15.1 (0.5)	11.0 (1.1)			
	F	25-55	2000	14	C	12.3 (0.3)	11.7 (3.1)			
Hansson et al. (2009)	M	20+	1998-2002	1647	C[c]	16.7	16.5			
Hergens et al. (2005)	M	45-70	1992-1994	60	C[d]	18.6	16.4			
Janzon and Hedblad (2009)	M	45-73	1991-1996	250	C	16.1 (0.2)	12.3 (0.6)			
	F	45-73	1991-1996	21	C	12.9 (0.1)	7.8 (0.7)			
Lund and McNeill (2013)	M	16-74	2005-2010	226	C	11.5 (0.3)	8.1 (0.5)			
Rodu et al. (2002)	M	25-64	1986-1999	NA	C	15.8	10.8	0.42	0.25	cans/wk
Sundbeck et al. (2009)	M	30-75	2001-2003	116	C[e]			3.7	3.4	cans/wk
Wennmalm et al. (1991)	M	18-19	Unknown	30	C	12.2 (0.8)	7.8 (1.3)	25 (1)	27 (3)	g/day

[a] Standard errors are given in brackets, where available

[b] The source also presents data showing that dual users have consistently lower cigarette consumption and snus use than do single users in each of five age groups (<24, 25-34, 35-44, 45-54 and 55+ years)

[c] Current snus use; ever smoking
[d] Among former smokers, consumption was 20.6 cigs/day in non-snus users and 18.4 cigs/day in snus users
[e] Current snus use; former smoking

TABLE 6-10. Current smoking and current snus use – selected recent data for Sweden (or other Scandinavian countries)[a]

					Frequency (%)				
Source	Year	Age (yrs)	Sex	N[b]	Dual	Snus[c]	Smo-king[c]	Neither	OR (95% CI)
Studies in adults									
VIP survey[d]	2002-7	40	M	6055	5.6	28.1	7.1	59.1	1.66 (1.42-1.93)
		50	M	6348	5.9	23.8	11.3	58.9	1.29 (1.13-1.48)
		60	M	6413	3.5	17.5	13.1	66.0	1.01 (0.86-1.18)
		40	F	6286	2.1	11.8	12.2	74.0	1.08 (0.88-1.32)
		50	F	6698	2.0	6.2	19.4	72.3	1.20 (0.98-1.47)
		60	F	6610	0.6	2.5	18.2	78.7	1.04 (0.73-1.48)
Skåne Public	2004	18-80	M	11855	3.8	15.7	15.3	65.2	1.03 (0.92-1.16)
Health survey[e]		18-80	F	14050	0.5	1.8	21.8	75.9	1.01 (0.78-1.32)
SIRUS Norway[f]	2006	21-30	M	1198	1.5	15.3	16.4	66.8	0.40 (0.24-0.67)
Stockholm	2006	18+	M	15428	2.4	17.0	11.3	69.3	0.86 (0.76-0.97)
Public Health survey[g]		18+	F	18761	0.5	3.1	15.2	81.2	0.88 (0.71-1.10)
SCB Norway[h]	2008/9	16-74	M	4444	0.9	9.9	20.0	69.1	0.31 (0.23-0.44)
		16-74	F	4592	0.1	1.3	20.2	78.4	0.30 (0.12-0.77)
SSLC survey[i]	2008-11	16-34	M	1729	4.3	35.6	15.9	0.8	0.95 (0.72-1.24)
		35-54	M	1631	5.6	42.8	21.9	1.2	0.78 (0.61-1.00)
		55-64	M	1760	2.4	28.8	29.7	1.1	0.42 (0.30-0.58)
		75+	M	1128	0.5	8.0	7.0	0.4	1.12 (0.47-2.67)
		16-34	F	1711	0.8	7.2	25.0	0.9	0.63 (0.35-1.13)
		35-54	F	1848	0.8	8.0	32.9	0.8	0.47 (0.27-0.81)

		55+	F	3212	0.3	1.8	25.4	0.2	0.92 (0.44-1.93)
Health on equal terms survey[j]	2009-12	16-29	M	2554	1.8	17.4	6.8	74.1	1.10 (0.78-1.56)
		30-44	M	3524	1.8	20.4	7.0	70.7	0.91 (0.68-1.21)
		45-64	M	6491	3.0	17.8	12.3	66.9	0.92 (0.77-1.09)
		65-84	M	5246	1.2	10.0	9.0	79.8	1.09 (0.83-1.43)
		16-29	F	3465	0.4	4.5	11.3	83.8	0.71 (0.41-1.22)
		30-44	F	4748	0.5	4.2	9.8	85.6	1.05 (0.68-1.63)
		45-64	F	7621	0.5	3.0	16.9	79.6	0.74 (0.52-1.05)
		65-84	F	5559	0.3	1.4	10.7	87.6	1.67 (0.96-2.90)
Studies in adolescents									
Postal surveys[k]	2003	13,15,17	M	1398	3.0	6.0	3.0	88.0	14.6 (9.05-23.7)
Norway	2004,7	16-20	M	2441	5.9	15.7	12.6	65.8	1.96 (1.56-2.46)
telephone survey[l]		16-20	F	2374	1.4	3.5	18.4	76.7	1.73 (1.15-2.62)
Norway school survey[m]	2005	15-16	M	809	2.5	5.4	6.1	86.0	6.53 (3.58-11.9)
Finnish	2005-11	14	M	3360	0.1	0.3	6.0	93.6	7.02 (2.30-21.5)
adolescents[n]		16	M	2739	0.8	1.3	20.5	77.4	2.22 (1.29-3.83)
		18	M	2190	1.0	1.8	28.7	68.6	1.34 (0.78-2.28)
Norway telephone survey[o]	2006	15-18	M	2896	12.7	25.6	7.6	54.2	3.56 (2.94-4.29)
CAN school	2009-12	15-16	M	9578	1.0	4.6	4.8	89.6	4.02 (3.16-5.11)
surveys[p]		17-18	M	7513	1.5	12.0	7.0	79.5	1.38 (1.11-1.71)
		15-16	F	9615	0.1	0.3	7.3	92.3	7.45 (3.86-14.4)
		17-18	F	7446	0.3	1.7	12.7	85.3	1.20 (0.76-1.89)

[a] Except where stated, surveys are national, and are in Sweden

[b] Number of subjects. Where annual or bi-annual data are available, results shown are pooled from the four most recent surveys

[c] Only the stated habit

[d] VIP = Västerbotten Intervention Program. Current snus = regular, current smoking = daily or intermittent. Source : Norberg et al. (2011)

[e] Postal survey conducted in Skåne County. Current snus = daily, current smoking = daily or intermittent. Source : Lindstrom (2007)

[f] SIRUS = Statens institutt for rusmiddelforskning (National Institute of Drug Abuse). Drug use among young adults survey (Rusmiddelbruk blant unge voksne). Source : Lund et al. (2007)

[g] Definitions of smoking and snus are for daily use. Source : Engstrom et al. (2010)

[h] SCB = Statistisk sentralbyrå (Statistics Norway). Definitions of smoking and snus are for daily use. Source : Helleve et al. (2010)

[i] SSLC = Swedish Survey of Living Conditions (Undersknigar on levnadsförhållanden, ULF). Definitions of smoking and snus are for daily use. Source : Statistiska Centralbyrån (SCB Statistics Sweden) (2013)

[j] Definitions of smoking and snus are for daily use. Source : Statens Folkhalsoinstitut (Swedish National Institute of Public Health) (2012)

[k] Definitions of smoking and snus include regular and occasional use. Source : Nilsson et al. (2009)

[l] Definitions of smoking and snus include daily or weekly use. Source : Overland et al. (2010)

[m] Definitions of smoking and snus are for daily use**.** Source : Aaro et al. (2008)

[n] Survey conducted in alternate years. Definitions of smoking and snus are for daily use. Source : Raisamo et al. (2011)

[o] Survey conducted in 11 of 19 Norwegian counties with high prevalence of snus use. Definitions of smoking and snus include daily or weekly use. Source: Larsen et al. (2013)

[p] CAN = Central Alliance for Alcohol and Drug Information. Definitions of smoking and snus are for daily use**.** Source : Liefman (2013)

TABLE 6-11. Ever smoking and ever snus use – data from the VIP survey for 2002-2007 (Norberg et al. 2011)

			Frequency of ever use[b]				
Sex	Age (yrs)	N[c]	Dual	Snus[d]	Smoking[d]	Neither	OR (95% CI)
Males	40	6055	24.6	22.4	8.7	44.2	5.58 (4.95-6.28)
	50	6348	34.2	14.2	17.5	34.0	4.68 (4.21-5.70)
	60	6413	32.2	6.5	29.8	31.6	5.25 (4.65-5.94)
Females	40	6286	15.9	6.2	25.2	52.8	5.37 (4.71-6.13)
	50	6698	11.5	1.1	46.0	41.3	9.39 (7.35-12.0)
	60	6610	4.1	0.2	50.4	45.3	18.4 (10.6-32.1)

[a] VIP = Västerbotten Intervention Program
[b] Daily or intermittent
[c] N = number of subjects
[d] Only ever used

6.1.2.5.3.2. Effect of snus use on smoking initiation

Though evidence is somewhat limited, dual users are more likely to have started on cigarettes than to have started on snus. For example, in the Swedish twin study of men born before 1959 (Furberg et al. 2005), 2422 (89.3%) started on cigarettes compared to 291 (10.7%) starting on snus. In the Your Country and Your Life study in Stockholm (Ramström and Foulds 2006) 338 (77.2%) started on cigarettes compared to 100 (22.8%) starting on snus. The percentage starting on snus is likely to increase as the acceptability of snus among adolescents has increased. This may explain why, in a recent analysis of six surveys in Norway (Lund and McNeill 2013), the proportion of men with a history of dual use who started on snus increased steadily with decreasing age, from 3.9% for age 45+ years, through 25.9% for age 25-44 years, to 42.3% for age 15-24 years. (All the above estimates exclude the small proportion of dual users where the time of start of both products was the same.)

A number of cohort studies presented follow-up data on never smokers or non-smokers. The probability of smoking at the end of follow-up can be related to snus use at baseline. The largest study to present such data is the VIP study, which has recently reported results of 10-year follow-up from baseline during 1990-97 (Norberg et al. 2011). In both sexes, the probability of initiation during follow-up was significantly ($p < 0.05$) higher for those using snus at baseline than for those not using snus (males 6.1% vs. 2.6%, RR 2.35 95%, CI 1.89-2.92; females 8.1% vs. 3.2%, RR 2.53, CI 1.76-3.63). An increased probability is also consistently seen in other studies (Lee 2011). Interpretation of this association is hindered by the minimal adjustment for

factors predictive of initiation. One study (Haukkala et al. 2006) reported that adjustment for school, sport participation, and school achievement substantially reduced the association.

Two studies of Swedish adults (Furberg et al. 2005; Ramström and Foulds 2006) used retrospective data to study effects on initiation. Both studies reported that the percentage initiating smoking among those who started on snus was substantially lower than among those who had not started on snus. However, as demonstrated earlier (Lee 2011), these analyses are considerably biased by the time available for initiation being controlled for in the analysis. For a given follow-up period, those starting on snus can only initiate smoking from that time point, but those not starting on snus can initiate smoking from the start of the period.

There is thus little reliable information on snus use and initiation. The RRs in the analyses of the cohort data are biased upward by lack of confounder control, while the retrospective analyses are biased downwards.

6.1.2.5.3.3. Effect of snus use on smoking cessation

A number of cohort studies present follow-up data on smokers. In these studies, the probability of quitting at the end of follow-up can be related to snus use at baseline. The VIP study presents the most comprehensive data on initiation. Recent results (Norberg et al. 2011) show that, in both sexes, the probability of quitting is higher for dual users at baseline than for those who only smoked (males 57.3% vs. 41.5%, RR 1.38, 95% CI 1.27-1.50; females 68.2% vs. 41.5%, RR 1.64, 95% CI 1.44-1.88). This increased probability is consistent with data presented in Table 8 of the earlier review (Lee 2011), though the data generally suffer from lack of adjustment for any potential confounding variables. However, results from a telephone helpline cohort (Helgason et al. 2004) showed that adjustment for age, sex and factors related to smoking abstention did not modify the association between snus use and quitting.

Consistent with the results of the cohort studies are findings from an analysis of seven Norwegian cross-sectional studies (Lund et al. 2011) which reported a consistent tendency for the quit ratio (the proportion of ever smokers who have quit) to be higher in those who were snus users at the time of interview, as compared to those who had never used snus. However, the analysis does not adjust for sex, age, or any factor possibly related to quitting, and does not fully take into account the time sequence of tobacco product use. Thus, some of the current snus users who quit smoking may not have used snus until after they had quit.

A number of publications (Furberg et al. 2005; Furberg et al. 2008; Gilljam and Galanti 2003; Ramström and Foulds 2006) present analyses of retrospective studies which consistently show that snus use is associated with increased quitting. However, as discussed earlier (Lee 2011), these analyses are biased. This is partly because snus users may include some people who started snus use after quitting, and partly because the time available for quitting has not properly been controlled for. These biases, however, seem unlikely to explain the association, and generally all the evidence seems consistent with snus use facilitating quitting, though it is subject to limitations.

Randomized controlled trials avoid issues of bias. Two placebo-controlled trials of snus as a

quitting aid have been conducted, one in the USA (Fagerstrom et al. 2012) and one in Serbia (Joksic et al. 2011). A meta-analysis based on the combined results (Rutqvist et al. 2013) recently reported a relative success rate of 2.83 (95% CI 1.63-7.75) of borderline significance for the primary outcome, which was biologically confirmed cessation over a 6-month period. These results confirm the conclusions drawn from the epidemiological studies.

6.1.2.5.4. Discussion

The possibility of any special risk associated with dual use of snus and smoking has been investigated by testing whether the RR/OR associated with snus use in smokers exceeds that seen in non-smokers, i.e. whether there is any significant interaction (on a multiplicative scale). As shown in Tables 2 to 5, the available data on specific diseases are generally quite limited, except perhaps for IHD/CHD/AMI. Overall, however, there seems to be little evidence of any special risk from dual use. Of the 51 RR/OR estimates with 95% CIs shown in the main body of these tables, a significant ($p<0.05$) positive interaction was seen only for gestational hypertension (see Table 4), which may be a chance finding given the number of estimates considered. In fact, there is some tendency for the interaction estimates to show a less than expected risk in dual users, with 32 of the 51 estimates below 1.0, seven (7) being significantly negative, as compared to only 15 above 1.0, with only that for gestational hypertension being significantly positive. This may be because, where variation in risk by tobacco habit is seen, it is much more likely to be due to effects of smoking than to effects of snus, and cigarette consumption in dual users is clearly lower than in those who only smoke cigarettes, by an estimated 26% (SE 15%). Many of the RRs relating to snus use in smokers did not however adjust for smoking.

In Sweden, the frequency of dual current use in adults is relatively low, particularly in older populations, but the frequency of dual ever use in adults, and the frequency of dual current use or dual ever use in adolescents is much higher. This is consistent with many tobacco users trying both products in adolescence, and tending later in life to settle for one or the other, given that they have not quit both. For diseases such as cancer or vascular disease, occurring mainly in older men and women, any special hazard from dual use (if indeed it existed) would have little overall effect on risk.

In older populations, dual users predominantly started tobacco use with cigarettes and, where dual users end up using snus only, the data indicate that they will be better off, health-wise, than if they had continued smoking. In younger populations, a larger proportion of dual users are starting on snus, and there is concern that this might act as a "gateway" to cigarette smoking. It is unfortunate that there is little reliable information on this. Retrospective studies suggesting that initiation of smoking is reduced by previous snus use (Furberg et al. 2005; Furberg et al. 2008; Gilljam and Galanti 2003; Ramström and Foulds 2006) are biased by failure to control for the time available for initiation (Lee 2011), while cohort studies showing a moderate tendency for previous snus use to be associated with increased initiation of smoking are biased (in the opposite direction) by failure to control for factors associated with initiation. Thus, if a proportion of the population would never take up tobacco, and the probabilities of uptake of smoking and of snus in the remainder are in fact independent in the whole population, there will be an apparent tendency for the two habits to be associated, and for previous snus use to be

associated with initiation of smoking, despite the assumed independence.

The evidence relating dual use to the subsequent probability of quitting smoking is stronger, but still suffers from limitations due to failure to control for relevant confounding variables, though any biases seem less severe than for the evidence on quitting (Lee 2011). Generally, the evidence consistently suggests that concomitant snus use is associated with an increased probability of quitting smoking, a conclusion that is supported by recent results from randomized controlled trials (Rutqvist et al. 2013) using snus as an aid to smoking cessation.

6.1.2.5.5. Conclusion

Notwithstanding the medical consensus that snus is far less harmful than cigarettes, the concern remains that availability of snus might result in dual use, thereby jeopardizing the role of snus in tobacco harm reduction. One the one hand, Swedish snus could theoretically reduce the risk of harm and tobacco-related disease associated with cigarettes by serving as a partial or complete substitute for cigarettes among continuing (and especially inveterate) smokers. However, even if snus has the potential to reduce exposure to HPHCs in smokers, it could also have the undesirable effect of delaying cessation of tobacco use (Lund and McNeill 2013).

Notwithstanding this concern, the existing evidence for a wide variety of health endpoints does not suggest any special hazard associated with dual use of snus and smoking. Of 51 interactions tested, only that for gestational hypertension was significantly ($p<0.05$) positive, with the increase in risk associated with snus use generally somewhat lower in smokers than in non-smokers. In adults, the frequency of current dual use is quite low, with dual users more likely to quit smoking than smokers who do not use snus.

6.1.3. Health Risks Associated with Switching from Cigarettes to Swedish Snus compared to Switching to FDA-approved Tobacco Cessation Products or Medication

This section of the Application summarizes the available data on the health risks associated with the use of Swedish snus compared to the health effects associated with switching from cigarettes to the various FDA-approved smoking cessation products. These products include NRTs such as over-the-counter ("OTC") transdermal skin patches, chewing gum, and lozenges, along with other prescription-only nicotine replacement products such as Nicotrol nasal sprays or oral inhalers and two non-nicotine prescription-only medications (Chantix (varenicline tartrate) and Zyban (bupropion)) (FDA 2010).

6.1.3.1. Health Outcomes

Like Swedish snus, FDA-approved smoking cessation products such as NRTs and non-nicotine pharmacological products are considerably safer than cigarettes, as the user is not exposed to any of the harmful products of tobacco combustion (Apelberg et al. 2010; Molyneux 2004). The health risks of current snus users who have previously smoked cigarettes (i.e., switchers from cigarettes to snus) were presented in Section 6.1.2. The health outcomes examined included oral

cancer, metabolic syndrome, diabetes, and various cardiovascular outcomes, including overall CVD, MI, IHD, SCD, coronary heart disease ("CHD") and stroke. Overall, the risk estimates among switchers were clearly lower than those observed among individuals who continued to smoke cigarettes, and were generally comparable to, or had lower point estimates than the risks estimates observed among those who quit tobacco entirely. This section of the Application compares these health outcomes with the available data on the health effects of NRTs and non-nicotine medications.

6.1.3.1.1. Nicotine Replacement Therapies

NRTs are designed to help people stop smoking by supplying controlled amounts of nicotine to ease the withdrawal symptoms associated with a quit attempt.[39] NRTs do not contain the carcinogens and other HPHCs that are found in cigarette smoke, and researchers have not identified any safety risks associated with the long-term use of these products.

Comparing the health risks associated with switching from cigarettes to snus to those of switching to NRTs instead requires an assessment of nicotine delivery products generally, including their contribution to smoking cessation and their overall benefit to population health. In recent years, FDA has been examining the health effects associated with long-term use of NRT products. In October 2010, FDA's Center for Drug Evaluation and Research (CDER) hosted the scientific workshop *Risks and Benefits of Long-Term Use of Nicotine Replacement Therapy (NRT) Products* featuring several presentations, some of which cited the Swedish Experience evidence (e.g., Dr. Neal Benowitz, Smokeless Tobacco and Disease: Evidence Related to Long-term Safety of Nicotine).

In December 2012, FDA sponsored the public hearing *FDA Actions Related to Nicotine Replacement Therapies and Smoking-Cessation Products; Report to Congress on Innovative Products and Treatments for Tobacco Dependence* for the purpose of obtaining input on the regulation and development of innovative products and treatments for tobacco dependence. The Swedish Experience evidence was cited by several speakers, including Dr. David Abrams, Executive Director of the Schroeder Institute for Tobacco Research and Policy Studies at American Legacy Foundation (Legacy).

In April 2013, FDA announced its conclusion that, in light of the currently available evidence, "certain statements set forth in the FDA-approved labels of over-the-counter nicotine replacement therapy products, related to concomitant use with other nicotine-containing products and duration of use, can be modified."[40] (2013) FDA summarized as follows the extensive research conducted on NRT products and the effects of nicotine in general:

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39 FDA, Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use, 78 Fed. Reg. 19718 (Apr. 3, 2013).

40 FDA, Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use, 78 Fed. Reg. 19718 (Apr. 2, 2013).

> In the years since NRT products became available for OTC use, a number of studies have examined the use of NRT products over periods longer than 12 weeks. We have reviewed the published literature on this longer-term use of NRT products and have not identified any safety risks associated with such use. A well-known and highly regarded study on the effects of long-term use of NRT products is the Lung Health Study, in which almost 6,000 smokers were given access to free nicotine gum for up to 5 years (see Murray et al., 1996). In this study, over 1,000 subjects were still using the gum after 1 year. The adverse effects of long-term nicotine gum use reported by these subjects were described as minor and transient, and there was no correlation between long-term gum use and cardiovascular events. A follow-up study found that long-term *ad lib* use of nicotine gum neither increased nor decreased the Lung Health Study subjects' likelihood of developing cancer (see Murray et al., 2009). Other informative studies on the effects of long-term use of NRT products include a 52-week study of NRT product use in which nearly half of the subjects used two or more OTC NRT products in combination (see Joseph et al., 2011), and a trial involving the use of nicotine patches for 6 to 12 months by nonsmokers with mild cognitive impairment (see Newhouse et al., 2012). Both of these studies had high rates of completion and reported few adverse events from long-term use of NRT products." (2013)

In addition, various published studies have found that the abuse liability and dependence potential of NRT products is low, particularly as compared to cigarettes.

6.1.3.1.2. Non-Nicotine Tobacco Cessation Medications

In June 2011, FDA issued a Drug Safety Communication for Chantix (varenicline) regarding a possible association with a "small, increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease."[41] This safety announcement was based on a randomized, double-blind, placebo-controlled clinical trial of 700 smokers to assess the efficacy and safety of Chantix for smoking cessation. In the trial, certain cardiovascular events, (including angina pectoris, nonfatal myocardial infarction, a need for coronary revascularization, and peripheral vascular disease) were reported more frequently in patients treated with Chantix than in patients treated with placebo. Although the trial was not designed to have statistical power to detect differences between arms on these safety endpoints, a 1.4% increase was observed for any cardiovascular event among individuals treated with Chantix compared to those

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[41] FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease, available at http://www.fda.gov/Drugs/Drugsafety/ucm259161.htm (last accessed September 11, 2013).

treated with a placebo (Rigotti et al. 2010).

In July 2011, the Agency approved an updated label for Chantix that stated that the drug more than doubled the chance that patients remain abstinent from smoking, an independent and major risk factor for CVD.[42] The revised label further stated that Chantix may also be associated with a small, increased risk of certain cardiovascular adverse events in patients with CVD based on the observations of Rigotti and colleagues (2010).

The authors of two meta-analyses of clinical trials involving Chantix came to different conclusions with respect to a possible association with adverse cardiovascular events. Singh and colleagues (2011) reported a significant, 72% increased risk of serious adverse cardiovascular events and concluded that their analysis of fourteen (14) trials with at least one reported cardiovascular event "raises safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with the use of varenicline among tobacco users." By contrast, Prochaska and Hilton (2012) conducted a meta-analysis of twenty-two (22) trials (including fourteen (14) with at least one cardiovascular event) and found no significant increase in cardiovascular serious adverse events associated with Chantix use.

Analyses based both on all 22 trials and on the subset of 14 studies with at least one event both indicated a non-significant difference between Chantix and placebo groups. The risk among studies that included only patients with a history of CVD was not separately examined in either study. Prochaska and Hilton (2012) noted that the discrepancy between the conclusions of the two meta-analyses is explained by the fact that Singh and colleagues (2011) considered adverse events at any time during the trial duration, which was, on average, twice the duration of study drug exposure. Prochaska and Hilton (2012) also noted that differences in statistics used to summarize the results contributed to this discrepancy. A separate review and comment on the Prochaska and Hilton (2012) meta-analysis by Krebs and Sherman (2012) indicated that the authors used appropriate meta-analytic and review methods. Krebs and Sherman (2012) concluded that any increase in cardiovascular events with Chantix is "probably small and would be overshadowed by the reduced risk associated with smoking cessation, particularly because the odds of successful smoking cessation with varenicline are higher than for any other monotherapy."

The other FDA-approved tobacco cessation medication, Bupropion, was found to be safe at a one-year follow-up in a multicenter, randomized study of 629 smokers with stable CVD (Rigotti et al. 2010; Tonstad et al. 2003).

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[42] FDA Drug Safety Communication: Chantix (varenicline) drug label now contains updated efficacy and safety information, available at http://www.fda.gov/Drugs/DrugSafety/ucm264436.htm (last accessed September 11, 2013).

6.1.3.1.3. Swedish snus

The available data suggest that the health risks of switching from cigarettes to Swedish snus are similar to switching from cigarettes to NRTs or non-nicotine tobacco cessation medications. This conclusion follows from an examination of the potential impact of increased NRT use for smoking cessation on future US mortality conducted by Apelberg and colleagues (2010). Because there were limited data to quantify the potential risks from long-term nicotine use from NRTs, the authors instead used an estimate of the risk of all-cause mortality of snus users from the Swedish Construction Worker cohort. The use of Swedish snus as a surrogate to estimate the risk of NRT products suggests that snus is safer than cigarettes, and that any potential risks posed by Swedish snus are likely not much different than NRT products or tobacco cessation medications.

These findings comport with a recent review (Lee 2013c) of epidemiological cohort or case-control studies, all from Sweden, which allowed comparison of cancer or cardiovascular disease risk in current snus users who formerly smoked (‘‘switchers’’) with that of never snus users who continued to smoke (“continuers”) or of never snus users who quit smoking (“quitters”). Based on 13 sets of comparisons, one for oral cancer, one for stomach cancer and 11 for various cardiovascular disease endpoints, switchers had a consistently lower risk than continuers, with relative risks varying from 0.35 to 0.61, and a similar risk to quitters. Meta-analyses from four studies for ischaemic/coronary heart disease or acute myocardial infarction, gave combined relative risk estimates of 0.55 (95% confidence interval 0.45–0.68) for switchers vs. continuers and 1.02 (95% confidence interval 0.83–1.26) for switchers vs. quitters (Lee 2013c). Though based on limited evidence with some weaknesses, these results are consistent with a recent review which found no increased risk of cancer or heart disease from snus use (Lee 2011).

6.1.3.2. Conclusion

The data consistently demonstrate that switching from cigarettes to snus substantially reduces individual risk and is associated with a clearly lower risk of CVD and cancer than continuing to smoke. The risk in switchers appears to be no different from that in smokers who quit smoking. The findings are consistent with other evidence which demonstrate that adverse health effects of snus are, at most, minimal. In sum, although the use of snus may pose a slight risk, if any, to cardiovascular health, the risk posed by continued smoking likely far exceeds any potential risk from Swedish snus.

Comparing the switch from cigarettes to snus with the switch from cigarettes to NRT use necessitates an assessment of nicotine delivery products generally, including their contribution to smoking cessation and their effect on overall population health. The role of NRT products has recently been reconsidered by FDA (2013) and the UK Medicines and Healthcare Products Agency (“MHRA”). FDA and MHRA have essentially permitted NRTs to be labeled as both harm reduction products and smoking cessation devices, and both agencies have apparently determined that NRT label changes and a concurrent risk communication campaign will benefit the health of the overall population. Given that both public health agencies relied on the Swedish human health evidence when assessing the risk posed by long-term use of NRTs and

othe nicotine-containing products, it is reasonable to consider the health effects of Swedish snus as being comparable to that of NRTs.

Even though this MRTP Application does not make the case for use of the Snus Products as smoking cessation aids, the scientific literature is increasingly documenting how snus is preferred over NRTs as a cessation device in certain contexts. Most notably, the research conducted by SIRUS to evaluate public measures to prevent the use of tobacco demonstrates the contribution of Swedish snus in facilitating smoking cessation in Norway (Lund and McNeill 2013).

6.1.4. Additional Health Risk Information

6.1.4.1. Biomarkers

Biomarkers may be used to assess the actual internal dose of a tobacco component to which a tobacco user might be exposed. A biomarker to a chemical or component is defined as, "*the chemical, or its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism*" (IOM 2012). Because biomarkers may represent the integrated exposure from all routes, use of biomarkers reduces uncertainties in the assessment of exposures that are based on the concentrations if components in tobacco products coupled with extraction and uptake of these components via different routes, e.g., oral tobacco use versus smoking or due to different use patterns may be bypassed (IOM 2012). Biomarkers for tobacco components may also be contributed to by other exposure sources, however, such as diet, automobile exhaust, and occupational exposure, with the exception of tobacco-specific biomarkers.

Biomarker levels vary between individuals, due to potential differences in product use behavior, genetic polymorphisms and other host differences, and differences in the characteristics of products used (among other possible variables). Comparisons of biomarker levels on a population basis, however, provide an indication of general trends in internal exposure to certain components/constituents due to use of a specific well-characterized product. In its report, *Scientific Standards for Studies on Modified Risk Tobacco Products*, the IOM (2012) concluded: "In summary, biomarkers can provide a more realistic assessment of the consumer's exposure to carcinogens and toxicants in tobacco products than simple analyses of the products because laboratory analyses cannot fully duplicate human use conditions. In most cases, the general trend of laboratory results is reflected in the biomarker data."

Aside from inter-individual variation, there are other limitations to the use of biomarkers to assess exposure to certain components from tobacco products. First, even though a large number of components have been quantitated in various tobacco products, to date only a limited number of exposure biomarkers have been measured and validated in tobacco users. Furthermore, downstream metabolites, such as those measured in urine, may reflect not only differences in exposure to the component of origin, but also a potential change in upstream metabolism (Hecht et al. 2010) (e.g., impact of genetic polymorphisms, other components competing for metabolizing pathways).

While some studies have shown associations between exposure biomarkers and risk of specific health endpoints, the specific tobacco components that might ultimately be responsible for tobacco-related diseases has not been established. As pointed out by the IOM (2012), "it is possible that constituents that play a decisive role in disease causation are simply not being measured…." Furthermore, mixture effects due to "potential interactive effects among components that are critical in disease etiology" may not have been taken into account in the analyses. Thus, due to all these limitations, conclusions from these studies with respect to harm reduction should be interpreted carefully and in the context of additional data from clinical or epidemiological studies.

Hecht and colleagues (2010) suggested a panel of carcinogen and toxicant biomarkers that could be used in product regulations. The panel consists of analytically validated exposure biomarkers, most of which have been analyzed in multiple studies on large number of smokers and non-smokers (Hecht et al. 2010). These authors also point out that all tobacco components that were identified as priority components in cigarette smoke for regulation under the Framework Convention on Tobacco Control (FCTC) by the WHO are included in their suggested panel (Burns et al. 2008). The panel includes the following biomarkers that are likely more relevant for exposure to smokeless tobacco, including snus:

- Urinary biomarkers of nicotine (nicotine equivalents[43]), NNK (total NNAL[44]), NNN (total NNN[45]), PAHs (1-HOP[46]), acrolein (HPMA[47]), crotonaldehyde (HBMA[48]), and cadmium;
- hemoglobin adducts of acrylamide (carbamoylethylvaline);
- leukocyte DNA adducts of formaldehyde (N6-hydroxymethyl-deoxyadenosine) and acetaldehyde (N2-ethylidene-deoxyguanosine)

The sources of the following tobacco-related biomarkers on the panel suggested by Hecht and colleagues (2010) are likely combustion products in cigarette smoke and these biomarkers are probably less relevant for exposure to smokeless forms of tobacco, but could, in studies where STPs are used for smoking cessation, be indicative of reduced exposure following smoking reduction:

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43 Nicotine equivalents: The sum of nicotine, cotinine, 3′-hydroxycotinine, and their glucuronides

44 Total NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides

45 Total NNN, *N*′-nitrosonornicotine and its glucuronides

46 1-HOP: 1-hydroxypyrene and its glucuronides/sulfates

47 HPMA: 3-hydroxypropyl mercapturic acid

48 HBMA: 4-hydroxybut-2-yl mercapturic acid

- Urinary biomarkers of 1,3-butadiene (MHBMA[49]), benzene (SPMA[50]), ethylene oxide (HEMA [51]);

- hemoglobin adducts of ethylene oxide (hydroxyethylvaline), 4-aminobiphenyl (4-aminobiphenyl-globin), and acrylonitrile (cyanoethylvaline);

- biomarkers of carbon monoxide (exhaled CO, carboxyhemoglobin)

In addition to the above listed, other frequently measured biomarkers of tobacco include cotinine in plasma or serum for exposure to nicotine; anatabine and anabasine, which are used to distinguish nicotine exposure from tobacco products from that of nicotine-replacement products, which contain only trace levels, if any, of these components; and urinary metabolites of B[*a*]P, naphthalene, phenanthrene, and fluorene (Hatsukami et al. 2003; Hecht 2002). Unchanged NDMA, NPYR as well as several nitrosamino acids have been measured in the urine of smokers, but correlation with tobacco use has been mixed due to endogenous formation of these nitrosamino compounds so they have not been frequently measured (Hecht 2002; USDHHS 2010).

To date, the available literature provides information on nicotine, TSNAs, cadmium, and selenium biomarkers investigated in traditional Swedish snus users. The data are presented in the following sections. The outline follows the same order for tobacco components as established in Section 2 (Product Chemistry) of the ENVIRON Snus Monograph (2013) and includes a brief introduction to provide relevant available information on the formation, significance, and limitations of the discussed biomarker.

In Appendix III of the ENVIRON Snus Monograph (2013), the available data on biomarkers for traditional Swedish snus users, supplemented with available data for users of new products marketed as snus, is discussed in comparison with data for smokers and Nicotine Replacement Therapy (NRT) users. Where no data was identified for users of snus or new products marketed as snus, select studies of traditional US STP users are discussed. Study details are provided in Table A III-7 of the ENVIRON Snus Monograph (2013).

6.1.4.1.1. Biomarkers of Tobacco Alkaloids: Nicotine

No studies were identified in which biomarkers of other alkaloids were measured in snus users. Therefore, this section focusses on biomarkers of nicotine.

The uptake and fate of nicotine in the body are important determinants in the evaluation of its biomarkers. In addition, since nicotine is thought to be the primary addictive component of

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[49] MHBMA: The sum of 1-hydroxy-2-(*N*-acetylcysteinyl)-3-butene and 1-(*N*-acetylcysteinyl)-2-hydroxy-3-butene

[50] SPMA: *S*-phenyl mercapturic acid

[51] HEMA: 2-hydroxyethyl mercapturic acid

tobacco, its pharmacokinetics are relevant for the assessment of the abuse liability of a tobacco product. Parameters associated with a greater likelihood of abuse are faster speed of drug delivery, clearance, and greater amount of drug absorption (Carter et al. 2009). The IOM (2012) stated that "In particular, acute blood nicotine absorption profiles in response to both single and repeated use of products is a relevant component in assessing the addictive potential of MRTPs." Acute dose effect studies that measure respective parameters (e.g., time to and maximum nicotine blood level (t_{max} and C_{max}) and the area under the curve (AUC)) often together with other physiological, psychomotor, and subjective effects are part of suggested study types for abuse liability assessments (Carter et al. 2009). Also, the IOM (2012) noted "A standard with regards to human abuse liability drug testing are acute dose-effect comparison studies, because of the correspondence between subjective ratings of drug effects and real-world abuse potential."

6.1.4.1.1.1. Nicotine Pharmacokinetics

During use of oral smokeless tobacco products as well as NRTs, nicotine is absorbed mainly in the oral cavity via the buccal mucosa and in part from swallowed tobacco juices in the gastro-intestinal tract (Benowitz 2009; Ebbert et al. 2004). This is in contrast to nicotine absorption from smoking, where inhaled nicotine is mostly absorbed through the alveoli in the lung into the blood stream.

Nicotine is a weak base and in its ionized form does not easily cross biological membranes (as reviewed in Benowitz et al. 2009). Hence, absorption of nicotine is dependent on pH and is more rapid from alkaline tobacco products or in a more alkaline body environment. The absorption of nicotine through the lung is thought to be rapid and comprehensive due to the large surface area of the alveoli and small airways and dissolution of nicotine in lung fluid of pH 7.4; by comparison, absorption of nicotine from oral products is a slower process. For oral tobacco products, the extent and speed of oral absorption into the systemic circulation is largely dependent on product pH, e.g., the buffering capacity of moist snuffs were shown to be 10 to 20 times higher than the buffering capacity of human saliva (Ciolino et al. 2001), excluding the potential influence of foods and drinks that influence acidity in the mouth. Though oral absorption is rapid for more alkaline tobacco products, the rise in brain nicotine level is slower than with smoking, where high levels of nicotine reach the brain in 10-20 seconds (faster than with intravenous administration) (as reviewed in Benowitz et al. 2009; Hukkanen et al. 2005). A slower, more gradual increase in nicotine levels is thought to result in lower abuse liability (as reviewed in Benowitz et al. 2009). The fraction of swallowed nicotine from oral products can be well absorbed in the small intestines due to its alkaline pH and large surface area, but its bioavailability is low since it undergoes first-pass metabolism in the liver to cotinine and other metabolites before reaching the systemic circulation (as reviewed in Benowitz et al. 2009; Hukkanen et al. 2005; USDHHS 2010).

Nicotine is primarily and extensively metabolized in the liver to a variety of different substances. About 70-80% of nicotine in humans is converted to cotinine via a cytochrome P450-catalyzed pathway (as reviewed in Benowitz et al. 2009; Hukkanen et al. 2005). The main enzymes involved in this step are CYP 2A6 and 2A13 (Murphy et al. 2011). While nicotine has a short

half-life in blood (~2 hours after intravenous administration or smoking), cotinine's blood half-life is much longer (~16 hours) (as reviewed in Hukkanen et al. 2005).

A considerable inter-individual variability in the elimination rate of nicotine and cotinine exists, due to genetic polymorphisms, a variety of other physiological influences (such as diet, age, time of day, gender, pregnancy), other influences (such as pathological conditions, medications, racial and ethnic differences), and finally, smoking itself. For example, the clearance of nicotine in smokers is lower compared to those in nonsmokers, which may be due to other components in tobacco products. There is some indication that long-term STP use may also decrease cotinine levels as shown in a study of STP users where cotinine in saliva was measured (Mushtaq et al. 2011). It is thought that this effect is due to increased cotinine metabolism and elimination, similar to what has been observed with smokers (Mushtaq et al. 2011).

6.1.4.1.1.2. Nicotine Pharmacokinetics in Users of Swedish snus and snus-like products

Pharmacokinetic parameters of nicotine in blood absorbed from snus have been investigated in several studies. Three of these studies (Digard et al. 2012; Holm et al. 1992; Lunell and Lunell 2005) were conducted with regular snus users and one study was conducted among smokers who switched to snus for the purpose of the experiment (Lunell and Curvall 2011). In all studies, the experiment started after a minimum overnight (12-hour) period of abstinence. Nicotine parameter data as measured in these studies is provided in Table A III-1 of the ENVIRON Snus Monograph (2013).

Rise of Nicotine Blood Concentration and Time to Maximum Concentration (t_{max})

The time to maximum plasma nicotine concentration in users of Swedish snus or some novel snus-like products appears to be dependent on the product usage time, but not nicotine content or portion size. In a recent study, Digard and colleagues (2012), reported that though different portion sizes of a loose (i.e., no pouch) snus-like product (*Granit*) were used (i.e., nicotine exposures were different depending on the portion size) each for 60 minutes, the median t_{max} was the same - 60 minutes (range, 45-90 minutes). This was similar to the finding for two pouched snus-like products (*Lucky Strike Original Brown and Bold*), with different nicotine contents (median t_{max} 60 min; range, 20-90 min and 45-90 min, respectively). By contrast, previous product-specific studies of Swedish snus used experimental times of 30 minutes snus use and the reported mean or median t_{max} values were between 30 and 37 minutes (Holm et al. 1992; Lunell and Curvall 2011; Lunell and Lunell 2005).

Maximum and Total Nicotine Blood Concentration (C_{max} and AUC)

The mean maximum plasma concentrations (C_{max}) for snus users varied between studies and ranged from 10.8 to 29 ng/mL. The highest mean C_{max} values were measured in users of *General* and *Catch* snus brands under continuous use conditions with 12 administrations of 30 minutes each (Lunell and Lunell 2005). In the three other studies, the experimental design included only a single administration. The lowest C_{max} (10.8 ng/mL) was measured in users of a loose snus-like product (*Granit*) and a pouched snus-like product (*Lucky Strike Original Brown*) that had slightly higher nicotine content (10.8 mg and 10.7 mg per 1-g portions), but also had a

slightly lower pH than the product-specific snus brands (pH 8.0-8.3 vs. 8.4-8.7) tested by Lunell and colleagues (Digard et al. 2012; Lunell and Curvall 2011; Lunell and Lunell 2005).

Within each study, a correlation of the C_{max} with the total nicotine content of a product could be observed: Increasing the portion size of the loose snus-like product from a 1-g to 2.5-g portion (nicotine content 27.1 mg/2.5 g) resulted in a respective increase of the geometric mean C_{max} (10.8 to 17.9 ng/mL) (Digard et al. 2012). In the same study, similar but smaller effects were seen with two pouched snus-like products of different nicotine content (difference of 4 mg nicotine per 1-g pouch). Under the continuous use conditions, *General* snus with a nicotine content of 8.84 mg/1-g portion resulted in a mean C_{max} of 29 ng/mL compared to a C_{max} of 20.95 ng/mL resulting from *Catch Mini* snus with a nicotine content of 4.53 mg/0.5-g portion (Lunell and Lunell 2005). In the same study, use of *Catch Dry Mini*, a novel brand of traditional Swedish snus, with similar nicotine content *as Catch Mini* (4.82 mg/0.3-g portion)), but lower moisture and pH (pH 7.3), resulted in halving of the C_{max} (10.85 ng/mL).

A single use of *General* snus brands (*Onyx* and *White Large*) with nicotine contents of 8.65 or 9.92 mg/1-g portion by smokers naïve to snus use, resulted in mean C_{max} values of 13.7-14.8 ng/mL (Lunell and Curvall 2011).

A single use of a 2-g portion of *Ettan* snus resulted in a mean C_{max} of 17 ng/mL (at 35.5 min; the plasma cotinine level at 60 minutes was 279 ng/mL) (Holm et al. 1992).

The average plasma concentrations for nicotine after a single use of 2.5 g unspecified Swedish snus during supine rest increased slowly from 0.3 ng/mL at zero minutes after 24 hours of abstinence to a plateau of 20.9 ng/mL nicotine at 110 min (plasma cotinine at time 0 was 117.1 ng/mL, the maximum 126.3 ng/mL at 140 min). The sampling period was 140 minutes (Hirsch et al. 1992).

In study 1 by Gray and colleagues (2008) in which habitual traditional STP users were given a 2-g portion of loose snus, plasma nicotine increased from approximately 2 ng/mL at baseline after overnight abstinence to 8.7 ng/mL immediately after the 30-minute consumption of the snus. This study used a cross-over design (Latin square) where subjects used four different products, including snus, separated by 48 hours. Each condition was four hours and consisted of 30 minute product use and 30 minute rest period.

Area under the curve ("AUC") values are difficult to compare between these studies since all were determined using different time periods. The lowest mean AUC was reported in the study with 2-g portions of *Ettan* snus and for a time period of 0-60 minutes (747.4 ng*min/mL) (Holm et al. 1992). The geometric mean AUCs for the time period of 0-120 minutes were calculated to be 960 and 1,614 ng*min/mL for the two different portion sizes of loose snus-like product (nicotine content, 10.8 and 27.1 mg, respectively) (Digard et al. 2012). In the same study and consistent with their different nicotine contents (10.7 vs. 14.7 mg/1-g portion) geometric mean AUCs for the two pouched snus-like products differed (*Lucky Strike Original Brown* and *Bold*, 1,008 vs. 1,224 ng*min/mL). Mean AUCs for a time period of 0-720 min (12 hours) were reported in the experiment with multiple uses to range from 1,141 to 1,570 ng*min/mL (19.02-

26.16 ng*hrs/mL) for *General* and *Catch* snus brands with nicotine contents of 4.53-8.84 mg/portion (Lunell and Lunell 2005). Similar to what was observed with the C_{max}, the AUC value for *Catch Dry Mini* was approximately half of what was measured for the other two *Catch* brands in the same study (589 ng*min/mL or 9.81 ng*hrs/mL). The highest mean AUC values reported, 2,829 and 3,062 ng*min/mL, were for the time period zero to infinity for two *General* snus brands with nicotine content of 8.65 or 9.92 mg/portion (Lunell and Curvall 2011).

Summary

In sum, the time to maximum plasma nicotine concentrations in users of Swedish snus and some novel snus-like products appears to be dependent on the usage time, but to a lesser extent on nicotine content or portion size. On the other hand, C_{max} and AUC appear mostly dependent on total nicotine content (per pouch or portion size) as well as pH of the product. Whether the snus or snus-like product was loose or pouched had little influence on these parameters.

6.1.4.1.1.3. Nicotine Biomarkers

Nicotine and its multiple metabolites have been measured in blood, saliva, urine, hair, toenails, and other bodily fluids. Cotinine in serum or plasma is a commonly measured biomarker of nicotine exposure.

While exposure estimates to tobacco are also often based on external tobacco use measures (e.g., in cigs/day), Benowitz and colleagues (2011) concluded that "CPD [cigs/day] does not provide an accurate estimate of nicotine and carcinogen exposure". In their study, they observed that the reliability of this measure varies by race and it was particularly poorly correlated in black smokers. These authors noted that both urine nicotine equivalents and plasma cotinine are useful for estimating carcinogen exposure. However, Zhu and colleagues (2013b) found that plasma cotinine levels and tobacco carcinogen exposure were different in subjects with different CYP2A6 activity and were therefore not a good quantitative marker to compare between CYP2A6 genotypes, sexes, and races. These parameters should therefore be accounted for in studies that use these measurements to compare nicotine exposures from any tobacco product.

Due to its relatively short half-life, blood nicotine concentrations fluctuate significantly throughout the day. Cotinine with its longer half-life is considered a more stable indicator of nicotine exposure for a single individual, depending largely on CYP2A6 activity. A high correlation among cotinine concentrations in plasma, saliva, and urine has been noted (as reviewed in Benowitz et al. 2009).

However, in addition to the factors contributing to inter-individual variability in nicotine and cotinine elimination described above, cotinine levels may not be representative of nicotine uptake when comparing different uptake routes. While nicotine plasma levels were shown to be similar in smokeless tobacco users (including snus users) and smokers, cotinine plasma and urinary levels tend to be higher than in smokers (Benowitz et al. 1989; Hecht et al. 2007; Holm et al. 1992) (ENVIRON Snus Monograph 2013, Appendix III Section A III 3.1.2). This is due to the extended first-pass metabolism of swallowed nicotine after gastro-intestinal uptake. Frequency of swallowing tobacco juice was an independent predictor of higher serum cotinine

levels whereas no correlation was found for serum nicotine levels (Ebbert et al. 2004).

Urinary nicotine or cotinine concentrations are frequently measured. Total nicotine or 'nicotine equivalents' is the sum of nicotine and its metabolites in urine: cotinine, and 3' hydroxycotinine, and their respective glucuronides, nicotine-GlcA, Cotinine-GlcA, 3' hydroxycotinine-GlcA; occasionally, nicotine-N'-oxide and cotinine-N-oxide are also included. Nicotine equivalents measured under steady-state account for 73-96% of the daily nicotine dose received by a tobacco user and are therefore considered a valuable biomarker (Hecht et al. 2010).

6.1.4.1.1.4. Biomarkers of Nicotine in Snus Users

This section describes nicotine biomarkers after traditional Swedish snus use as analyzed in a clinical or interventional study, or in cross-sectional, population-based studies. Nicotine data as measured in these studies are provided in Table A III-2 of the ENVIRON Snus Monograph (2013).

Nicotine and Cotinine in Plasma/Serum

In Swedish studies of regular snus users (N=21-92) with an average daily snus consumption between 21 and 32 g[52] mean nicotine plasma levels ranged from 3.2 to 15.5 ng/mL, but the time of blood sampling was not specified (Bolinder et al. 1997b; Bolinder 1997; Bolinder et al. 1997a; Bolinder and de Faire 1998; Eliasson et al. 1991; Eliasson et al. 1995). In these same studies of Swedish firemen and individuals from the general Swedish population, the mean cotinine plasma levels were between 326 and 359 ng/mL. In one study of 27 regular snus users with an average snus consumption of 22 g/d where blood was sampled immediately after a use, the mean nicotine plasma level was 36.7 ng/mL (standard deviation (SD), 14.3), while the mean plasma cotinine level was 399.3 ng/mL (SD, 160.5) (Holm et al. 1992). In a study of 11 snus users in a Norwegian industrial worker cohort with an average snus consumption of 11 g/d (range, 0.3-29 g/d), the respective geometric mean serum cotinine level was 137 ng/mL (range, not detected-1312 ng/mL) (Ellingsen et al. 2009).

A study in Serbia was conducted to test the efficacy of Swedish snus as an aid to smoking cessation (Joksic et al. 2011). Smokers willing to quit (N= 319; average cigarette consumption 26-28 cigs/day) were offered snus or placebo and by the end of the study at week 48, the target date for complete smoking cessation, self-reported cigarette consumption had decreased to less than 10 cigarettes/day in both groups. The serum cotinine levels in snus and placebo users were decreased to 66.1 and 69.1 ng/mL, respectively, approximately 68% of baseline levels. The mean exhaled breath carbon monoxide levels were also similar (approximately 12 ppm) in both groups.

Nicotine and Cotinine Levels in Urine

In the available studies, biomarkers of nicotine are presented in four ways: nicotine itself,

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[52] This indicates a main use of loose snus based on average loose snus of 29 g/day and average pouched snus use of 12 g/day (Digard et al. 2009)

cotinine, total cotinine, and nicotine equivalents.

In the study by Ellingsen and colleagues (2009), urinary nicotine and cotinine were also analyzed and were 26 (0.4-560) and 159 (8.2-428) µg/mmol creatinine; if corrected for the median urinary creatinine in men[53], the corresponding nicotine and cotinine concentrations were approximately 348 and 1908 ng/mL, respectively. In a Swedish study of snus users who consumed an average of 25 g/day, the mean urinary cotinine level was 1210 ng/mL (Wennmalm et al. 1991).

Two independent studies where STP users were switched from their own brands of STP to *General* snus were conducted in which urinary cotinine as well as total cotinine levels were measured (Gray et al. 2008; Hatsukami et al. 2004).

In study 2 by Gray and colleagues (2008) a Latin Square design was used to test two different potentially reduced exposure products (PREPs), one of which was loose *General* snus, in a group of 19 regular STP users for 5 days each, with wash-out periods over the weekends during which participants were allowed to use their own STPs. Each participant completed four conditions (placebo, own STP, 2 PREPs). Users were given 45 g of snus on each of days 1-4 to use *ad libitum* over the next 24 hours. On day 5 of the switch to snus, the average urinary cotinine level was with approximately 1000 ng/mL not different from day 1.

In the study by Hatsukami and colleagues (2004), STP users were followed for 4 weeks after switching to reduced exposure products or medicinal nicotine patches, with 19 STP users switching to snus. At week 4 after the switch to snus, the mean snus consumption was 3.7 tins/week (approximately 13 g/day[54]) and the mean urinary total cotinine (cotinine and its glucuronide) level was 5926 (4415 to 7437) ng/mL. This was similar to those measured at week 1, although there was a significant "overall visit effect", because the mean cotinine level was decreased at the week-2 visit and increased again at the week-4 visit.

Nicotine Equivalents in Urine and Cotinine in Saliva

Two studies in Swedish snus users measured nicotine equivalents (nicotine and seven metabolites) in urine, as well as cotinine levels in saliva (Andersson et al. 1994; Andersson et al. 1995), and one study measured only saliva cotinine (Post et al. 2005).

The first study compared nicotine extraction (see ENVIRON Snus Monograph 2013, Section 2.3.3) and uptake in 23 portion-bag users and 22 loose snus users (Andersson et al. 1994). Portion bags had slightly higher nicotine content, but lower pH than loose snus (pH 7.9-8.2 vs. 8.5-8.6, respectively) and users consumed on average 14.4 g/d of portion bags versus 20.8 g/d of loose snus. The tobacco was kept in the mouth for about the same number of hours a day by

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[53] 26 µg/mmol creatinine x 12 mmol creatinine/L = 348 µg/L = 348 ng/mL, with a median urinary creatinine concentration of 12 mmol creatinine per L urine in men (Cocker et al. 2011)

[54] One tin of *General* snus is assumed to contain 24 1-g portions. 3.7 tins/7 d x 24 g/tin /7 d = 13 g/d

both groups (averages, 12.3-13.1 hrs). The degree of extraction from pouched snus was significantly lower than from loose snus. Together with the lower overall daily consumption of pouched snus, the total nicotine extracted per 24 hours from portion bags was approximately half of what was extracted from loose snus. Despite these differences in extraction and consumption however, there was no statistically significant difference between the portion-bag and loose snus users for either the systemic nicotine dose, measured as nicotine equivalents in urine (34.5 ±23.1 mg/24 hrs and 35.6 ±18.6 mg/24 hrs, respectively), or in saliva cotinine concentrations (342.9 ±180.8 and 326.6 ±135.6 ng/mL, respectively). The authors speculated that "This discrepancy between the amount extracted and the actual uptake of nicotine may be due to the fact that users of loose snus have a higher salivary secretion rate and therefore spit or swallow much more saliva than users of portion-bag snus". In addition, Andersson and colleagues (1994) also evaluated changes in the oral mucosa of the subjects (see ENVIRON Snus Monograph 2013, Section 5.2.2 for details).

The second study by the same researchers, conducted to evaluate short-and long-term effects of switching to a reduced-nicotine snus, compared biomarker levels in 24 snus users that switched for 10 weeks from their regular high nicotine content brand A to a brand B with approximately half the nicotine content (Andersson et al. 1995). Brand B snus also had a lower product pH (pH 7.9-8.2 vs. 8.2-8.5, respectively; Study 1). Both were pouched products. In a second part of the study (Study 2), 18 regular brand B users were investigated. While tobacco consumption increased slightly in users that switched from brand A to B from 16.4 g/day before the switch to 18.6 g/day at the end of the study, urinary nicotine equivalents and saliva cotinine decreased to similar levels as those measured in the regular brand B users, even though the consumption in brand B users was approximately 3 g lower (15-15.2 g/day). The authors concluded that "these results indicate that snus users compensate to a small extent for the lower nicotine delivery by increasing their consumption on short-term switching, but the same does not apply to long-term users".

Despite their increased intake, biomarker levels of internal nicotine exposure decreased in brand A users to approximately half of baseline to similar levels as those measured in regular brand B users: Nicotine equivalents and saliva cotinine level averages were 25.2 mg/24 hrs (range: 4 to 65 mg/24 hrs) and 336 ng/mL (range: 70.4 to 731 ng/ml), respectively, the week before the switch compared to 14.4 mg/24 hrs and 153 ng/mL, respectively, at the end of the study. By comparison, the average levels in regular brand B users was 14.3 mg/24 hrs (range: 2 to 41 mg/24 hrs) and 159 ng/mL (range: 31 to 335 ng/ml), respectively. Andersson and colleagues (1995) also investigated the subjects for oral mucosal soft tissue changes (see ENVIRON Snus Monograph 2013, Section 5.2.2 for details).

Saliva cotinine levels were also measured in adolescent Swedish tobacco users (Post et al. 2005). In this cross-sectional study study, conducted to assess the reliability of self-reported tobacco use based on internal biomarkers of nicotine, the median[55] cotinine level measured in 28 snus users

[55] Data was provided in a box-plot. Although the legend implies that means were indicated, it appears to be a typo and is likely a median.

was approximately 80 ng/mL.

Summary of Nicotine Biomarkers Identified in Snus Users

A number of studies in regular snus users show that mean or median cotinine levels in plasma or serum range from 137 to 399 µg/L depending on the amount of snus consumed (average 11-32 g/day). In other studies, that included adolescent snus users (who consumed less snus), average saliva levels ranged from 80 to 343 ng/mL. Fewer studies in regular snus users measured urinary biomarkers of nicotine. Results were as follows: for nicotine itself (based on one study) 29 µg/mmol creatinine; cotinine (as measured, based on two studies) was approximately 1000-1210 µg/L; total cotinine (based on one study) was 5926 µg/L; and nicotine equivalents (based on two studies) was 14.3-35.6 mg/24 hrs.

6.1.4.1.2. Biomarkers of Trace Level Components

As noted in the Introduction, the available scientific literature provides information for some biomarkers of TSNAs, cadmium, and selenium in snus users.

6.1.4.1.2.1. N-Nitroso Compounds: TSNAs Biomarkers

Biomarkers of TSNAs are the main biomarkers measured and reported in the published literature; there is little information on biomarkers of other non-tobacco specific *N*-nitroso compounds for tobacco users. Formation, significance and limitations of the main TSNA biomarkers are briefly discussed below.

TSNAs and their metabolites have been determined in various human bodily fluids, including saliva, blood, and urine, as well as in toenails (IARC 2007; Shah and Karnes 2010). Furthermore, DNA adducts in leukocytes, lung and liver tissue as well as hemoglobin adducts have been measured in humans (Hecht 2008; Nilsson 2011). To date, the most commonly measured TSNA biomarkers are urinary metabolites of NNK.

Urinary NNAL and Total NNAL (Biomarkers of NNK)

In both primates and rodents, NNK is converted largely to NNAL. Subsequent major metabolic pathways are the same for NNK and NNAL. Both compounds can be activated via cytochrome P450-catalyzed α-hydroxylation, a pathway considered to be major with respect to NNK's ultimate carcinogenic potential. Recent studies suggest that NNK and NNAL levels are not directly impacted by CYP2A6 enzyme polymorphisms (Zhu et al. 2013a). NNAL, but not NNK, can be detoxified via glucuronidation (Hecht 2008; Stepanov et al. 2008). NNAL and its glucuronides (N- and O- isomers: NNAL-*N*-Gluc and NNAL-*O*-Gluc), which together are referred to as "total NNAL" can be measured in urine, while unchanged NNK has not been detected in urine (Hecht 2008; Stepanov et al. 2008). Urinary NNAL and its glucuronides are the most frequently quantified biomarkers of NNK (Shah and Karnes 2010).

Quantification of total NNAL reflects the activation pathway. The activation pathway is thought

to be the major route of NNK metabolism in both smokers and smokeless tobacco users based on experiments by Hecht and colleagues: To investigate the extent of α-hydroxylation, urinary metabolites attributed to different NNK metabolism pathways were quantified under regular use conditions for smokers smoking cigarettes spiked with [pyridine-D_4]NNK (Stepanov et al. 2008). In this study, the metabolites from NNK α-hydroxylation accounted for 86% and total NNAL accounted for 12% of all identified urinary compounds in smokers. To determine the fraction of the NNK dose excreted as total NNAL in STP users, the amount of NNK extracted from tobacco after a single administration of an US STP after 3 weeks of abstinence was compared with the amount of excreted total NNAL (Hecht et al. 2008b). An average of 59% NNK was extracted from the moist snuff product and the amount of urinary total NNAL was calculated to be 14-17% of the NNK dose. Considering the very different study designs of these two studies, it appears difficult to conclude the extent of potential differences in NNK metabolism between STP users and smokers and how those might impact the percentage of NNK dose reflected in urinary total NNAL. Citing the studies described above, Hecht and colleagues (2010) stated that total NNAL captures approximately 12-17% of the NNK dose.

Because of the limitations described above, Hecht et al. (2010) cautioned that a decrease in urinary total NNAL could also hypothetically mean that activation increases. This limitation should be considered when evaluating the meaning of a decrease in urinary NNAL levels for risk, although in general a decrease in exposure to NNK is likely. An ideal risk marker would be related to pathways that provide information about the activation to ultimately critical reactive metabolites or reaction products, such as adducts (Shah and Karnes 2010). However, urinary metabolites from the α-hydroxylation pathway are not specific to NNK and the same compounds can also be formed with nicotine.

Despite these limitations, in studies of smokers, urinary levels of total NNAL were strongly associated with risk for lung cancer (Church et al. 2009, Yuan et al. 2009, both cited in USDHHS 2010). Further, the ratio of NNAL-glucuronide to free NNAL as a marker of NNK detoxification has been suggested to be correlated to an individual's risk of developing some tobacco-smoke induced cancers (Chung et al. 2011; Derby et al. 2009). With respect to head and neck cancer, a new matched case-control study with smokers did not observe increased urinary NNAL levels in cases, but levels of NNN and 1-hydroxypyrene, a metabolite of pyrene, were significantly increased (Khariwala et al. 2012). The same has not been established for any potential cancer risks in STP users (of any kind). In his recent review and analysis of published data of DNA and hemoglobin adducts in human and animal tissues, Nilsson (2011), concluded that "[w]hereas smoking and use of snuff [Swedish snus] result in similar exposures to the systemic carcinogens NNK and NNN, only smoking is associated with human lung cancer. This observation gives further support to the notion that TSNA probably play a minor role in the induction of smoking-related cancers." For more details on this study, see the ENVIRON Snus Monograph (2013), Appendix III, Section A III 3.2.1.3.

In general, urinary NNAL levels were well correlated with serum or urinary cotinine levels, numbers of cigarettes smoked, or environmental tobacco smoke exposure in non-smokers (as

reviewed in CDC 2012[56]). However, in both smokers and STP users, it has been observed that urinary total NNAL levels do not increase linearly at higher nicotine intakes that are measured by urinary cotinine (Hecht et al. 2008a; Lubin et al. 2007). The reason for these findings has not yet been established and the authors hypothesized that alternate pathways of NNK metabolism could be induced at higher nicotine and other tobacco constituents doses (Hecht et al. 2008a), but this is not known, and no biomarker measures for these possible alternate pathways are currently available.

Unlike cotinine, NNAL and its glucuronides are much more slowly eliminated in urine and hence total NNAL has a long terminal half-life; averages for smokers have been reported to be between 10 to 18 days (Carmella et al. 2009; Goniewicz et al. 2009). In studies that compared smokers and STP users, averages were 45 and 26 days, respectively, but this difference was not statistically significant due to large interindividual variations (Hecht 1999; Hecht 2002). Other authors have speculated that the half-life of NNAL in smokeless tobacco users might be similar to that in smokers (Goniewicz et al. 2009). NNAL could still be detected in urine 6 to 12 weeks after smoking cessation. Based on these findings, Goniewicz et al. (2009) concluded that in "testing of novel [tobacco] products, it will take 6-12 weeks for NNAL levels to reach a new steady state."

Some differences between oral and inhalation exposure have been identified for parts of the NNK metabolism, e.g., *N*-glucuronidation was significantly greater in smokers than in STP users, however, there was no significant difference in the percentage of free NNAL to total NNAL (41.4% vs. 36.6%, respectively) (Carmella et al. 2002). No studies were identified that provided information to establish how potential differences in NNK absorption, metabolism, distribution and excretion for the different routes of uptakes in humans may impact interpretation of urinary NNAL levels with respect to cancer risk.

Based on studies of predominantly US STP users, the CDC stated that the similar or slightly higher total NNAL levels in users of STPs compared to active smokers is "indicative of the higher levels of TSNA and NNK that may be present in smokeless tobacco" (CDC 2012). It should be noted that NNN, and to a lesser extent, NNK concentrations in both conventional STPs as well as traditional Swedish snus have been declining over the past decades (see Section 2.3.6.1), although concentrations were formerly consistently higher in US conventional STPs, than those detected in Swedish snus, with only few exceptions (Nilsson 2011).

Urinary NNN and Total NNN

Similar to NNK, NNN can be α-hydroxylated, a reaction thought to be primarily catalyzed by CYP2A6 (as reviewed in Zhu et al. 2013a). Different from NNK, both NNN itself and its glucuronides; can be detected in urine and are often measured as total NNN. Total NNN is estimated to reflect approximately 1% of the NNN dose taken in (as reviewed in Hecht et al. 2010).

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[56] CDC 2012. http://www.cdc.gov/biomonitoring/NNAL_BiomonitoringSummary.html , accessed April 2013.

Higher urinary NNN levels in smokers have been associated with increased esophageal and head and neck cancer risk (as reviewed in Hecht et al. 2010; Khariwala et al. 2012; Yuan et al. 2011). Khariwala et al. (2012) also reported higher risk of head and neck cancers associated with 1-hydroxypyrene, a metabolite of pyrene. It should be noted however, that certain polymorphisms impact metabolism of NNN, and may therefore contribute to differences in NNN levels. For example, higher urinary NNN levels were also observed in smokers with lower CYP2A6 activity, indicating lower activation via the α-hydroxylation pathway (Zhu et al. 2013a). NNN has also been detected in some users of nicotine replacement therapy demonstrating its endogenous formation (Stepanov et al. 2009b; Stepanov et al. 2009a). In an *in vitro* study with saliva, these researchers recently showed that NNN could be formed in detectable amounts from nornicotine without any addition of other substances, while incubation of saliva with nicotine and sodium nitrite resulted in only trace amounts of NNN (Knezevich et al. 2013). This indicates that there is a potential for endogenous formation of NNN from nornicotine that is already present in NRTs or metabolized from nicotine. However to date, the extent of NNN's endogenous formation in other tobacco users has not been thoroughly investigated.

Adducts of NNK and NNN

As described above, NNK and NNN can be activated via cytochrome P450-catalyzed α-hydroxylation and form DNA and hemoglobin adducts, such as 7-methylguanine, O^6-methylguanine, O^4-methylthymidine and/or pyridyloxobutyl (POB) (also called HPB-releasing[57]) adducts (Nilsson 2011). The activation pathway is considered to be a important with respect to the ultimate carcinogenic potential of NNK. Studies of DNA and hemoglobin adducts of NNK and NNN were recently reviewed (Nilsson 2011). Similar to what was observed for HPB-releasing hemoglobin adducts, a new study did not find any correlation between HPB-releasing DNA adducts in oral cells of smokers with urinary total NNN or total NNAL (Stepanov et al. 2013).

Biomarkers of TSNAs in Snus Users

Studies of biomarkers of TSNA from traditional Swedish snus are limited. Only two studies were conducted with regular snus users (Heling et al. 2008; Österdahl and Slorach 1988), while two others investigated changes in US STP users after they switched to snus (Gray et al. 2008; Hatsukami et al. 2004). TSNA biomarker of exposure data as measured in these studies are provided in Table A III-3 of the ENVIRON Snus Monograph (2013).

Urinary Total NNAL in Snus Users

No studies of urinary NNAL or total NNAL measured in regular users of traditional Swedish snus were identified. Two clinical studies were identified in which total NNAL was measured in conventional STP users who were switched to potentially reduced exposure products (PREPs), including traditional Swedish snus (*General*) (Gray et al. 2008; Hatsukami et al. 2004).

In the study by Hatsukami and colleagues (2004), 41 adult male conventional STP users were

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[57] Unstable POB adducts can be measured as released 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB).

switched from traditional STPs to *General* snus. These researchers reported a decline in total NNAL levels by more than half in most users after two weeks with not much additional decline after 4 weeks (1.5 and 1.4 pmol/mg creatinine, respectively) compared to baseline levels (3.2 pmol/mg creatinine), measured during the two weeks prior to the switch. The average consumption in tins per week increased slightly during snus use compared to baseline STP consumption, and at week 4 the urinary total cotinine levels were similar to those at baseline. The week 4 snus consumption was 3.7 tins per week (~12.7 g/day). It should be noted that tins of pouched STPs often contain less total tobacco than those with loose STPs, e.g. one tin of pouched *General* snus contains 24 1-g portions while one tin of loose *General* snus contains 45 g. The authors concluded that, "[u]sing Swedish smokeless tobacco products marketed in the United Sates may not only reduce carcinogen exposure but also may decrease cancer risk."

In the study by Gray and colleagues (2008), described previously, a Latin Square design was used to test four different potentially reduced exposure products (PREPs) in a group of 19 regular STP users for 5 days each, with wash-out periods over the weekends during which participants were allowed to use their own STPs. Each participant completed four conditions, one of which was snus use. Users were given 45 g of snus on each of days 1 to 4 to use *ad libitum*. Gray and colleagues (2008) did not observe a significant difference in total NNAL levels of conventional STP users 5 days after switching to loose *General* snus compared to levels on day 1 (~600 pg/mL versus ~700 pg/mL, respectively). Limitations of this study, compared to that of Hatsukami and colleagues (2004) include a smaller sample size (only 19 STP users were investigated) and the shorter duration of snus use (lasting only 5 days). Given the long half-life of NNAL (10-45 days), it is possible that the duration of use (5 days) was insufficient to reveal differences in product NNK concentrations. Another limitation was that actual snus consumption was not reported in this study. Cotinine levels on day 5 were comparable to those on day 1, similar to what was seen for the NNAL levels.

Urinary Total NNN in Snus Users

No studies of urinary NNN or total NNN measured in users of traditional Swedish snus were identified.

TSNAs in Saliva of Snus Users

One study conducted by researchers of the Swedish National Food Administration investigated the TSNA levels in the saliva of four habitual snus users (3 pouched snus users, 1 loose snus user) before, during and after 30-minute use of a single dose of snus (Österdahl and Slorach 1988). Saliva samples were taken on two different days. The TSNA concentrations as well as the extraction of the TSNAs from the pouched products were determined by analyzing the snus before and after consumption (see ENVIRON Snus Monograph 2013, Section 2.3.6.1). TSNA levels in saliva samples taken before and 20 minutes after the end of use were undetectable or trace amounts, which is in agreement with other studies that analyzed saliva samples of moist snuff users and smokers after the product was removed from the mouth (as reviewed in Caraway and Chen 2012). Saliva levels in samples taken during the dipping process varied strongly between users and day: NNK, NNN, and NAT levels ranged from not detected to 16 ng/g, 3 to 140 ng/g, and trace levels to 85 ng/g saliva, respectively. The average total TSNA concentration

during dipping was calculated to be between 15 to 125 ng/g saliva. Loose snus use resulted in higher maximum saliva levels compared to pouched snus use. The investigators calculated that with a saliva production of approximately 60 milliliter (mL) per hour the snus users were exposed to 0.9-7.5 µg TSNAs per hour of snuff dipping. It should be noted that the TSNA concentrations in the snus products used in this study was considerably higher than TSNA concentrations detected in snus in recent years (see ENVIRON Snus Monograph 2013, Section 2.3.6.1 for more details on how TSNA concentrations in snus have decreased over time).

TSNA Adducts in Snus Users

Results from analyses of adduct levels extrapolated based on animal data and estimated intake of Swedish snus are discussed in the ENVIRON Snus Monograph (2013), Appendix III Section A III 3.2.1.4 (Nilsson 2011). Nilsson (Nilsson 2011) also cited a study abstract that reported POB-DNA adduct levels detected in oral mucosa samples of snus users (Richter et al. 2009b, as cited in Nilsson 2011). Another abstract was located that appears to refer to the same study or samples (Heling et al. 2008), but no full publication was located. POB-DNA adducts levels detected in oral mucosa of 33 Swedish snus users were 5280 ±372 adducts/10^9 total normal nucleotides (TN) (Richter et al. 2009b, as cited in Nilsson 2011) or 17.61 ±7.1 pmol HPB/mg DNA (Heling et al. 2008). These adduct levels were approximately nine times higher than those detected in tissue samples of 45 nonsmokers (600 ±102 adducts/10^9 TN (Richter et al. 2009b, as cited in Nilsson 2011) or 2.00 ±2.31.1 pmol HPB/mg DNA (Heling et al. 2008). POB-DNA adducts levels were also reported for smokers (ENVIRON Snus Monograph 2013, Appendix III Section A III 3.2.1.3). Considering this comparison, and the results from epidemiological studies, Nilsson (2011) concluded that the POB-DNA adduct study "results cast doubt on the involvement of POB-DNA adducts in causing oral cancer, especially from Swedish "snuff" […]".

Summary of TSNA Biomarkers Identified in Snus Users

In summary, there were four studies investigating TSNA biomarkers in regular snus users identified. Of those, one older publication from 1988 measured TSNA levels in saliva during snus use. TSNA concentrations in the snus products used were considerably higher than those reported in recent analyses of Swedish snus. Urinary total NNAL was measured in two clinical studies where conventional US STP users were switched to snus use, however only one study had an observation period of sufficient duration to examine for and detect differences in levels before and after the switch (Hatsukami et al. 2004). In this study, total NNAL levels decreased significantly (to half the concentration measured at baseline) by week 4 of *General* snus use; it is not known if the study was of sufficient duration (6-12 weeks) to reach NNAL steady-state levels after the switch (Goniewicz et al. 2009). Importantly, urinary total cotinine levels in this study did not change significantly, indicating the decreased toxicant exposure could not be explained by a decrease of product use (nicotine intake). No studies measuring biomarkers of NNN in snus users were identified. POB-DNA adducts were significantly higher in oral mucosa of Swedish snus based on a study abstract; however, the importance of these adducts in oral cancer development has been questioned.

PAHs Biomarkers

No studies were identified in which biomarkers of PAHs were measured in snus users. More

information on biomarkers of PAHs is provided in the ENVIRON Snus Monograph (2013), Appendix III Section 3.2.2, where available data for use of new products marketed as snus and US STPs in comparison with smoking is discussed.

Aldehydes Biomarkers

No studies were identified in which biomarkers of aldehydes were measured in users of snus, new products marketed as snus, or STPs.

Metals and Metalloids Biomarkers

No studies that analyzed arsenic, beryllium, chromium, cobalt, lead, mercury, nickel, and barium levels in blood or urine in snus users were identified. More information on biomarkers of metals is provided in the ENVIRON Snus Monograph (2013), Appendix III Section 3.2.4, where available data for use of snus, new products marketed as snus and/or US STPs in comparison with smoking is discussed. The data is provided in Table A III-4 of the ENVIRON Snus Monograph (2013).

6.1.4.1.3. Biomarkers of Cadmium

Due to its long half-life in the body, cadmium levels in the blood reflect both recent as well as cumulative exposures, whereas cadmium levels in the urine reflect both cumulative exposure and the concentration of cadmium in the kidney (CDC 2009). Urinary levels thus reflect primarily total body burden of cadmium, and can be used as a marker of long-term exposure (ATSDR Draft 2008, Nordberg et al. 2007, as cited in Sand and Becker 2012).

Smoking is a significant source of cadmium exposure, and smokers have been shown to have increased biomarker levels of cadmium (ATSDR 2012). A recent analysis of National Health and Nutrition Examination Survey (NHANES) data concluded that urinary cadmium concentrations decreased markedly between 1988 and 2008 and the authors attributed this to declining smoking rates and changes in exposure to tobacco smoke (Tellez-Plaza et al. 2012). In this study, the geometric mean urinary cadmium concentrations declined for both smokers and non-smokers, but the ratio between current smokers and never-smokers stayed approximately the same over the years. The concentrations in smokers were approximately twice as high as those in never-smokers. It should be noted that cadmium uptake via inhalation is significantly higher than via the oral route (ATSDR 2012).

Cadmium blood levels have been reported to be in the range of 0.4-1.0 µg/L in nonsmokers and the unadjusted geometric mean in non-tobacco users based on NHANES data from 1999-2008 was 0.30 µg/L (as reviewed in IARC 2012; Naufal et al. 2011). The geometric mean in the U.S. population 20 years and older in 2003-2004 was reported to be 0.378 µg/L (CDC 2009).

Cadmium levels in 24-hr urine of non-smokers were 1.34-8.04 nmol (0.15-0.904 µg) (IOM 2012). The unadjusted geometric mean levels in urine from non-tobacco users based on NHANES data from 1999-2008 was 0.24 µg/g creatinine (Naufal et al. 2011). Never-smokers in 2003-2008 were reported to have geometric mean urinary cadmium levels of 0.19 µg/g creatinine (Tellez-Plaza et al. 2012). The geometric mean in the U.S. population 20 years and

older in 2003-2004 was 0.260 µg/L and corrected for creatinine was 0.268 µg/g creatinine (CDC 2009).

Cadmium Biomarkers in Users of Snus

Two studies have investigated cadmium levels in snus users (Table A III-4 of the ENVIRON Snus Monograph 2013). Ellingsen et al. (2009) measured blood cadmium levels in 11 Norwegian snuff users from a former chlor-alkali worker cohort. Their levels were similar to those of 49 non-smoking controls (mean, 2.9 nmol/L or 0.33 µg/L versus 3.3 nmol/L or 0.37 µg/L, respectively. The control cadmium blood levels in this study are in the range of those reported in the US population (CDC 2009).

In a study that measured time trends in burdens of several metals in the population in Northern Sweden, the authors noted that the use of snus (called moist snuff) had no influence on cadmium concentrations in erythrocytes among never-smoking men: 28 snuff users had median erythrocyte cadmium concentrations of 0.24 µg/L versus 0.26 µg/L as measured in 110 non-smoking non-snuff users (Wennberg et al. 2006). While this study also analyzed lead and mercury erythrocyte concentrations, no distinctions for snuff users were reported.

In summary, levels of cadmium biomarkers in snus users were similar to those detected in non-tobacco users.

6.1.4.1.4. Biomarkers of Selenium

Blood and urinary levels are most often used to detect recent exposures to high levels of selenium (ATSDR 2003). The geometric mean serum selenium concentration reported for the adult US population ages 20-59 years old, based on NHANES data from 1988-1994, was 124.17 µg/L (ATSDR 2003). Further, erythrocyte and blood glutathione peroxidase (GPX, a seleno-protein that protects from oxidative damage) activity is thought to be a biomarker for selenium deficiency, but not overexposure (ATSDR 2003). GPX activity has been shown to be decreased in smokers. While the precise mechanism of this effect is unknown it has been speculated that inflammatory processes caused by smoking might lead to an increased need for antioxidant protection, including by the seleno-protein GPX (ATSDR 2003, as cited in Ellingsen et al. 2009).

Selenium Biomarkers in Users of Snus

In the Norwegian study, mean blood and serum selenium levels in 11 snuff users from a former chlor-alkali worker cohort were similar to those of 49 non-smoking controls: 1.50 µmol/L in blood or 1.55 µmol/L in serum (122.4 µg/L in serum) versus 1.52 µmol/L in blood or 1.54 µmol/L in serum (121.6 µg/L in serum) (Ellingsen et al. 2009). The control selenium levels in this study were in the range of those reported for the US population (ATSDR 2003). Further, the geometric mean of selenium serum levels in non-users of tobacco, reported for an NHANES population-based sample in 1999-2008 was in the same range, although slightly higher (unadjusted geometric mean, 137 µg/L) (Naufal et al. 2011).

Mean GPX activity in the snuff users was 140 (106-182) U/L and not statistically significantly different from non-smoking controls (146 (105-203) U/L) (Ellingsen et al. 2009).

In summary, levels of selenium biomarkers in snus users were similar to those detected in non-tobacco users.

Radionuclides Biomarkers

No studies were identified in which biomarkers of radionuclides were measured in users of snus, new products marketed as snus, or other STPs.

Biomarkers of Other Trace Levels Components

No studies were identified in which biomarkers of other trace level components were measured in snus users. More information on biomarkers of other trace level components is provided in the ENVIRON Snus Monograph (2013), Appendix III Section 3.2.6, where available data for new products marketed as snus and/or US STPs in comparison with smoking is discussed.

6.1.4.1.5. Discussion and Summary of Biomarkers of Snus

Biomarkers may be used to assess the actual internal dose of a tobacco component to which a tobacco user might be exposed. While limitations to the available biomarkers exist, they can be used to supplement information from product analyses as they reflect total exposure, bypassing differences in routes of exposure and product use behavior. In addition, biomarker levels on a population basis may give an indication of general trends in internal exposure to certain components of a well characterized product. With respect to harm reduction, conclusions from these studies should be interpreted carefully and in the context of additional data from clinical and/or epidemiological studies.

A panel of biomarkers of components in tobacco products has been recently proposed for the use in product regulations. Many biomarkers are less relevant for non-combusted tobacco products such as snus; however, the panel does include the potentially relevant biomarkers of nicotine, TSNAs, PAHs, aldehydes, cadmium, and acrylamide.

To date, published studies are available that have investigated biomarkers of nicotine, TSNAs, cadmium, and selenium in regular users of traditional Swedish snus.

Commonly measured biomarkers of nicotine are cotinine in plasma or serum. However, their levels may be impacted by the route of exposure, i.e., first pass metabolism of nicotine to cotinine via the oral route may result in higher blood concentrations of cotinine that do not necessarily reflect increased exposure to the parent compound, nicotine. This metabolic pathway does not occur following exposure to nicotine via the inhalation route. Total nicotine equivalents in urine are considered to better represent the total nicotine dose absorbed. Information from nicotine pharmacokinetic parameters is relevant for nicotine delivery, total dose, and abuse liability assessments. The time to maximum plasma nicotine concentrations in snus users appears to be dependent on the usage time, but not on nicotine content or portion size. On the other hand, C_{max} and AUC appear mostly dependent on total nicotine content (per pouch or portion size) as well as pH of the product. Whether the snus were loose or pouched had no influence on these parameters.

A number of studies in regular snus users show that mean or median cotinine levels in plasma or serum range from 137 to 399 ng/mL depending on the amount of snus consumed (average 11-32 g/day). In the saliva, average levels ranged from 80 to 343 ng/mL. Urinary biomarkers of nicotine measured in regular users of snus were as follows: for nicotine itself, 29 µg/mmol creatinine; for cotinine, approximately 1000-1210 µg/L; for total cotinine, 5926 µg/L; and for nicotine equivalents was 14.3-35.6 mg/24 hrs.

TSNAs and their metabolites have been determined in various human bodily fluids, including saliva, blood, and urine, as well as in toenails. Urinary NNAL is the most commonly-measured biomarker of TSNA exposure, and is considered to reflect 12-17% of the NNK dose.

Four studies of TSNA biomarkers in users of Swedish snus were identified. Of those, one publication from 1988 measured TSNA levels in saliva during snus use; snus in the 1980s contained considerably higher TSNA concentrations than more contemporary snus products. More recently, urinary total NNAL was measured in users of conventional US STPs that were switched to *General* snus use. Of the two clinical studies available, only one appears to have a sufficient duration to examine for and detect differences in levels before and after the switch. In this study, total NNAL levels decreased significantly (to half the concentration measured at baseline) by week 4. Importantly, urinary total cotinine levels in this study did not change significantly, indicating the decreased toxicant exposure could not be explained by a decrease in tobacco intake and mean product use was similar to that reported for regular snus users. No studies measuring biomarkers of NNN in snus users were identified. POB-DNA adducts were significantly increased in oral mucosa of Swedish snus users based on information provided in a study abstract; however, the importance of these adducts in oral cancer development has been questioned.

With respect to the available studies of biomarkers of metals/metalloids, both levels of cadmium and selenium biomarkers in regular users of traditional Swedish snus were similar to those detected in non-tobacco users.

6.1.4.2. Product Analyses

6.1.4.2.1. Harmful and Potentially Harmful Constituents in Swedish Snus

Unlike combustible tobacco products such as cigarettes, the Snus Products do not expose non-users to the HPHCs they contain. Nevertheless, the product analyses information below assesses users' potential exposure to HPHCs in the Snus Products.[58] These data, coupled with the information regarding actual use of the Snus Products, further support that use of the Snus

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[58] For more information on the levels of HPHCs in Swedish snus, Swedish Match respectfully refers CTP to the company's comment letter submitted to the FDA Docket on "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke," 76 Fed. Reg. 50226 (Aug. 12, 2011).

Products reduces the individual risks of harm and tobacco-related disease associated with cigarettes and other commercially available tobacco products.

As shown in **Table 6-12 (Table 7:13 in SM GOTHIATEK Report 2013)**, the Snus Products' average concentrations (on a dry weight basis) of constituents on CTP's abbreviated list of HPHCs for smokeless tobacco products are as follows:

- Three HPHCs (i.e., arsenic, benzo[a]pyrene and crotonaldehyde) are present at concentrations so low that they were below the limit of quantification (LOQ).

- Two TSNAs are present at extremely low concentrations, around 0.6 ppm for NNN and around 0.2 ppm for NNK. In no case did the addition of the two exceed 1 ppm.

- Cadmium concentrations are consistently around 0.6 ppm, probably reflecting "*naturally occurring soil components and materials that are added to the soil*" (Borgerding et al. 2012).

- Acetaldehyde and formaldehyde are present consistently at approximately 20 and 12 ppm, respectively. It is difficult to present comparative information on these two materials, since there appears to be very little published information available. In addition, since both materials are largely gases at ambient temperatures, the likely dose presented to smokeless tobacco users is questionable.

- Nicotine concentrations are effectively 1.5% for each product, with calculations of "free" nicotine resulting in concentrations of approximately 1.3%. The exception was for General Dry Mint Portion Original Mini, where much lower free nicotine concentrations were reported. The pH of this particular product may be an important factor here.

The data presented in **Table 6-12** for non-tobacco-specific HPHC (rows 1 to 6) are broadly similar to concentrations that have been recorded for foodstuffs, and are therefore toxicologically acceptable. A specific analysis comparing estimated HPHC intakes from snus consumption compared to dietary intakes is presented in the following subsection.

The tobacco-specific items (rows 7 to 10) present data on robust nicotine deliveries, in the absence of significant deliveries of TSNA. The total concentrations of (NNK+NNN) at less than 1 ppm are well below suggestions made by various regulatory authorities (SCENIHR 2008; WHO 2009) for smokeless tobacco products that could be considered to be acceptable-risk MRTPs.

CTP's HPHC List for smokeless tobacco products, albeit in the abbreviated form, produces *de minimis* results for the ten Snus Products which are the subject of this Application. These data integrate well with results of epidemiological studies, where any increases in risk were minimal or absent (Lee 2013a), and with mechanistic data on genotoxicity in Snus Products and other

commercial snus brands, where any results obtained were also minimal or absent (Coggins et al. 2012).

These three different data sets converge to a position of minimal risk to users of Swedish snus such as those described in this Application, certainly compared with users of combustible tobacco products where all three toxicological approaches indicates substantial risk as sequelae of use.

Table 6-12. Average concentrations (dry weight basis) of HPHCs in the Snus Products*

HPHC	General Loose (SKU 4852)	General Dry Mint Portion Original Mini (SKU 4800)	General Portion Original Large (SKU 4880)	General Classic Blend Portion White Large (SKU 4877 and SKU 4878)	General Mint Portion White Large (SKU 4352)	General Nordic Mint White Large (SKU 4876 and SKU 4875)	General Portion White Large (SKU 4881)	General Wintergreen Portion White Large (SKU 4882)
Acetaldehyde (ppm)	21	10	25	20	23	23	20	24
Arsenic (ppm)	<0.10	0.15	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
Benzo[a]pyrene (ppb)	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6
Cadmium (ppm)	0.57	0.59	0.52	0.63	0.53	0.59	0.57	0.45
Crotonaldehyde (ppm)	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25
Formaldehyde (ppm)	10	11	15	11	14	12	15	9.5
NNK (ppm)	0.18	0.18	0.10	0.23	0.22	0.24	0.23	0.22
Nicotine (%)	1.5	1.8	1.4	1.6	1.4	1.6	1.5	1.4
Nicotine (free, %)	1.2	0.37	1.1	1.3	1.2	1.4	1.3	1.2
NNN (ppm)	0.47	0.68	0.39	0.63	0.49	0.60	0.56	0.50

*List includes the HPHCs identified on CTP's abbreviated list for STPs

6.1.4.2.1.1. General Loose (SKU 4852)

Table 6-13. Listing of HPHCs in General Loose (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS Number	Unit of Measure	Quantity of Constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		4
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1		3
4	Cadmium		7440-43-9	µg/g	0.45	0.38-0.53	4
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.21	0.16-0.26	4
8	Nicotine		54-11-5	%	1.48	1.40-1.56	4
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.45	0.37-0.53	4

Table 6-14. Listing of HPHCs in the Tobacco Flour of General Loose (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituent name	Common name	CAS Number	Unit of Measure	Quantity of Constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.22	0.17-0.27	76
8	Nicotine		54-11-5	%	2.20	1.71-2.69	76
9	Nicotine (free)						

10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.65	0.50-0.79	76

Table 6-15. Listing of References to the Analyses of HPHCs in General Loose

Item	Constituent Name	Common Name	CAS number	Method of Measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-16. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Loose

Item	Constituents Name	Common Name	CAS-number	Method of Measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.2. General Dry Mint Portion Original Mini (SKU 4800)

Table 6-17. Listing of HPHCs in General Dry Mint Portion Original Mini (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		4
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1		3
4	Cadmium		7440-43-9	µg/g	0.60	0.40-0.79	4
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.20	0.16-0.24	4
8	Nicotine		54-11-5	%	1.78	1.70-1.85	4
9	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.65	0.60-0.71	4

Table 6-18. Listing of HPHCs in the Tobacco Flour of General Dry Mint Portion Original Mini (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.17	0.04-0.30	7
8	Nicotine		54-11-5	%	2.80	0.73-4.87	7
9	Nicotine (free)						

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.68	0.18-1.19	7

Table 6-19. Listing of References to the Analyses of HPHCs in General Dry Mint Portion Original Mini

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-20. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Dry Mint Portion Original Mini

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
8	Nicotine		54-11-5	(b) (4)		
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.3. General Portion Original Large (SKU 4880)

Table 6-21. Listing of HPHCs in General Portion Original Large (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	0.16	<0.10-0.39	4
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1		3
4	Cadmium		7440-43-9	µg/g	0.43	0.34-0.52	4
5	Crotonaldehyde						
6	Formatldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.26	0.20-0.31	4
8	Nicotine		54-11-5	%	1.45	1.36-1.54	4
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.62	0.47-0.77	4

Table 6-22. Listing of HPHCs in the Tobacco Flour of General Portion Original Large (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.28	0.19-0.36	42
8	Nicotine		54-11-5	%	2.16	1.51-2.82	42

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.75	0.52-0.98	42

Table 6-23. Listing of References to the Analyses of HPHCs in General Portion Original Large

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-24. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Portion Original Large

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.4. General Classic Blend Portion White Large – 15 ct (SKU 4877)

Table 6-25. Listing of HPHCs in General Classic Blend Portion White Large – 15 ct (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		1
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	1.2		1
4	Cadmium		7440-43-9	µg/g	0.49		1
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.36		1
8	Nicotine		54-11-5	%	1.4		1
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.6		1

Table 6-26. Listing of HPHCs in the Tobacco Flour of General Classic Blend Portion White Large – 15 ct (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-27. Listing of References to the Analyses of HPHCs in General Classic Blend Portion White Large – 15 ct

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-28. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Classic Blend Portion White Large – 15 ct

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.5. General Classic Blend Portion White Large – 12 ct (SKU 4878)

Table 6-29. Listing of HPHCs in General Classic Blend Portion White Large – 12 ct (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		1
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	1.2		1
4	Cadmium		7440-43-9	µg/g	0.49		1
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.36		1
8	Nicotine		54-11-5	%	1.4		1
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.6		1

Table 6-30. Listing of HPHCs in the Tobacco Flour of General Classic Blend Portion White Large – 12 ct (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-31. Listing of References to the Analyses of HPHCs in General Classic Blend Portion White Large – 12 ct

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-32. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Classic Blend Portion White Large – 12 ct

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.6. General Mint Portion White Large (SKU 4352)

Table 6-33. Listing of HPHCs in General Mint Portion White Large (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		3
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1		2
4	Cadmium		7440-43-9	µg/g	0.44	0.39-0.49	3
5	Crotonaldehyde						
6	Formaldehyde						
7	4- (methylnitrosamino) -1- (3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.35	0.12-0.58	3
8	Nicotine		54-11-5	%	1.40	1.15-1.65	3
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.66	0.45-0.86	3

Table 6-34. Listing of HPHCs in the Tobacco Flour of General Mint Portion White Large (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-35. Listing of References to the Analyses of HPHCs in General Mint Portion White Large

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-36. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Mint Portion White Large

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.7. General Nordic Mint Portion White Large – 15 ct (SKU 4876)

Table 6-37. Listing of HPHCs in General Nordic Mint Portion White Large – 15 ct (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		1
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	1.1		1
4	Cadmium		7440-43-9	µg/g	0.4		1
5	Crotonaldehyde						
6	Formaldehyde						
7	4- (methylnitrosamino)-1- (3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.3		1
8	Nicotine		54-11-5	%	1.3		1
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.53		1

Table 6-38. Listing of HPHCs in the Tobacco Flour of General Nordic Mint Portion White Large – 15 ct (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)- 1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-39. Listing of References to the Analyses of HPHCs in General Nordic Mint Portion White Large – 15 ct

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-40. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Nordic Mint Portion White Large – 15 ct

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.8. General Nordic Mint Portion White Large – 12 ct (SKU 4875)

Table 6-41. Listing of HPHCs in General Nordic Mint Portion White Large – 12 ct (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10		1
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	1.1		1
4	Cadmium		7440-43-9	µg/g	0.4		1
5	Crotonaldehyde						
6	Formaldehyde						
7	4- (methylnitrosamino)-1- (3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.3		1
8	Nicotine		54-11-5	%	1.3		1
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.53		1

Table 6-42. Listing of HPHCs in the Tobacco Flour of General Nordic Mint Portion White Large – 12 ct (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)- 1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-43. Listing of References to the Analyses of HPHCs in General Nordic Mint Portion White Large – 12 ct

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-44. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Nordic Mint Portion White Large – 12 ct

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.9. General Portion White Large (SKU 4881)

Table 6-45. Listing of HPHCs in General Portion White Large (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0.10	<0.10-0.25	4
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1		3
4	Cadmium		7440-43-9	µg/g	0.48	0.41-0.57	4
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.39	0.15-0.62	4
8	Nicotine		54-11-5	%	1.50	1.37-1.63	4
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.67	0.43-0.90	4

Table 6-46. Listing of HPHCs in the Tobacco Flour of General Portion White Large (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61
8	Nicotine		54-11-5	%	2.19	1.6-2.7	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-47. Listing of References to the Analyses of HPHCs in General Portion White Large

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
4	Cadmium		7440-43-9			
5	Crotonaldehyde					
6	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-48. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Portion White Large

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-	NNK	64091-91-4	(b) (4)		

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
	(3- pyridyl)- 1-buta none			(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.1.10. General Wintergreen Portion White Large (SKU 4882)

Table 6-49. Listing of HPHCs in General Wintergreen Portion White Large (quantity of constituent is based on dry weight per gram of product)

Item	Constituent name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
1	Acetaldehyde						
2	Arsenic		7440-38-2	µg/g	<0,10		4
3	Benzo[a]pyrene	BaP	50-32-8	µg/kg	<1	<1-1.98	3
4	Cadmium		7440-43-9	µg/g	0,45	0.42-0.47	4
5	Crotonaldehyde						
6	Formaldehyde						
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0,33	0.23-0.43	4
8	Nicotine		54-11-5	%	1,38	1.22-1.53	4
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0,61	0.48-0.74	4

Table 6-50. Listing of HPHCs in the Tobacco Flour of General Wintergreen Portion White Large (quantity of constituent is based on dry weight per gram of tobacco flour)

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4	µg/g	0.33	0.25-0.41	61

Item	Constituents name	Common name	CAS-number	Unit of Measure	Quantity of constituent	Confidence Interval 95%	Total # of samples tested
8	Nicotine		54-11-5	%	2.19	1.64-2.74	61
9	Nicotine (free)						
10	N-nitrosonornicotine	NNN	16543-55-8	µg/g	0.90	0.68-1.13	61

Table 6-51. Listing of References to the Analyses of HPHCs in General Wintergreen Portion White Large

Item	Constituent name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
1	Acetaldehyde			(b) (4)		
2	Arsenic		7440-38-2			
3	Benzo[a]pyrene	BaP	50-32-8			
5	Cadmium		7440-43-9			
6	Crotonaldehyde					
7	Formaldehyde					
7	4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone	NNK	64091-91-4			
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

Table 6-52. Listing of References to the Analyses of HPHCs in the Tobacco Flour of General Wintergreen Portion White Large

Item	Constituents name	Common name	CAS-number	Method of measuring	Swedish Match Method	Reference Method
7	4-(methylnitrosamino)-1-(3- pyridyl)- 1-buta none	NNK	64091-91-4	(b) (4)		
8	Nicotine		54-11-5			
9	Nicotine (free)					
10	N-nitrosonornicotine	NNN	16543-55-8			

6.1.4.2.2. Estimated HPHC Intakes from Snus Consumption – Comparison with Dietary Intakes or Smoking

Using the HPHC product analysis data provided by Swedish Match for its products, ENVIRON conducted an analysis that compared estimated daily intakes of these HPHCs from consumption of Swedish Match snus products to intakes from the diet (for details see ENVIRON HPHC Report 2014, attached as Appendix 6C). The exceptions are the TSNAs, for which a comparison with estimated exposure from smoking was made, and the alkaloids, for which intakes from snus are summarized, but not further compared to intakes from other sources. For a comparison of nicotine intake from snus consumption with smoking the reader is referred to the Appendix 3, Section A III 3.1 of the ENVIRON Snus Monograph (2013).

To estimate HPHC intakes from snus consumption, the average concentrations reported under the Swedish Match Brands Testing program in 2012 for each of the eight Swedish Match snus products investigated were obtained from the report, Swedish Snus According to GOTHIATEK (Table 7:21 of the SM GOTHIATEK Report 2013). To estimate "worst case" exposures from snus consumption, maximum values were obtained from Swedish Match Brands Testing 2011 of 45 snus products and, thus, are not specific to the Snus Products (Table 7:20 of the SM GOTHIATEK Report 2013). Average and upper bound snus consumption was obtained from a recent survey of snus users in Sweden (Digard et al. 2009). Where supported by research, adjustments for extraction of HPHCs from snus were made. The "upper bound" intake estimates (using the maximum concentrations in snus products and upper bound snus consumption) represent a "worst case" scenario, assessing consumption of a heavy (upper bound) user of snus who consistently uses the Swedish Match snus product which contains the highest concentration of the given constituent. For HPHCs where no maximum concentrations in snus products were available, "worst case" exposures were not calculated.

For the comparison to dietary intakes, average population-based intakes were obtained from public health agencies, and comparisons to health-based guidelines were also drawn where these values were available for the specific HPHCs. In instances where neither of these values was available, intakes estimated from consumption of certain foods provides context.

For the comparison to smoking, an average of 20 cigarettes per day was assumed, and adjustments for absorption were made. For TSNAs and for some of the other potential carcinogens detected in Swedish snus, cancer risk estimates from published risk assessments were presented and discussed.

Results of the analysis revealed that the estimated daily intakes of all analyzed PAHs, acetaldehyde, formaldehyde, arsenic, chromium, nickel, mercury, selenium, acrylamide, and aflatoxins, even under worst case conditions and assuming 100% extraction, are within or below the average or range of estimated dietary intakes of these components. NDMA intake even under worst case conditions of snus consumption is below the range of the estimated combined intake of NDMA from air, water and food. However, because of the limited amount of data for dietary exposure to NDMA, this comparison remains speculative.

The estimated daily intakes of beryllium under average snus consumption, cadmium under worst case conditions of General Loose Snus consumption, and lead under worst case conditions of snus consumption, adjusted to an extraction rate of 10-50%, are all below or similar to the average dietary intakes of these metals.

The estimated daily intake of Po-210 and uranium (radioisotopes), assuming 100% extraction and average pouched snus consumption, and for ethyl carbamate under worst case conditions of pouched snus consumption, are close to or within the range of average dietary intakes.

Under worst case conditions of snus consumption, Po-210 is on the upper end of what has been reported for dietary intakes in various countries; particular seafood and fish products are a background source of this radioisotope. Under worst case conditions of General Loose Snus consumption, ethyl carbamate is within the range (on the lower end) of intake estimated for the 95th percentile consumption level of different types of alcoholic beverages.

Under worst case conditions assuming the conservative 100% extraction rate, the estimated uranium (radioisotopes) intake from pouched snus products and General Loose Snus is higher than the estimated usual dietary intake. This estimated intake from snus is, however, lower than TDIs and RfDs established based on kidney toxicity. It should also be noted that, although no values for extraction of uranium from snus were available, it is likely much lower than 100%.

While the estimated daily intake of crotonaldehyde from average snus consumption is above the estimated usual dietary intake, it is not higher of what may be ingested from consumption of 100 to 200 g of certain meats or fish and less than what might result from drinking alcoholic beverages, such as a glass of wine.

Dietary intake estimates were not available for acrolein, NSAR, NDELA, and most individual VNAs. Intake of total VNAs (10 VNAs) from average snus consumption was similar to what has been reported for dietary intake by one author for the sum of only four VNAs.

The estimated daily intake of acrolein from average snus consumption is approximately 10 times lower than the current RfD for acrolein. Even under worst case conditions of snus consumption,

the intake of NSAR is not higher than what may be ingested from a small portion of smoked meat. Similarly, NDELA intake from snus consumption is likely in the range of what might be ingested from a small portion of cured meat, but due to the variability of the analytical data for NDELA in the snus products and the lack of reliable data for concentrations in foods, little confidence is given to the comparison of this component.

In summary, for the 39 HPHCs and additional analyzed VNAs and PAHs discussed in this report, concentrations were generally in a close range for all snus products on a per gram basis. Variability in the estimated intakes was largely the result of different portion sizes, consumption patterns, and, to some extent, differences in moisture contents of the products.

Comparisons of the estimates of average and upper bound HPHC intakes from use of any of the eight Swedish Match snus products compared to usual or customary intakes of these components from consumption of foods shows that use of snus results in intakes that are generally either lower or similar to those from food. Much like exposure from foods, however, exposure to these components from snus use is variable and dependent on an individual's product use pattern. This analysis, a comparison between intakes of HPHCs, is not intended to address health risks. Any impact on health risks from the intake comparisons can be inferred from those components in common to both Swedish snus and foods; that is, that any health risks from these exposures would be those that might be subsumed under a usual human diet.

Comparison of the exposure estimates for HPHC components that are part of snus but not part of the diet, such as nicotine and TSNAs, shows that intakes from average snus use are similar to those from the average cigarette smoking. These conclusions are based on several assumptions about extraction and absorption, which may have some uncertainties. It is also not known how the differences in routes of exposure between exposure to cigarettes via inhalation and Swedish snus via the oral route might contribute to health risks even if ultimate exposures to users are about the same.

The strengths of this analysis include the conservative assumptions used in calculating the estimated exposures from Swedish snus as well as for the comparator exposures. The component concentrations that were below the laboratory limits of detection (LOD) were assumed to have a distribution below the LOD and used to generate estimated exposures for several of the HPHCs. The upper range of extractions was also used so as not to underestimate the amount of an HPHC that might be extracted in the mouth during snus use. As discussed in the report, the comparisons with intake from food assume similar extraction and uptake of the HPHCs from food and snus, which is likely not the case, as absorption (and thus exposure) from foods is likely to be more complete because of swallowing and digestion in the gastrointestinal tract. However, any comparison of intakes from snus versus diet will not be able to account for any potential local effects on the oral mucosa.

Sources of variability that contribute to uncertainty in the estimates include use of a single (recent) year of annual mean HPHC concentrations in the eight Swedish Match snus products. Variability within the year, and concentrations from previous years were not considered. The worst case calculations, however, which used the highest reported HPHC concentration from

additional Swedish Match data, and the reported upper bound daily snus consumption, would be expected to capture some of the variability in the laboratory measurements such that estimated exposures from use of Swedish snus for most contemporary users would not likely be higher than calculated in this report. Actual internal/systemic exposures can be measured by use of appropriate exposure biomarkers.

The amounts of HPHCs in foods are also highly variable, and thus estimates of human exposures, which reflect not only the amounts in foods, but factors such as use patterns, extraction and absorption, are also variable. The dietary estimates are not intended to apply to any one individual but are population averages where these data were available and are meant to represent usual intakes.

Though the exposure estimates and cancer risks presented in this report support the epidemiological research on Swedish snus, in which no increased cancer risk has been observed for cancer sites observed in animal studies of TSNAs, such as oral and lung cancers, there are some inconsistencies in the epidemiology for other cancer sites, such as pancreatic cancer, which remain to be confirmed by further research.

Clearly, however, the HPHC exposures to users of Swedish snus are generally no more than that from foods, and for HPHC components unique to tobacco, namely nicotine and TSNAs, exposures from Swedish snus are no more than that of smoking.

6.1.4.2.3. Contraindications for the Snus Products

A contraindication can be defined as "a symptom or condition that makes a particular treatment or procedure inadvisable." Swedish Match uses the term in this Application to indicate situations where use of Swedish snus would not be advisable.

Swedish snus contains tobacco and therefore nicotine, a chemical that has been linked to several fetal and neonatal disorders (Bruin et al. 2010). In snus users the nicotine is quickly absorbed and transferred to the blood (Holm et al. 1992), as is likely also the case in users of NRTs. Similar nicotine absorption occurs in smokers, who unlike snus users, are also exposed to the products of tobacco combustion.

As with all products containing nicotine, the use of Swedish snus is not advisable in women who are pregnant or who are lactating. Thus, Swedish Match believes that use of Swedish snus, including the Snus Products, is contraindicated during pregnancy.

6.1.4.2.3.1. Fetal and Neonatal Effects

Cigarettes

Cigarette smoking—including nicotine exposure—during pregnancy is associated with a large number of adverse fetal, obstetrical, and developmental outcomes (Cnattingius 2004; Howe et al. 2012; USDHHS 2010). Various components of cigarette smoke have been linked with different reproductive outcomes, including the suggestion that carbon monoxide in cigarette smoke is

responsible for lower birth weights for infants born to mothers who smoked during pregnancy (Carmines and Rajendran 2008; USDHHS 2010). In addition, Baba et al. (2012) have suggested that "antenatal exposure to nicotine is involved in the mechanisms by which tobacco use increases the risk of preterm birth."

Paradoxically, smoking during pregnancy has been consistently associated with a reduced risk (by about a third) of pre-eclampsia (England and Zhang 2007). Until very recently, the mechanisms behind this seemingly protective relationship were unknown, but it is now thought that the anti-inflammatory enzyme heme oxygenase-1 and its metabolite carbon monoxide may have a significant role (Ahmed 2011).

NRTs

According to Bruin et al. (2010), NRTs have "been developed as a pharmacotherapy for smoking cessation and [are] considered to be a safer alternative for women to smoking during pregnancy." However, there do not appear to be many studies on the long-term use of NRT during pregnancy (Coleman et al. 2012), and the use of NRT during pregnancy was strongly discouraged (Slotkin 2008). Thus, there do not appear to be any reports on the effect of NRT use on pre-eclampsia.

Animal studies "suggest that nicotine alone may be a key chemical responsible for many of the long-term effects associated with maternal cigarette smoking." (Bruin et al. 2010). Bruin et al. (2010) reviewed the long-term effects of fetal and neonatal nicotine exposure on post-natal health. Based on this extensive review, largely based on animal studies, the authors concluded that "nicotine should no longer be considered the 'safe' component of cigarette smoke. In fact, many of the adverse postnatal health outcomes associated with maternal smoking during pregnancy may be attributable, at least in part, to nicotine alone."

In light of the foregoing, the labeling for NRTs contain important warnings for users who are pregnant or breastfeeding. For example, the insert for Nicorette gum warns that, "[s]moking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known."[59]

Swedish Snus

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. These results have been reproduced elsewhere (Wikstrom et al. 2010a; Wikstrom et al. 2010c), with the authors concluding that the "tobacco combustion products rather than nicotine are the probable protective ingredients against

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[59] *See* Nicorette Label (current version approved Februrary 15, 2012), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018612s061_020066s042lbl.pdf.

pre-eclampsia in cigarette smoke" (Wikstrom et al. 2010c).

Maternal snus use has also been reported to be associated with increased stillbirth (Wikstrom et al. 2010b) and neonatal apnea (Gunnerbeck et al. 2011) when compared with tobacco non-users (Lochen et al. 2012). Based on these data, Swedish Match believes that use of Swedish snus is contraindicated during pregnancy.

6.1.4.2.3.2. Conclusion

As with all products containing nicotine, the use of Swedish snus is not advisable in women who are pregnant or who are lactating. Because both Swedish snus and NRTs deliver nicotine without the combustion products and risks associated with smoking, the cautions (or contraindications) for Swedish snus are expected to be the same as those used for NRTs.

The use of NRTs and smoking cessation medications in pregnant and lactating women is controversial, but it is generally considered to be acceptable when compared with the risks of continued smoking (Coleman et al. 2011; Coleman et al. 2012). Nevertheless, pregnant smokers are well known to have lower risks of pre-eclampsia than pregnant non-smokers (Ahmed 2011), an "advantage" that is not seen in pregnant Swedish snus users (England et al. 2003). In light of this complicated scientific literature, Swedish Match believes that that the use of snus is not advisable in women who are pregnant or who are lactating.

6.1.4.2.4. Toxicology Data on Swedish Snus

This section reviews all scientific papers found describing both *in vitro and in vivo* toxicology studies with Swedish snus, and with STPs other than Swedish snus, where such results may be mechanistically relevant to the toxicologic evaluation of Swedish snus. In particular, this review is limited to work performed using "the types of moist snuff that are used in northern Europe and North America," along with studies using STP components and TSNAs.

Toxicology data on Swedish snus are sparse, likely because the strength of the epidemiology data from Sweden obviates the need to obtain toxicology data retrospectively. Indeed, in its report titled *Scientific Standards for Studies on Modified Risk Tobacco Products*, the IOM recommended that existing epidemiologic evidence "weigh heavily" in CTP's decision making, while preclinical studies would "play relatively minor roles (e.g., providing mechanistic context) in justifying a modified-risk claim for a product that is already on the market" (IOM 2012).

A review of the toxicology testing of STP and oral cancer in laboratory animals has been published by Grasso and Mann (1998). Other reviews of various materials relating to STP in general and oral cancer are also available from the earlier literature, including (Eveson 1981; IARC 1985; Nilsson 1998; Shklar 1999), and from more recent publications including National Toxicology Program (2002). Yet the SCENIHR report states:

> [T]he majority of animal studies of snuff-associated carcinogenesis are old and the results are difficult to interpret. The experimental

> groups tended to be small and/or the animal models used were invasive, with tissue trauma possibly confounding the results. Most of the studies with snuff have been negative or equivocal. Studies with snuff inserted into a surgically created canal of the lower lip of the rat do, however, indicate that snuff has a carcinogenic potential in this model. (SCENIHR 2008)

Notwithstanding this position, SCENIHR concluded, based on very few toxicology data points on STPs, that "[t]hese data coupled with evidence of genotoxic effects of extracts of moist snuff on various in-vitro systems, and the presence of carcinogenic nitrosamines in the products, lead to the conclusion that moist snuff is carcinogenic in animals." Since the SCENIHR report was published, a major review of commercial Swesish snus products have clearly shown that these products have minimal (if any) activity in *in vitro* toxicology systems (Coggins et al. 2012). The role, if any, of TSNAs in STP-induced disease has also been questioned (Nilsson 2011).

6.1.4.2.4.1. *In vitro* Mutagenicity and Genotoxicity Testing

Extracts of Swedish snus (e.g., water, dimethyl sulfoxide, artificial saliva, etc.) and other STPs have been tested in a variety of *in vitro* toxicology assays, using tests designed to predict carcinogenicity in humans (Coggins et al. 2012; Jansson et al. 1991; Neilson et al. 2009; Rickert et al. 2007; Shirname-More 1991a; Shirname-More 1991b).

Mutagenicity of "four popular American moist snuff brands" was studied using a *Salmonella* mutation assay (Shirname-More 1991a). Aqueous extracts of the four (4) brands, and dichloromethane and methanol extracts of one (1) of the four (4) brands, did not produce mutagenicity either in the presence or absence of S9 metabolic activation. Aqueous and organic extracts were mutagenic, however, when treated with "physiological levels" of sodium nitrite (0.25 mM) at acidic pH. These results led the author to conclude that "the STP[s] tested contain polar and non-polar chemicals which become mutagenic in *S. typhimurium* under nitrosation conditions." The chemicals were not identified.

Shirnamé-Moré (1991b) again tested aqueous extracts of American moist snuff using human TK-6 and AHH-1 cells. Extracts showed low levels of mutagenic activity in both cell lines. Following treatment with sodium nitrite, the mutagenicity of both extracts for TK-6 and AHH-1 cells was decreased. The author concluded that "tobacco contains precursors for the formation of mutagens whose activity is not cytochrome P450 mediated."

A more comprehensive set of testing designed to investigate the potential genotoxicity of aqueous and methylene chloride extracts of Swedish snus was reported by Jansson et al. (1991). The test systems included assays for the induction of mutation in four strains of *Salmonella* (described by McCann et al. 1975), sister chromatid exchanges in human lymphocytes, chromosome aberrations and gene mutations in Chinese hamster ovary (CHO) cells, and micronuclei in mouse bone marrow cells. The methylene chloride extract was also tested for the induction of sex-linked recessive lethal mutations in *Drosophila*. Results from the testing of the

methylene chloride extract of Swedish snus were broadly negative (Jansson et al. 1991).

Most of the results obtained for the aqueous extract were also negative, with the exception of chromosome aberrations in the CHO cells, with and without metabolic activation. The CHO activity was considered by the authors to be attributed to "the high salt concentration in one of the batches of the snus." More favorable results were found for the methylene chloride extract than with the aqueous extract. Using a sequential testing model, the probabilities that the two extracts are carcinogenic due to a genotoxic mechanism were predicted to be low. Based on these results, the authors concluded that "the carcinogenic potential of Swedish 'snus' should be considered to be low, a conclusion in agreement with the low incidence of oral cancer in Sweden compared to other countries" (Jansson et al. 1991). In contrast, a recent review (DeMarini 2004) concluded that cigarette smoke is markedly genotoxic, using similar methods as those described above.

The most recent *in vitro* evaluation (Coggins et al. 2012) tested commercial and experimental Swedish snus, along with a reference moist snuff (i.e., Kentucky 2S3). A comprehensive study report is found in Appendix 2M. No positive results were reported for both the commercial and experimental Swedish snus in any of the assays, even at very high doses.

Three *in vitro* genotoxicity assays were used:

- Aqueous extracts of the commercial Swedish snus (1), *General Original Portion Large*, (2), *Catch White Portion Large, Licorice*, and (3), *Catch Dry White Portion Mini, Licorice,* did not induce clear increases in mutation frequency in five strains of *Salmonella typhimurium,* both in the presence and absence of S9 (a procedure also known as the "Ames test"). Data obtained for negative and positive controls confirmed that the test system was working correctly.

- Aqueous extracts of the commercial Swedish snus (1), *General Original Portion Large*, (2), *Catch White Portion Large, Licorice*, and (3), *Catch Dry White Portion Mini, Licorice,* did not induce clear increases in mutation frequency in L5178Y $tk^{+/-}$ cells, both in the presence and absence of S9 (a procedure also known as the "mouse lymphoma assay"). Data obtained for negative and positive controls confirmed that the test system was working correctly.

- Aqueous extracts of the commercial Swedish snus (1), *General Original Portion Large*, (2), *Catch White Portion Large, Licorice*, and (3), *Catch Dry White Portion Mini, Licorice,* did not induce increased numbers of micronucleated binucleate Chinese hamster fibroblast cells *(*a procedure also known as the "micronucleus test"). Data obtained for negative and positive controls confirmed that the test system was working correctly.

A related *in vitro* test that is commonly used in combination with the above assays is the neutral red uptake (NRU) assay, a test for cytotoxicity. Cytotoxicity is a major concern in genotoxicity assays (dead cells cannot mutate), and this factor has the potential to confound the interpretation of negative results.

- Aqueous extracts of the commercial Swedish snus (1), *General Original Portion Large*, (2), *Catch White Portion Large, Licorice*, and (3), *Catch Dry White Portion Mini, Licorice*, did not produce obvious differences between the cytotoxicity results obtained using Balb/c 3T3 cells. Data obtained for negative and positive controls confirmed that the test system was working correctly.

The authors concluded that "these negative findings in a laboratory setting concur with the large amount of epidemiological data from Sweden, data showing that three different brands of commercial Swedish snus are associated with considerably lower carcinogenic potential when compared with cigarettes."

6.1.4.2.4.2. *In vivo* Testing

Hamster Cheek Pouch and Oral Mucosa

Cheek pouches are a unique anatomic feature of Syrian golden hamsters (*Mesocricetus auratus*). The pouches are a cavernous "out-pouching" of the oral cavity on both sides, extending alongside the head and neck to the shoulders. The pouches are used to store food and allow the hamster to transport food from where it is gathered to the den or nest. The numerous early studies with STPs and the hamster cheek pouch and oral mucosa have been reviewed by Grasso and Mann (1998) who concluded that STP were not carcinogenic in this animal model. Subsequent studies by Ashrafi et al. (1992); Alonge et al. (2003); Barley et al. (2004); Summerlin et al. (1992) are reviewed below.

The cheek-pouch carcinogenesis model in Syrian golden hamsters is probably the best known animal system that is closely comparable with the development of pre-malignant and malignant lesions in human oral cancer. This makes it one of the most well-characterized animal system models for studying squamous cell carcinogenesis (Chen et al. 2005; Schwartz et al. 2000; Slaga and Gimenez-Conti 1992). The cellular and molecular changes that occur in the hamster cheek pouch carcinogenesis process have been compared to the mouse-skin system, in which a number of critical events have been well characterized (Slaga and Gimenez-Conti 1992). This article describes multiple applications of 7,12-dimethylbenz(a)anthracene ("DMBA"), showing papillomas and squamous cell carcinomas after as short a period of administration as 10 weeks (Slaga and Gimenez-Conti 1992).

Ashrafi et al. (1992) used conventional light microscopy, transmission- and scanning-electron-microscopy to examine the hamster cheek pouch after 24 months of treatment with STPs. Two grams of a "commercially available" STP were placed into the blind end of the right cheek pouch of each experimental animal, once a day five days a week, for 24 months. The control animals did not receive the STP. No tumors were seen in this study. The long-term histological and electron-microscopic changes produced by STP treatment were correlated with each other and were considered to be "similar to those reported in human leukoplakia without dyskeratosis" (Ashrafi et al. 1992).

Archived cheek pouch tissues from this study (Ashrafi et al. 1992) were re-examined using novel

techniques by Alonge et al. (2003). Volume densities of mitochondria were assessed by morphometry. In both control and experimental groups mitochondria were concentrated between the nucleus and basal cell plasma membrane. A decrease in the mean mitochondrial volume density (Vvmit) was observed from the basal layer to the more superficial layers in both groups. The STP-treated cheek pouch epithelium displayed more mitochondria than the control, and the granular epithelial cell layer in the treated group showed a significantly higher mean Vvmit than the control group ($P = 0.03$). The authors concluded that greater numbers of mitochondria were retained in STP-treated granular cells of the hyperplastic epithelia than in the normal epithelium, with unknown toxicological significance (Alonge et al. 2003).

Barley et al. (2004) conducted analyses to determine the component(s) of STPs that might be responsible for the changes previously reported. The authors hypothesized that tobacco-related compounds are cytotoxic and induce quantifiable DNA single-strand breaks in immortalized hamster cheek pouch (POII) cells, and that an amino acid marker of peroxynitrite (ONOO-), namely, 3-nitrotyrosine (3-NT), is detectable in hamster cheek pouch tissues chronically exposed to these compounds (Barley et al. 2004). A dose-dependent decrease in POII cell viability with increasing tobacco-related compound concentrations was reported, as well as a dose-dependent increase in DNA strand breaks. Semi-quantitative immunohistochemistry showed intense 3-NT immunoreactivity in hamster tissues treated with tobacco-related compounds compared with controls ($p < 0.005$). The authors concluded that "tobacco-related compounds, including nicotine, are genotoxic, and that 3-NT is a quantifiable marker of ONOO- damage in intact hamster cheek pouch tissues" (Barley et al. 2004).

Summerlin et al. (1992) used the hamster cheek pouch in a study designed to determine the histologic effects of combined exposures to a commercial STP and ethyl alcohol. Eighty (80) hamsters were divided into four (4) groups: STP only, alcohol only, STP and alcohol, and "negative" (untreated) control. Two hundred (200) mg of STP were placed in each pouch of the two tobacco groups five times a week. In the alcohol groups, 2 ml of 15% ethyl alcohol were placed in each pouch five times a week. The negative control group had mechanical stimulation of the right pouch to simulate the placement of the STP. After 26 weeks, significant acanthosis of the pouch epithelium was noted in the STP and STP plus alcohol groups. According to the authors, "this study reaffirms the lack of carcinogenic potential of smokeless tobacco upon the hamster pouch mucosa and internal organs." The authors also suggested that the increased thickness of the epithelia of the pouch was similar to that noted in human STP users (Summerlin et al. 1992).

Artificial Lip Canal in Rats

A surgical procedure to produce a "lip canal" in rats has been used to implant STPs (Hecht et al. 1986; Hirsch et al. 1986; Hirsch and Johansson 1983; Hirsch and Thilander 1981; Schwartz et al. 2010) and other solid products. The surgical procedure used to create the canal causes a substantial inflammatory response. After healing, a mildly hyperplastic epithelium remains with formation of scar tissue, for up to 13 months (Hirsch and Thilander 1981). It is difficult to meaningfully interpret findings in animals with such compromised tissues.

Hirsch and Thilander (1981) injected test material, namely 0.2 - 0.4 g of STP, twice daily for

nine (9) months into lip canals that were open at both ends with a plastic syringe and the inserted material was retained for "5-8 hours". After 9 months, the epithelium of the canal was found to be mildly to moderately hyperplastic, and the adjacent connective tissue exhibited an inflammatory reaction which varied in degree from mild to severe (Hirsch and Thilander 1981).

Hirsch and Johansson (1983) subsequently used this model in a study of the long-term application of STP, using twice-daily applications for up to 22 months. After 9-12 months of treatment, the squamous epithelium of the canal exhibited mild to moderate hyperplasia, with mild to moderate inflammation in the underlying connective tissue (Hirsch and Johansson 1983). The lesions in the epithelium and submucosa showed virtually no further changes (such as neoplasia) during the course of the study.

Hecht et al. (1986) also used the rat lip canal in a two-part experiment that examined the roles of STPs and TSNAs. In the first part, a test canal was surgically created in the lower lip of groups of 21-32 rats and either STP, a water-extract of STP, or STP enriched with water extract were inserted in the test canal five (5) times weekly for 116 weeks. A group of ten (10) control rats had surgery only. Among the 32 rats treated with STP, three had oral cavity tumors; one was a squamous cell carcinoma originating in the test canal and invading the gingiva, one was a papilloma of the test canal, and one was a papilloma of the hard palate. Oral cavity tumors were also observed in 2 of 21 rats treated with water-extracted STP and 1 of 32 rats treated with STP enriched with water extract. Oral tumors were not observed in control rats, and the differences in tumor incidences among the groups were not statistically significant. Based on these results, the authors concluded that "snuff can induce oral cavity tumors in F344 rats," which they suggested "support the epidemiological observations which indicate that snuff dipping causes oral cancer in man" (Hecht et al. 1986).

Notwithstanding serious concerns over relevance because of background inflammation, Schwartz et al. (2010) conducted a study of four STPs, including the commercial Swedish snus Ettan using the rat lip canal model over a 12-month period. The authors concluded that "while all [smokeless tobacco] products caused dysplasia, the products with lower levels of TSNA and un-protonated nicotine caused less, consistent with the model that tobacco with low levels of nitrosamines might potentially induce fewer carcinomas in human users." The concentrations of TSNA in the four products tested ranged from 64 to 0.28 ppm; the concentration in the Swedish snus product was reported to be approximately 5 ppm. However, this concentration is questionable, since in 2010, the manufacturer reported a TSNA concentration in *Ettan* Swedish snus of approximately 1.4 ppm. Moreover, the Swedish snus produced much less pronounced changes in the oral mucosa of treated rats than the STPs with much higher TSNA values (Schwartz et al. 2010). Using a cell proliferation assay, Swedish snus did not show any differences from the control treatment (Schwartz et al. 2010).

Mouse Oral Mucosa

Kim et al. (2002) used SENCAR mice (i.e., a mouse strain SENsitive to CARcinogens, commonly used in tobacco skin painting experiments (Meckley et al. 2004) to examine oral mucosal carcinogenesis. In this study, thirty (30) SENCAR mice were initiated by brush application of palatal, buccal and tongue mucosa with 200 nmol DMBA using 3 treatment

regimens, and promoted by brush application of 5 nmol 12-O-tetradecanoylphorbol-13-acetate ("TPA") for a total of 28 weeks. In addition, five (5) mice were treated with 0.5% 4-nitroquinoline-1-oxide ("4NQO"), a positive control in studies of oral carcinogenesis, for 28 weeks. Another control group of six (6) mice was treated with vehicle alone. The tumor samples were analyzed for the presence of H-ras codon 61 gene mutations using a mutant-allele-specific amplification-polymerase chain reaction (MASA-PCR) technique (Kim et al. 2002).

Among the group of twenty-four (24) mice initiated with DMBA for 2 or 6 weeks, a range of lesions were seen on the buccal mucosa comprising papillomas, papillomas with dysplasia and 7 squamous cell carcinomas (SCC). In the six (6) mice initiated with 1 week of DMBA, only papillomas developed. In the five (5) mice treated with 4NQO, one (1) developed papillomas with dysplasia and two (2) had SCCs in the tongue mucosa but not the buccal mucosa. Both carcinogens induced codon 61 mutation of the H-ras gene at a high frequency. The results indicated that DMBA/TPA and 4NQO in SENCAR mice reliably produced pre-neoplastic and malignant oral cavity lesions, which the authors considered to "resemble the multi-stages for human oral carcinogenesis". The authors concluded that "SENCAR mice can be used as a model of oral carcinogenesis with the potential for detailed molecular studies of neoplastic progression to SCC" (Kim et al. 2002).

Initiation/Promotion Experiments

The concept of initiation and promotion in carcinogenesis has received considerable attention (Armitage and DOLL 2004), as was noted above with respect to the mouse skin painting assay with SENCAR mice (Meckley et al. 2004).

Johansson et al. (1989) used this concept to evaluate whether STPs possessed any "promoting" activity in rats subsequent to an "initiating" treatment with 4NQO. A total of 150 male Sprague-Dawley rats were used with the lip canal surgery mentioned above (Hirsch and Johansson 1983; Hirsch and Thilander 1981). The animals were randomized into five groups of 30 each. Group I received "snuff" twice a day, 5 days per week. Group II was painted with propylene glycol (solvent control) on the hard palate 3 times a week for 4 weeks; Group III were painted on the hard palate with 4NQO dissolved in propylene glycol, 3 times a week for 4 weeks; Group IV received 4NQO as in Group III, followed by "snuff" application as in Group I; and Group V received a cotton pellet dipped in saline twice a day, 5 days a week. Treatment continued for up to 108 weeks.

There was no significant difference in mean survival time between the groups. Squamous cell tumors of the lip, oral and nasal cavities, esophagus, and fore stomach were seen in Groups I (snuff), III (4NQO), and IV (4NOQ followed by snuff). Nine (9) tumors of these organs were found in Group I (i.e., six carcinomas and three papillomas), nine (9) in Group III (i.e., seven carcinomas and two papillomas), and ten (10) in Group IV (i.e., eight carcinomas and two papillomas). The difference between each of these groups and the control groups (II and V) with regard to tumor incidence was statistically significant ($P<0.05$). In Group I, four oral cavity or lip carcinomas were found in 29 rats, a significant difference in relation to control rats ($P<0.05$). In addition, hyperplastic lesions of the lip, palate, and fore stomach were significantly more common in Groups I and IV compared with Groups II, III, and V. Initiation with 4NQO

followed by snuff did not significantly promote tumor formation. The complicated study design and poor use of controls make these results difficult to interpret.

Larsson et al. (1989) conducted a much smaller study to examine whether STPs could promote the carcinogenicity of 4NQO, again using rats with artificial lip canals. The study did not show any promoting effects of "snuff" in the oral cavity after initiation with 4NQO.

A third study by Johansson et al. (1991) examined the effect of STP on rats treated with either 4NQO or DMBA. Two hundred and thirty rats were randomized into six (6) groups, five containing forty (40) rats and one containing thirty (30) rats. After two weeks of recuperation from the surgery, the animals were treated as follows: Group I was initiated with DMBA 3 times/wk for 4 weeks, followed by cotton pellet administration. Group II was initiated with DMBA for 4 weeks followed by STP twice a day, 5 days/week. Group III received STP twice a day, 5 days/week. Groups IV and V were initiated with 4NQO 3 days/week for 4 weeks. Thereafter, Group IV received a cotton pellet once a day, 5 days/week, and Group V rats were treated with STP twice a day, 5 days/week. Group VI received cotton pellet only, 5 days/week. Treatment of all groups continued for a maximum of 104 weeks.

Results showed that Group V rats had a significantly lower mean survival time than did the other groups because of the development of lip sarcomas in 66% of the rats as compared with 23% in Group II and 26% in Group III. One rat in each of Groups IV and VI developed lip sarcomas. The increased incidence of sarcomas in Group V as compared with the other groups was statistically significant ($P<0.05$). Spindle cell proliferation, a possible precursor lesion of lip sarcoma, was found in five (5) rats of Group II, seven (7) of Group III, and four (4) of Group V. These results show that STP has "strong promoting capability" for the development of lip sarcomas after 4NQO initiation, but not after DMBA initiation. STP by itself caused three squamous carcinomas of the palate, two squamous cell papillomas of the lip, and ten lip sarcomas in 38 rats—as compared with one lip sarcoma in 30 control rats. The 4NQO was used at a much higher dose than in previous studies (Grasso and Mann 1998).

STP Feeding Studies

Homburger et al. (1976) conducted a chronic feeding study to investigate systemic carcinogenic effects of STP in inbred Syrian hamsters. Male Syrian hamsters, aged 60-90 days, received a standard diet reduced in caloric content by the inclusion of 20% methylcellulose for two years. Alternative treatments included a diet containing 20% STP (powdered tobacco), or 50 (5mg) gavages of 20-methylcholanthrene ("MC") (which is assumed to be a non-carcinogenic dose) in addition to chow, or 50 (0.5mg) gavages of MC with a cellulose-containing diet, or 50 (0.5mg) gavages of MC with a diet containing 20% STP (Homburger et al. 1976). As noted by others (Grasso and Mann 1998), "the dietary concentrations, in most groups, was much higher than that normally used for non-toxic materials (5%) in these types of experiments, suggesting that the dose level was sufficiently high to reveal any potential carcinogenicity." The presence in serum of cotinine derived from nicotine, together with food consumption and body weight studies, confirmed the ingestion of STP. Tumors in the MC-fed animals demonstrated the "susceptibility of the two inbred lines of Syrian hamsters used in this study."

The only effect of STP noted was a slower growth of the animals in one of the inbred lines, but not in the other. The authors concluded that 20% STP in the diet is neither carcinogenic nor co-carcinogenic for these animals (Homburger et al. 1976). The authors stated "it is especially noteworthy that there were no tumors of the oral cavity, salivary glands, esophagus, nasopharynx, larynx, urinary bladder, gonads, or ear ducts in any of these animals" (Homburger et al. 1976). Physiologic parameters were measured in sub-groups of animals (i.e., for only one of the inbred strains) after two years of treatment. Heart rate, blood pressure (systolic and diastolic), ECG tracings, and packed cell volume were not affected by chronic feeding of STP at 20% inclusion in the diet (Homburger et al. 1976).

Theophilus et al. (2012) recently conducted a 90-day feeding study using snus-like products in rats and mice at nicotine doses of up to 120 mg/kg/day. Key effects such as body weight reductions and organ weight changes occurred in rats and mice predominantly at the highest doses of test articles and positive control in the absence of treatment-related gross or histopathological changes. The doses evaluated spanned the no observable adverse effect level, the lowest observable adverse effect level and the maximum tolerated dose.

Drinking Water (NNK, NNAL, 4NQO)

Rivenson et al. (1988) assayed the tobacco-specific N-nitrosamine NNK and its major metabolite NNAL for carcinogenicity in male F344 rats by lifetime (108 to 128 weeks) administration in the drinking water. Groups of 30 to 80 rats were supplied with drinking water containing 0.5 ppm, 1.0 ppm, or 5.0 ppm of NNK; 5.0 ppm of NNAL; and water only in the control group. As in previous assays with NNK, the lung was the principal target organ.

Lung tumor incidences in the 0.5, 1.0, and 5.0 ppm groups were 9/80, 20/80, and 27/30, respectively, compared to 6/80 in the control rats. At the lower NNK doses and in the controls, the lung tumors were largely adenomas, but at the highest NNK dose there was a shift to adenocarcinomas, adenosquamous carcinoma, and squamous cell carcinoma. The NNAL response in the lungs was very similar to that of the highest NNK dose. None of these incidences were statistically significant (i.e. $P>0.05$), however, the NNK dose-response was found to be statistically significant ($P<0.005$). Tumors of the nasal cavity (both olfactory and respiratory epithelia) and liver tumors (mainly adenomas) were observed, mostly in the rats treated with 5.0 ppm of NNK (Rivenson et al. 1988).

Tumors of the exocrine pancreas were observed in 5/80 and 9/80 rats treated with 0.5 and 1.0 ppm of NNK, respectively, but in only 1/30 rats treated with 5 ppm of NNK. The majority of these tumors (88%) were acinar adenomas; only two (12%) were acinar adenocarcinomas. Of the rats treated with NNAL, three (3) had acinar adenomas, one (1) had an acinar adenocarcinoma, and four (4) had ductal adenocarcinomas. There was one (1) acinar adenoma in a control rat. The only incidence of pancreatic tumors to reach statistical significance ($P<0.05$) was the 8/80 acinar adenomas in the 1 ppm NNK group (Rivenson et al. 1988).

The authors stated that this "is the first example of pancreatic tumor induction by a constituent of tobacco smoke. It is also the first finding of duct-like carcinomas in the rat pancreas, including one tumor containing epidermoid, keratin-generating tissue." The main finding of the study was

that lung adenocarcinomas can be produced by treating rats over their lives with NNK (or NNAL) in the drinking water. The pancreatic responses were much less pronounced than were those in the lung, and most did not reach statistical significance (both benign and malignant tumors). There were no reports of oral tumors (Rivenson et al. 1988).

Tang et al. (2004) used a mouse model with 4NQO in the drinking water to induce tumorigenesis in the oral cavity. The 4NQO was delivered by either tongue painting, or by addition to the drinking water, of CBA and C57Bl6 mice. After treatment for 16 weeks with drinking water, "massive tumors were observed on the tongues of both CBA and C57Bl mice." There were 3-6 large papillomas per mouse and multiple squamous cell carcinomas over the surface of the tongue. Esophageal papillomas and squamous cell carcinomas were also observed, with no other tumors observed in the remainder of the digestive tract. The incidence of carcinogenesis was much higher when the 4NQO was delivered in the drinking water than when painted on the tongues. The authors concluded that their results "indicate that this murine 4NQO-induced oral and esophageal carcinogenesis model simulates many aspects of human oral cavity and esophageal carcinogenesis" (Tang et al. 2004).

Extracts of STP

Topical applications have been used to investigate the effects of STP extracts on oral carcinogenesis (Hecht et al. 1986). The tumorigenic activities toward the oral cavity of STP, its extracts, and the TSNAs N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were evaluated in male F344 rats. In this study, groups of 21-30 rats were treated beginning at age 10 weeks by swabbing of the oral cavity for 131 weeks with either (a) water, (b) a water extract of STP, (c) a water extract of STP enriched with ten times its indigenous concentration of NNN and NNK, or (d) a solution of NNN and NNK in water. The authors reported that the total doses of NNN and NNK administered over the 131 weeks in groups (c) and (d) were approximately the same, at approximately 100,000 and 20,000 μg/rat, respectively.

The incidence of oral cavity papillomas (small, benign epithelial tumors) in the rats treated with NNN and NNK was 8/30, compared to 0/21 in controls—which was a statistically significant difference. According to the authors, these results demonstrated that "NNN and NNK at the doses used can induce tumors locally in the oral cavity of F344 rats." No tumors were observed in rats treated with the STP extract alone. Papillomas were observed in 3/30 rats treated with the STP extract enriched with NNN and NNK, but these results were not statistically significant. The cumulative NNN and NNK doses administered were the same in the "enriched STP extract" and "neat TSNA" group (see above), suggesting that the STP extract in some way ameliorates the tumorigenic activity of "neat" NNN and NNK.

A total of four (4) adenocarcinomas were noted in the lungs in the group treated orally with NNN / NNK (Hecht et al. 1986). According to the authors, this confirmed that "NNK is a potent carcinogen in laboratory rodents that, independent of the route of administration, induces primarily lung adenocarcinomas" (Prokopczyk et al. 2005).

Viruses and STPs

Most oral cancer is etiologically linked to the use of tobacco and/or alcohol. Nearly two decades ago, evidence was produced for the presence of viral nucleic acids in oral squamous cell carcinoma ("OSCC") tissues. Subsequently, human papillomaviruses ("HPV") in particular have been implicated in OSCC (Hansson et al. 2005). Antibody responses to HPV are seen and HPV-DNA is detected in tumors, the virus being mainly HPV-16, the genotype associated with ano-genital cancer (Scully 2005). Recent studies have indicated that HPV may be etiologically important in some types of oropharyngeal cancer, at least in tonsillar carcinogenesis, and may represent an alternative pathway in carcinogenesis to the established factors of tobacco and alcohol. One review concluded: "It is likely that HPV plays a role in oral cavity carcinogenesis, though only in a small subset of cases. The difficulty in providing true causal evidence of HPV's role in oral cancer lies in our lack of understanding of the significance of mechanisms by which HPV leads to oral carcinogenesis, as well as limitations in the molecular analysis of HPV" (Ha and Califano 2004).

Studies of patients with OSCC have suggested possible sexual transmission of HPV. However, there do not appear to be any relevant studies from experimental animals which show the extent to which HPV might be involved in a neoplastic process or whether external agents can influence their possible activity (Talbot and Crawford 2004).

The other family of viruses that has been associated with oral neoplasia is the herpes simplex virus ("HSV"). Recent reports have indicated that HSV-1 may have a role in the treatment of oral cancer (Shillitoe and Pellenz 2005). There have also been several investigations into the role of STPs in experimental animals infected with HSV-1 (Grasso and Mann 1998), including reports of the inhibition of HSV-1 lesions by STP (Larsson et al. 1992; Sand et al. 2002; Stich et al. 1987). Other studies have investigated HSV-1 and 4NQO as possible "initiators" and STP as a "promoter", with no overall evidence for interactions between the two treatments (Hirsch et al. 1984; Larsson et al. 1989; Park et al. 1986). For these reasons, it is currently difficult to present an overall view on the interactions between HSV-1 infection, STP use, and oral cancer.

Transgenics

There have been recent reports on toxicologic studies with STP in transgenic mice (Song et al. 2010; Stenstrom et al. 2007). However, the value and interpretation of these studies is uncertain, at least until they have been replicated by others.

6.1.4.2.4.3. Conclusions

Although epidemiologic evidence, supported by biomarker data, should weigh most heavily in CTP's assessment of a proposed MRTP, non-clinical studies can still play a minor role in justifying a modified-risk claim. In *in vivo* studies, test material was administered mixed in the diet, placed in hamster cheek pouches, or inserted into surgical lip canals in rats. No tumors were reported in any of these studies. In addition, no cancer or other systemic effects were observed in a lifetime feeding study in rats, with STPs constituting 20% of the diet.

In the studies of individual chemicals and STP extracts, the test material was administerd via hamster cheek pouches, surgical lip canals, swabbing of the oral cavity, and additions to the

drinking water. No tumors resulted from treatment with STP extracts, unless the extracts used to swab the oral cavity were enriched by the addition of NNN and NNK. In these cases, small numbers (3) of oral papillomas were reported. Oral tumors were also observed in significant increases over controls with "neat" NNN and NNK, and with use of the positive control, 4-nitroquinoline oxide.

There are clear limitations in the reported *in vivo* and *in vitro* studies of STPs and their components reviewed above, as the test material does not lend itself well to classical toxicological assays. Treatment-induced results can in many cases be due instead to the highly invasive nature of the treatment, leading to considerable difficulties in interpretation of reported findings. Probably the best overall conclusion from these studies is that state-of-the-art genotoxicity assays on commercial Swesih snus products using simple extraction techniques and modern products (Coggins et al. 2012) concur with available epidemiology data. Further, it is difficult to see a novel toxicology assay used with STP having the ability to modify this concurrence.

6.1.5. References

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6.2 Effect on Tobacco Use Behavior among Current Users

6.2.1. Overview of Swedish and US Data

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

1. the likelihood that current tobacco users will start using the proposed MRTP;

2. the likelihood that tobacco users who adopt the MRTP will switch to or back to other tobacco products that present higher risk;

3. the likelihood that consumers will use the MRTP in conjunction with other tobacco products;

4. the likelihood that users who may have otherwise quit using tobacco products will instead use the MRTP; and

5. the likelihood that consumers will use the MRTP as intended.

Swedish Match provides below a summary of the available scientific evidence which addresses these areas of investigation. Most of the data relating to snus use and behavior patterns, including its effect on current tobacco users, were generated on populations in Sweden and other Scandinavian countries where snus use is common. There is little data relating specifically to

snus use in the United States due to the low rate of use.[60] Most of the relevant US studies considered the broad general category of smokeless tobacco products ("STPs") which, in addition to Swedish snus, includes products which are more commonly used in the United States such as moist and dry snuff and chewing tobacco. Nevertheless, as discussed below, the Swedish data are voluminous, compelling, specific to snus, and thus highly relevant to this MRTP Application. These Swedish data establish that (i) there is conclusive evidence of switching from smoking to snus use at both the population and individual levels, (ii) switching from cigarettes to snus is more common than switching from snus to cigarettes, and (iii) snus has been used as a smoking reduction and cessation aid by individuals in Sweden.

The general summary below is immediately followed by a more detailed analysis of the relevant data which addresses the specific questions posed in the MRTP Draft Guidance.

6.2.1.1. Usage Rates

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

U.S. data: In the United States, combined data for all forms of STPs[61] show that current (both daily and occasional) use is reported by approximately 7% of males and less than 1% of females. Currently, there are no published data to determine the proportion of snus use separately from total STP use in the United States. Similar to the trend observed in Sweden, the rate of STP use has remained stable since 2000, as have the rates of smoking. There is also a key geographic component to STP use in the United States, as STPs are more commonly used by those living in

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60 The study of tobacco use behaviors in the United States is continuing to develop. CTP is currently collaborating with NIH in the landmark PATH Study, a large, national, representative longitudinal cohort study which will measure tobacco use behaviors and related health effects. The PATH Study prospectively follows almost 60,000 people who are users of tobacco products and those at risk for tobacco-product use ages 12 and older in the United States. The study will examine what makes people susceptible to tobacco-product use; evaluate initiation and use patterns including use of new products, dual use, poly use, and switching of tobacco products; study patterns of tobacco-product cessation and relapse; evaluate the effects of regulatory changes on risk perceptions and other tobacco-related attitudes; and assess differences in attitudes, behaviors, and key health outcomes among racial/ethnic, gender, and age subgroups. The study will also collect biospecimens from adults to analyze biomarkers of tobacco use and disease processes. *See* http://www.pathstudyinfo.nih.gov/UI/HomeMobile.aspx.

61 The term STP includes Swedish snus, as well as a suite of products in the United States, including moist and dry snuff and chewing tobacco.

the southern and mid-western states. Use is also typically higher among those living in rural, less densely populated areas, and it is most common among white Americans and Native Americans as compared to other racial or ethnic groups. US military personnel also represent a subpopulation with higher STP use than the general population. (NSDUH 2004 as cited by Peterson et al. 2007).

6.2.1.2. Gateway Studies

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

U.S. data: The available US studies, which do not address snus specifically, are inconclusive regarding whether prior STP use may be associated with, or lead to, subsequent cigarette smoking among adults. Although most of the study authors concluded that there was some evidence that STPs may be a gateway to cigarette smoking, one well-conducted study (Kozlowski et al. 2003) found non-gateway use to be more common than gateway use. The authors highlighted the importance of determining temporality in studies of tobacco gateway, noting that correlation only is inadequate.

A majority of the US studies in adolescents and young adults found an increased risk of cigarette use among those who reported prior STP use. However, the strength of the association diminished significantly when factors such as access to tobacco, family smoking habits, cultural bans on smoking, and alcohol use were considered. Thus, the U.S. studies underscore the importance (i) of recognizing that tobacco habits are often not permanent during adolescence and (ii) of considering the psychosocial and behavioral variables which may affect smoking initiation.

Recurring limitations in the US gateway studies include study design variations, small and non-representative study populations, especially in youth studies, varying methods to estimate the risk of initiating cigarette smoking, and methods of predicting smoking variables. For example, in evaluating gateway patterns, few studies collected information on the age of tobacco initiation, investigated the initial and subsequent weekly use, and/or used national surveys in their analyses.

6.2.1.3. Transitioning and Cessation

Scandinavian data: The available clinical studies in which snus was specifically used for smoking cessation indicate that snus has been used more often than nicotine replacement therapies ("NRTs") by Scandinavian males as an aid for smoking cessation, and that such use has resulted in a success rate approximately equivalent to other NRTs. Thus, being a former smoker is common among Scandinavian snus users. These data have also consistently shown that male snus users are more likely to quit smoking than smokers who do not use snus. Indeed, the 2007 SCENIHR report concludes that "observational data from Sweden indicate that snus has been used more often than pharmaceutical nicotine products by some men as an aid to stop smoking. The data are consistent in demonstrating these male snus users are more likely to quit smoking than non-users." Subsequent clinical trials and two meta-analyses in Norway on the use of snus as a smoking cessation tool further support this conclusion. (Fagerstrom et al. 2012; Joksic et al. 2011; Lund et al. 2010; Lund et al. 2011; Rutqvist et al. 2013; Sharp et al. 2008).

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

U.S. data: There are few studies on STP use behaviors and transitioning between STP use and smoking in the United States, and available study findings are equivocal. Some of the US clinical trials and observational studies provide evidence that smokers who use STPs daily are prone to quit smoking. However, other studies suggest that tobacco users are more likely to transition from STPs to cigarette smoking than vice versa, and that smokers who used STPs were not more likely to quit smoking. The studies conducted among adolescents and young adults do not provide evidence of STP use as a cessation aid, though this is likely due in part to the low prevalence of smokeless tobacco use—and particularly snus use—in the United States. (Tomar 2003; Zhu et al. 2009)

6.2.1.4. Initiation

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

U.S. data: The rate of smokeless tobacco initiation in the United States was lower than rates of snus initiation in Scandinavia. Tobacco users in the United States were more likely to initiate

with cigarettes, and at a younger age than for STP initiation. (Tomar 2003; Zhu et al. 2009)

6.2.1.5. Dual Use

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

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

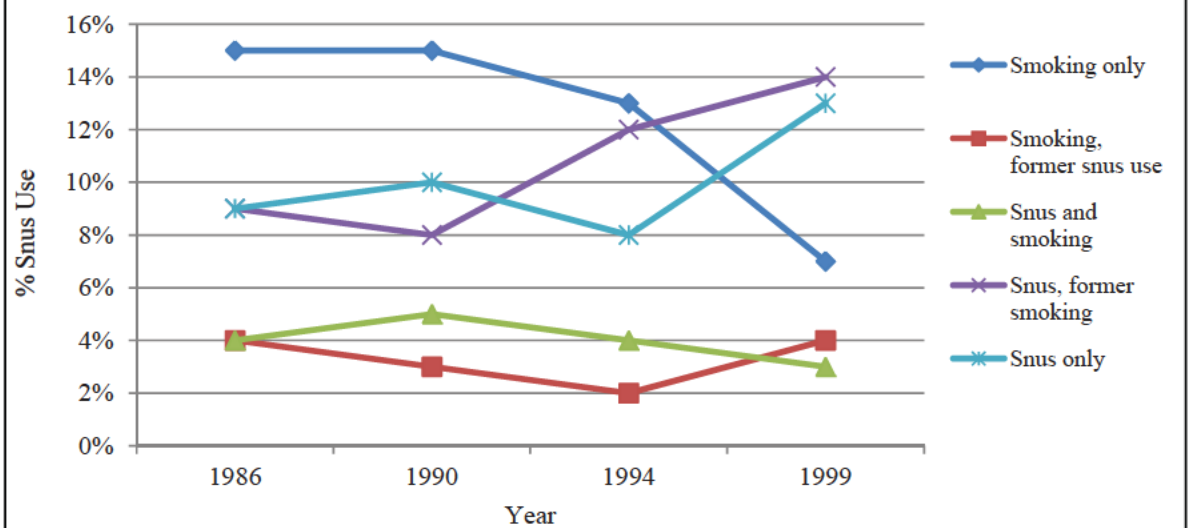
U.S. data: In the United States, the rates of dual tobacco use appear to range from <1 to 3%, but the rates may be higher among those in the military, those living in certain regions of the United States, among males, and by age (i.e., adolescents and young adults appear to have higher rates of dual use). Overall, the US studies reported low rates of switching between tobacco products. Among adults, dual users were most likely to transition to cigarette smoking than to smokeless tobacco use. (Wetter et al. 2002; Zhu et al. 2009).

Prospective studies on dual use patterns among adolescents are limited. Cross-sectional studies among U.S. adolescents showed that dual users were inclined to use STPs or smoke cigarettes either daily or occasionally. The evidence suggests that, in the United States, daily dual users consume fewer cigarettes than exclusive smokers, but some uncertainty exists as to whether dual users have lower rates of overall tobacco consumption

6.2.2. Likelihood that current tobacco product users will start using the product

As shown in **Figure 6-3**, below, between the mid-1980s and 1999, there was a population level shift from smoking to snus use in Northern Sweden (Rodu et al. 2002) that stabilized after 2000.

Figure 6-3: Tobacco Use Trends Among Males in Sweden



Source: Data from MONICA study (Rodu et al. 2002)

Although some women transitioned from cigarettes to snus, the population shift was far more pronounced in men, with a 56% increase in the proportion of those who smoked transitioning to snus use.

Data from the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases project in northern Sweden (which is an area with a high prevalence of snus use) and the Vasterbotten Intervention Programme ("VIP") provide evidence of this population-level transitioning (Lindahl et al. 2003; Rodu et al. 2002; Rodu et al. 2003; Stegmayr et al. 2005). From approximately the mid-1980s to 2007, these studies monitored trends in cigarette smoking and snus use and found a decreasing trend of daily smokers with a corresponding increase in snus users.

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

Lindstrom and Isaacson (2002b) assessed the proportion of adult daily or intermittent smokers that remained intermittent smokers, or became daily smokers, and those that quit smoking at one-year follow up, among participants from the Malmö shoulder-neck study, conducted in southern Sweden . In this study, the prevalence of daily smoking decreased from 23.8% to 21.7% ($p < 0.001$) at the one-year follow-up, while the prevalence of intermittent smoking increased from 4.8% to 5.4% ($p < 0.001$) and the proportion of study participants who had stopped smoking increased from 33.7% to 35.1% ($p < 0.001$). The majority of baseline intermittent smokers (59.9%) remained intermittent smokers, while 15.9% became daily smokers and 19% quit smoking completely. During the follow-up period, snus[62] use was higher in all intermittent smoking categories, intermittent/daily, intermittent/intermittent, and intermittent/stopped; suggesting an association between intermittent smoking and snus use. Notably, more than 90% of intermittent smokers were not snus users; therefore, it was unclear whether smoking cessation could be attributed to either their snus use or their intermittent smoking behavior. The authors concluded that intermittent smokers, or occasional smokers, are transitional stages for many smokers—that is, either an uptake phase of smoking or preparation for smoking cessation. The authors also assessed the psychosocial contributions to smoking cessation and suggested that several factors may contribute to intermittent use patterns compared to daily cigarette smoking. They concluded that intermittent smokers tend to be younger, more highly educated, have higher socioeconomic status (SES) and are less addicted to nicotine than daily smokers (Lindstrom and Isacsson 2002b).

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[62] The study refers to snus as "snuff."

Another prospective study examined patterns of tobacco use among Vasterbotten Intervention Programme cohort participants, which included adults aged 30, 40, 50 and 60 years, with a ten-year follow-up (Lundqvist et al. 2009). In this cohort, 34% of men and 20% of women who quit smoking initiated the use of snus, although a majority of them quit smoking without switching to snus. Among male smokers (n = 1,104), 25.9% quit smoking completely compared to 13.6% who switched to snus; while among female smokers (n = 1,914), it was four times more common to stop smoking without snus than to switch to snus (33% vs. 8.2%). The smoking cessation rate in this cohort was 4% over the 10-year period. The authors noted that this percentage is lower than cessation rates in other studies with shorter follow-up periods and that the rates might reflect the increasing risk for relapse over time. The authors also noted that sustained snus use over the follow-up period was common for both males and females, however, it was more common to remain nicotine free than to switch to cigarette smoking for those who were snus free at follow-up. Lundqvist et al. (2009) suggested that the sustained use of snus over the follow up period suggested a prolonged state of nicotine addiction; Norberg et al. (2011) have also suggested that snus use may prolong nicotine addiction.

The results from cross-sectional analyses support snus uptake as a cessation tool among adult Swedish male smokers (Furberg et al. 2005; Furberg et al. 2006; Gilljam and Galanti 2003; Lund et al. 2010; Lund et al. 2011; Ramström and Foulds 2006; Scheffels et al. 2012). Although the cross-sectional nature of these studies limits the ability to draw conclusions, they provide evidence for the use of snus as a smoking cessation aid.

In the prospective Swedish SALT survey, adult males who were regular snus users were three times more likely to be former smokers than current smokers at the cross-sectional analyses (Furberg et al. 2005; Furberg et al. 2006). In a retrospective study conducted among former and current Swedish adult smokers, Gilljam and Galanti (2003) found that there was an increased probability of being a former smoker among ever snus user rather than being a current smoker (OR= 1.72; 95% CI: 1.30 – 2.28) or current snus user (OR=1.81; 95% CI: 1.31 – 2.53), considering age, education and use of nicotine replacement therapy. Gilljam and Galanti (2003) also found that the mean duration of abstinence was longer among former smokers who were never snus users than among those who were ever snus users. The authors further reported that having used snus at the latest quit attempt increased the probability of being abstinent by about 50% (OR= 1.54; 95% CI: 1.09 – 2.20). These results suggest that Swedish male smokers who used snus may increase their overall chances of abstinence, though snus may not be a necessary component of smoking cessation at the population level (Gilljam and Galanti 2003).

Two cross-sectional studies published by the Norwegian Institute for Alcohol and Drug Research and UK Centre for Tobacco Control Studies and University of Nottingham surveyed a large sample of Norwegian adults for smoking cessation methods and outcome of last attempt to quit smoking (Lund et al. 2010; Lund et al. 2011). Among former (n = 1,775) and current Norwegian smokers (n = 1,808), snus use (17%) was reported as the most common method for quitting smoking compared to other medicinal nicotine products, such as nicotine patches (4%), nicotine chewing gum (10%), and Zyban (3%). For all quitting methods surveyed, the proportion of unsuccessful quitters (current smokers) was greater than the proportion of successful quitters

(former smokers); however, the ratio of successful to unsuccessful quitters was higher for snus than the other smoking cessation methods (Lund et al. 2010). In addition, total abstinence at time of survey was significantly higher for snus use-only than for any other methods of quitting (OR= 2.66, $p<0.001$). Among smokers who reported using snus to quit (n = 671), 62.4% reported still using snus at time of survey, while only 9.5% of smokers who had used nicotine chewing gum or patch still used these nicotine replacement products; however, 75% of those who were still using snus reported at least some reduction in the amount smoked.

Similar findings were reported by the same researchers in a meta-analysis of seven cross-sectional studies among Norwegian former/current smokers (Lund et al. 2011). The meta-analysis combined studies that provided usable information for calculating the quit ratio for smoking (number of former daily smokers as a proportion of ever smokers in a population), among Norwegian adults, aged 16- 74 years. Quit ratios for the individual studies varied, ranging from 32.2% in a nationally representative sample, among those aged 16-20 years to 67.4% in a student population in Oslo. In general, the quit ratio for smoking was significantly higher for daily snus users than for never snus users (6 out of 7 studies), though, the quit ratio for smoking among those who used snus occasionally was significantly lower compared to never snus users. Overall, former smokers formed the largest group of snus users (6 out of 7 studies); and daily snus use was associated with former smoking while occasional snus use was less likely to be associated with being a former smoker (Lund et al. 2011). Another pooled analysis, by the same researchers, of studies conducted among Norwegian adults who were surveyed as part of Statistics Norway, reached similar conclusions (Scheffels et al. 2012). The authors compared smoking cessation with snus to other nicotine replacement therapies. The study results showed that snus was the most common method for quitting smoking among male participants, while women were more likely to use nicotine replacement therapies. These studies showed that snus was the most prevalent method among all categories of Norwegian smokers and former smokers (Lund et al. 2010; Lund et al. 2011; Lund and Lindbak 2007).

Ramstrom and Foulds (2006) conducted a retrospective analysis of a cross-sectional survey among adult Swedish smokers, and found that among male primary smokers (n = 1,226), approximately one-third started secondary daily snus use. Eighty-eight percent of those secondary snus users had ceased daily smoking completely by the time of the survey as compared with 56% of those primary daily smokers who never became daily snus users (OR= 5.7; 95% CI: 4.9 - 8.1). When considered as the only cessation aid, Ramstrom and Foulds (2006) reported that snus was the most commonly used cessation aid among Swedish men who made attempts to quit smoking. When used in conjunction with other cessation aids (i.e., nicotine chewing gum, spray, tablets, inhaler, and bupropion tablets), snus was the third most common cessation therapy, following nicotine chewing gum and the patch. A success rate of 66% was observed among men who had used snus as a single cessation aid compared to a success rate of 47% observed among nicotine gum users and 32% for those using the nicotine patch. In addition, the likelihood of remaining a daily smoker at the time of the survey was significantly higher for those without a history of daily snus use as compared to those with a history of daily snus use (OR=4.4; 95% CI: 3.2 to 5.9).

Youth Behaviors: The gradual transitioning from smoking to snus observed in adults was not as apparent among adolescents. Experimentation with snus and smoking—without an inclination towards a tobacco type—was common through the teenage years, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. The Children's Smoking and Environment in Stockholm County, or BROMS cohort, is one of the larger studies that have collected information on tobacco use behaviors among Swedish adolescents. Galanti and colleagues (2001) reported that prevalence of cigarette smoking and snus use increased among students age 11 to 12 years followed from 5th to 6th grade by gender. Experimentation with both tobacco products was far more frequent among boys than among girls, and cigarette smoking often marked the onset of tobacco use. The authors reported that, at 1-year follow-up, 4 in 10 boys with initial experience of snus[63] had experimented with cigarette smoking, while only 2 in 10 smokers had experimented with snus. Overall, for both cigarette only users or snus only users at baseline, each were more likely to remain in their baseline category or become a mixed user (Galanti et al. 2001). In another study, Grotvedt et al (2013) examined patterns of tobacco use among 16-year old Norwegian students (n = 1,440) followed for three years. Baseline smokers were more likely to remain smokers or dual users at follow-up, while the odds for switching from smoking only to snus only were not significant (OR=1.53; 95% CI: 0.71 - 3.31).

Summary: Causal inferences are not possible from the cross-sectional studies cited above. The temporality of exposure and cessation outcome is unknown because, in most cases, data on smoking cessation was self-reported and not biologically verified. In addition, the definition of tobacco-use categories varies across studies making it difficult to measure success rates for smoking cessation. Also, several authors have discussed the importance of psychosocial contributions to smoking cessation and how this may impact an individual's decision to quit tobacco. Despite these limitations, tobacco patterns among Scandinavian adults provide evidence that snus is cited as a smoking cessation aid among smokers, and that longitudinal studies show transitioning from cigarettes to snus as compared to switching from snus use to cigarette smoking.

6.2.3. 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

Numerous studies have examined the relationship between snus and cigarette smoking (Furberg et al. 2005; Furberg et al. 2006; Galanti et al. 2001; Galanti et al. 2008; Grotvedt et al. 2013; Haukkala et al. 2006; Lindstrom and Isacsson 2002b; Lundqvist et al. 2009; Ramström and Foulds 2006; Rodu et al. 2003; Stenbeck et al. 2009). These studies evaluated the potential transitioning or switching from snus to cigarette smoking in Sweden and Norway either at a time point (cross-sectional) or by following a cohort over time (longitudinal).

Four longitudinal studies assessed the likelihood of transitioning from snus use to cigarette

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63 Snus is referred to as "oral snuff" in this study.

smoking among Scandinavian adults (Lundqvist et al. 2009; Norberg et al. 2011; Rodu et al. 2003; Stenbeck et al. 2009), and four studies conducted similar analyses among Scandinavian adolescents and young adults (Galanti et al. 2001; Galanti et al. 2008; Grotvedt et al. 2013; Haukkala et al. 2006).

Lundqvist et al. (2009) conducted a ten-year assessment of smoking and snus habits among northern Swedish participants from the Vasterbotten Intervention Programme (VIP) study. Study participants included men and women who were 30-years old in 1990, 1991, 1992, 1993 or 1994 and who were invited for follow-up 10 years later. The authors found that only 1.1% of baseline snus users (n = 1,800) became cigarette smokers. Among those who were snus-free at follow-up (n = 356), it was more common to remain nicotine free than to switch to cigarette smoking. For this cohort, sustained snus use over the follow-up period was most prevalent for both male and female snus users. A second look at the same longitudinal cohort and additional cross-sectional subjects, Norberg et al. (2011), similarly concluded that it was more common to switch from cigarettes to snus than to transition from snus to smoking. Norberg et al (2011) reported that approximately 1.2% of participants who used snus at baseline (n = 2,587) became smokers, while 9.4% of participants who smoked at baseline (n = 5153) became snus users within the ten-year follow-up period. Overall, trends from 1990 –1997 and 2000 – 2007 showed that smoking decreased and the use of snus increased, consistent with population trends observed in Sweden. Gender differences were apparent among this cohort, as never-smokers increased among male snus users while female snus users were dominated by former smokers.

The Swedish Level of Living Survey (ULF) is an annual national survey performed by Statistics Sweden which collects information on social and health conditions. Part of the survey includes a supplement conducted in 8-year waves. Using the ULF survey from 1988/9 and 1996/7, Stenbeck et al. (2009) examined whether the use of snus in 1988/9 was associated with smoking in 1996/7. Participants were stratified by age in a younger (16 – 44 year olds) and an older (45 – 84 year olds) sub-group to account for tobacco habits established at younger ages. Regarding smoking initiation based on prior snus use, Stenbeck et al. (2009) found that, compared to non-snus users at baseline, younger participants who were considered "snus beginners" and those who were consistent snus users were more likely to stop smoking than to initiate smoking. Among older participants, compared to non-snus users, those who began snus use in the follow up period had a nearly equal likelihood of either initiating or quitting cigarette smoking (OR 8.2 vs. 6.6), and consistent snus users were no different from non-snus users in initiating or quitting cigarette smoking. Among the younger cohorts, those who quit snus use during the follow-up period were more likely to initiate smoking (~6% of the snus users), although the authors noted that "the overall net effect was small, as this group represented very few people." In sum, the authors concluded that 1990s snus use was associated with a greater incidence of smoking cessation than smoking initiation and smokers who started using snus were much more likely than non-snus using smokers to quit smoking.

Rodu and colleagues (2003) conducted another prospective study in northern Sweden among adults, aged 25 – 64 years, enrolled in the MONICA project in 1986, 1990, 1994 with a follow-up in 1999 (which ranged from 5 -13 years for study participants). Rodu and colleagues reported

that snus was the most stable form of tobacco use among men: 75% remained snus users, only 2% of snus users switched to cigarettes, 3% became combined users, and 20% of snus users quit tobacco altogether. Smoking among males was less stable, in that 54% remained smokers, 27% were tobacco-free, 7% became combined users, and 12% used snus at follow-up. These data show that a transition from cigarette smoking to snus is more likely than a transition from snus to cigarette smoking. Similar patterns were observed by Furberg and colleagues (2006) among adult males participating in the Swedish Twin Registry over a four-year period ending in December 2002. Among men who began tobacco use with snus (n=1327), 21.9% took up smoking later in life, 67.1% remained snus users, while 32.9% of exclusive snus users quit using snus. Among cigarette starters (n=6490), 28.5% transitioned to snus. In sum, most tobacco use was initiated with cigarette smoking. However, the authors concluded that once snus use occurred, participants typically remained snus users instead of quitting.

In addition to the prospective studies discussed above, several cross-sectional studies on the relationship between snus use and cigarette smoking support some of the findings reported in the longitudinal studies (Furberg et al. 2005; Ramström and Foulds 2006). Furberg et al. (2005) evaluated the association between snus use and subsequent smoking initiation among adult males as part of the Swedish SALT twins study. Men who had used snus before they started smoking were compared to men who had never used snus in relation to any lifetime smoking while adjusting for age and other variables associated with smoking initiation. Results from this study suggested that "regular" and "now and then" snus use was inversely associated with smoking initiation.

Ramstrom and Foulds (2006) analyzed retrospective data from a cross-sectional survey completed by adult males participating in the Sweden Your Country and Your Life national survey. Among male primary snus users, 20% reported that they started daily smoking compared to non-primary snus users, among whom more than twice as many (47%) reported that they started daily smoking. Thus, male primary snus users had a decreased likelihood of initiating smoking compared to non-snus users (OR= 0.28; 95% CI: 0.22 - 0.36). The authors concluded that the likelihood of initiating daily smoking was significantly lower for those who had started using snus than for those who had not. Even among primary snus users who started secondary smoking (potential gateway subjects), 74% later ceased daily smoking, of those 56% returned to exclusive daily snus use and 18% reported that, by the time of the survey, they had quit all tobacco use.

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

In a study of the BROMS cohort, Galanti and colleagues (2001; 2008) assessed tobacco initiation among adolescents between the ages of 11 and 18 years in 5th grade through three years post-compulsory school (n = 2,938). At one-year follow-up (6th grade), the authors reported that 36%

of baseline snus users (n=52) had also smoked while the others remained snus-only users; among baseline cigarette smokers (n=419), 18% used snus at follow-up (Galanti et al. 2001).[64] In the longer follow-up (3-years post-compulsory school), a more established pattern was observed. The authors found that, compared to non-tobacco users, baseline snus users were not more likely to become cigarette smokers at follow-up (OR= 1.95; 95% CI: 0.96 – 3.8) while exclusive cigarette users (OR= 2.89; 95% CI: 2.25 – 3.71) and mixed starters (OR= 4.81; 95% CI: 3.09 – 7.5) were more likely to smoke cigarettes at the end of follow-up. Additionally, the likelihood of being a current smoker at end of follow up was higher, but not significantly increased, for cigarette starters compared with snus starters (OR=1.42; 95% CI: 0.98 - 2.1); those who were mixed starters (cigarette and snus) were more likely to smoke at follow-up (OR=2.54; 95% CI: 1.68 – 3.91) (Galanti et al. 2008). Due to the low rates of snus initiation and smoking progression among snus starters, the authors concluded that "at most 6% of the final smoking prevalence in this cohort could theoretically be attributable to the gateway effect of snus." Galanti and colleagues concluded that initiating tobacco use with both snus and cigarettes was a stronger predictor of being a current smoker by the end of follow up; that is, snus starters had a lower risk of ending up as a current smoker when compared to those who had experimented with both products at the earlier time point.

In another prospective study, Grotvedt and colleagues (2013) assessed smoking initiation among 16-year old Norwegian males (n = 1,440) who they followed for three years. The authors reported that baseline snus use was not associated with increased risk of smoking only at follow-up (OR= 0.86; 95% CI: 0.40 - 1.81) after adjusting for "previous smoking" experience. However, baseline snus users were more likely to be dual users, i.e. occasional smoking and daily snus use (OR= 1.88; 95% CI: 1.06 - 3.33). The authors emphasized that there were no trends of switching from use of snus alone to cigarettes alone and baseline smokers were most likely to remain smokers (OR= 13.31; 95% CI: 8.2 - 21.6) or become dual users (OR= 10.74; 95% CI: 6.56 - 17.57). In addition, adolescents using snus only at baseline were more likely to be tobacco free (24%) at follow-up than smokers and dual users (14% and 15%, respectively).

Finally, Haukkala and colleagues conducted a 3-year longitudinal study among students participating in their schools' (n = 27) smoking prevention program in Helsinki, Finland (Haukkala et al. 2006). Because the prevalence of snus experimentation was low among girls, the authors' examined the impact of snus experimentation upon later smoking among boys at three time points, 8th grade, and the start and end of 9th grade.[65] In predicting the impact of snus experimentation on later smoking, they compared those who had tried snus to those who had never tried. Among boys who were not regular smokers at baseline, those who had tried snus in 7th grade (baseline) had a higher risk for regular smoking in the 8th grade (OR= 6.21; 95% CI: 3.20 – 12.06). In a similar model, 8th grade snus experimentation predicted weekly smoking at the start of 9th grade (OR= 4.38; 95% CI: 2.82 – 6.80). Similarly, boys who were regular smokers at baseline had a higher risk of snus use at one year follow-up (OR= 7.26; 95% CI: 7.26

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64 This study refers to snus as "snuff."

65 This study refers to snus as "oral snuff."

– 14.67). The impact of snus experimentation upon later smoking experimentation was smaller than the impact of smoking experimentation on oral snus. The authors attributed this to the higher prevalence of smoking experimentation than snus experimentation. The authors did not, however, ask about "current snus use," but rather only about "experimentation" with tobacco. Thus, it is possible that snus experimenters could have stopped snus use before the study commenced.

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

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

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

6.2.4. Likelihood that consumers will use the product in conjunction with other tobacco products

Several studies have examined trends in dual use of snus and cigarettes in large cohorts in both Sweden and Norway. These studies have also assessed prevalence of dual use and the varying definitions applied (Engstrom et al. 2010; Galanti et al. 2008; Grotvedt et al. 2013; Janzon and Hedblad 2009; Lund et al. 2010; Lund and Lindbak 2007; Norberg et al. 2011; Ramström and Foulds 2006; Rodu et al. 2002; Rodu et al. 2003; Statistics Finland 2008; Stegmayr et al. 2005).

The 2011 Swedish National Tobacco Survey reported that the prevalence of daily snus and daily cigarette use has been stable at 2% since 2004. Cross-sectional studies in Sweden and Norway have reported similar prevalence rates for dual cigarette and snus use ranging from 2% to approximately 10%. Among adult male participants in the Swedish "Your Country and Your

Life" survey, dual use (daily snus, daily cigarette) was low (2%) and none was observed among female tobacco users (Ramström and Foulds 2006). When occasional dual use of combustible tobacco products among snus users was considered, (Digard et al. 2009) reported that 12.6% reported dual use of smokeless and any combustible tobacco product, and that 9.8% of the daily snus users also smoked cigarettes (daily or occasional) among both male and female study participants. Of these dual users of daily snus and occasional or daily use of cigarettes, 53.5% reported that they smoked daily.

In the northern Sweden-based MONICA cohort study of 25-64 year-olds, dual use was reported at 2-5% (Rodu et al. 2002; Stegmayr et al. 2005). This prevalence of dual use was stable for the study period, from 1986 to 1999. Dual use was classified as "use" of both products; the authors did not further elaborate on the definition. According to the authors, dual use reflects a temporary transition between cigarettes and snus and is an unstable and transient period. Rodu et al. (2003) examined the stability of dual users compared to other tobacco use groups, to determine whether the participants who were dual users at baseline remained in the dual use category at follow-up. They reported that combined use (smoking and snus) was the least stable category (39%), as 43% switched to snus and 6% switched to cigarettes. The use patterns of former users of both products were much less stable than former users of either cigarettes or snus alone.

In a cohort study, among participants surveyed as part of the northern Sweden VIP survey, overall smoking prevalence (i.e., smoking only plus dual use) decreased by 10 percentage points (from 26% to 16%) among men from 1990-1995 to 2002- 2007, and by 9 percentage points (from 27% to 18%) among women during the same period (Norberg et al. 2011). A dual user in this study was defined as a current (i.e., use intermittently or daily) smoker and snus user. In the Malmö study, conducted in southern Sweden, Janzon and Hedblad (2009) reported an overall prevalence of snus use among men (mean age 59 years) of 7%, and among women (mean age 57 years) of less than 1%. Among the male snus users, 34% were also current smokers, 57% were ex-smokers, and 9% were never smokers.

Among all age groups (16 through 74 years) surveyed as part of the Norway Tobacco Statistics (n=3,145), 7% used both snus and cigarettes, 27% were exclusive smokers, 8% were exclusive snus users, and 58% were non-tobacco users (Lund and Lindbak 2007; SCENIHR 2010). In this survey, dual use was defined as daily or occasional use of both snus and cigarettes. In a meta-analysis by Lund et al. (2011) of seven cross-sectional data sets from Norway, 3.1% to 10.6% of snus users smoked daily, while a higher percentage of participants reported that they smoked occasionally (16%–35%). Tobacco consumption was not quantified in the survey, and the authors noted that it is difficult to draw any conclusions about whether this combined use was more or less damaging than the amount of smoking that would have taken place without the influence of snus.

Youth Behaviors: In Norway, Grotvedt et al. (2013) examined patterns of tobacco use among tenth graders living in Oslo County surveyed as part of the Oslo Health study (n=1395), with a three-year follow-up. The prevalence of dual use was 10%, 6% were snus users, and 13% smoked. Hamari et al. (2013) conducted a study among young male military recruits (n = 1174)

living in Northern Finland. The prevalence of daily snus use in this study was 15.6%, which was higher than the rate (2.1%) observed in the general male population (Statistics Finland 2008). The authors found the prevalence of dual daily use of both snus and cigarettes to be 6.9%. Occasional smokers were twice as likely to be daily snus users than daily smokers, 30.1% vs. 15.1%. The authors concluded that concomitant snus use appeared to increase dependence on cigarettes in dual users, although the difference was not statistically significant. They also suggested that snus did not seem to serve as a substitute for cigarettes in adult daily smokers, but instead it served as an additional habit. This study has no information on duration of use and daily tobacco consumption.

Summary: Overall, dual use was more common among men in all age groups than women (Norberg et al. 2011; Ramström and Foulds 2006; Rodu et al. 2002; Stegmayr et al. 2005). Norberg and colleagues examined other factors that affected dual tobacco use. Males and those with low educational backgrounds seemed to have an increased likelihood of being dual users, as observed by Engstrom et al. (2010). Additionally, compared to non-tobacco users, dual users were more likely to be skilled and/or unskilled workers, binge drink, and engage in risky alcohol consumption. Compared to smokers, dual tobacco users were less likely to be binge drinkers, but more likely to engage in risky alcohol consumption (Engstrom et al. 2010). There were no significant differences in prevalence of dual use across all age groups (Ramström and Foulds 2006, Engstrom et al. 2010). Digard et al. (2009) reported a slightly higher prevalence of cigarette smoking among pouched snus users (10.5%) than among loose users (8.7%).

Transition patterns

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

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

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

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

Galanti and colleagues assessed development of tobacco use among adolescents and young adults between the ages of 11 and 18 years participating in the BROMS cohort survey (Galanti et al. 2008). The study conducted six follow-up assessments to understand how the initiation of the use of snus, cigarettes or both led to the development of a tobacco habit. Assessment at follow-up showed that 69.5% (1,582) started by smoking cigarettes, 11.2% (256) by using snus, and 19.3% (439) started by using snus and cigarettes during the same year. Baseline mixed starters (i.e., users of snus and cigarettes) had a significantly higher risk for being a current smoker at follow-up (OR= 2.54; 95% CI: 1.68 – 3.91). In general, the risk of current smoking or tobacco use was significantly higher for mixed starters compared with snus starters.

Amount of cigarettes and STPs used

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

Evidence also suggests that tobacco consumption among dual tobacco users may be different from exclusive users of either product with respect to the amount of product used (Galanti et al. 2008; Gilljam and Galanti 2003; Rodu et al. 2002), and that dual users consume less tobacco

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

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

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

Summary: Several studies have reported the frequency of daily dual use as approximately 2% in men and less than 1% in women, although the frequency appears to vary slightly depending on whether the criterion is daily dual use, or occasional use of one of the tobacco types. Other studies have reported a slightly higher prevalence of dual use in Sweden. For example, in the VIP cohort, 3.2% of male and 4.4% of female snus users in northern Sweden were found to smoke regularly (Lundqvist et al. 2009), and Digard et al. (2009) reported a prevalence of about 9.8% (daily and/or occasional). Taken together, among adults and adolescents, the range of dual use appears to be less than 10% in the Swedish population of snus users. Dual use appears to mark a transitional period in tobacco use. Among adult tobacco users, baseline dual users were most likely to transition to snus use or remain dual users; whereas among adolescents, approximately 38% of dual users transitioned to smoking (Galanti et al. 2008). Some evidence suggests slightly lower overall tobacco use among the dual tobacco users.

6.2.5. Likelihood that users who may have otherwise quit using tobacco products will instead use the product

Two randomized, double blind, placebo controlled clinical trials have been published in which snus was used as a cessation aid to smoking reduction (Fagerstrom et al. 2012; Joksic et al. 2011). and the results of these trials were combined in a pooled analysis (Rutqvist et al. 2013). A third clinical trial was conducted to assess smoking cessation in head and neck cancer patients (Sharp et al. 2008). Two large meta-analyses examined the use of NRTs and other aids for smoking cessation (Silagy et al. (2004) and Stead et al. (2012)). However, none of the cessation trials included in these meta-analyses included use of snus as an aid to smoking cessation or

reduction in the number of cigarettes smoked per day.

Numerous cross-sectional analyses are also available. Although the available data provide evidence of the successful use of snus as a smoking cessation aid, the data should not be interpreted to demonstrate that the use of snus is either a necessary or sufficient condition for smoking cessation.

Clinical Trials: A 48-week, randomized, double-blind, placebo-controlled clinical trial was conducted on 319 smokers in Serbia from January 2008 to March 2010 to assess the use of snus as a smoking reduction and cessation aid (Joksic et al. 2011). The study evaluated the reduction in smoking by 50% during the first 24 weeks of the trial, and eventual cessation of smoking during weeks 24 - 48. Smoking cessation using carbon monoxide (CO) measurements was verified at the clinical visits. Although the proportion of participants who achieved the ≥50% reduction in smoking was equivalent in the two groups, a higher proportion of participants in the snus group achieved extreme reduction (≥ 75%) in smoking after 24 weeks compared to the placebo group (snus group: 15/158, 9.5% vs. 4/161, 2.5%). The proportion of participants who achieved 24 week cessation by the end of trial was higher in the snus group (5.7%) compared to the placebo group (1.9%), with an odds ratio of 3.3 (95% CI: 0.9 - 12.5, p=0.08).

A double-blind, placebo-controlled trial in which snus was tested for smoking cessation was conducted at five U.S. trial sites from February 2009 to March 2010 (Fagerstrom et al. 2012). Smoking cessation using CO measurements was verified at weeks 6, 10, 16 and 28. The continuous abstinence rate at end of trial (cumulative for weeks 6-28, or 23 weeks total) in the snus and placebo groups, each with 125 participants, were 4.0% and 1.6% respectively; with an odds ratio of 2.5 (95% CI: 0.4 - 27, p=0.45), these differences were not statistically significant.

The data from these two placebo-controlled clinical trials using snus as a cessation aid were combined into a pooled analysis (Rutqvist et al. 2013). The single estimate of cessation at 23 or 24 weeks (6 months), pooled from the two studies, was 2.83 (95% CI: 1.03 – 7.75, exact p=0.06, chi squared p=0.03). Although neither of the individual studies achieved statistical significance, and the pooled estimate is of borderline significance, the point estimates of the likelihood of achieving smoking cessation using snus compared to a placebo are consistent with other nicotine replacement modalities, reported by Silagy et al. (2004) and Stead et al. (2012).

In an effort to avoid the risk of treatment failure and side effects of smoking, fifty (50) head and neck cancer patients in Sweden undergoing radiation therapy were enrolled in a 1-year smoking cessation program, using alternative nicotine products and with systematic support (Sharp et al. 2008). The primary study outcome was continuous abstinence during radiation therapy, while the secondary outcome was abstinence after the radiation therapy period. Alternative nicotine products included nicotine patches, nicotine chewing gum, nicotine lozenges, and portion Swedish snus, provided for the first 10 weeks, free of cost. At study entry, each patient was given the opportunity to test all the different nicotine products and use products *ad libitum*. The study showed that most patients used one or more than one alternative nicotine products as an aid for cessation. Nicotine patches were the most common product used (91%) followed by snus use (54%). Although the study was not intended to compare the effectiveness of the individual

products used for smoking cessation, the study showed that all but two patients were smoke-free at the 1-year follow up.

Longitudinal Studies: Several cohort studies have assessed snus use as a smoking cessation aid and observed trends in tobacco use patterns among adults (Furberg et al. 2008a; Lindstrom and Isacsson 2002b; Lundqvist et al. 2009), and two studies among youths (Galanti et al. 2001; Grotvedt et al. 2012).

Lindstrom and Isaacson (2002b) assessed the proportion of adult daily or intermittent smokers from the Malmö shoulder-neck study, conducted in southern Sweden that remained intermittent smokers, became daily smokers, or quit smoking at one-year follow up. The authors also evaluated socio-demographic and psychosocial factors that influence tobacco use. Prevalence of daily smoking decreased from 23.8% to 21.7% ($p < 0.001$) at the one-year follow-up, while the prevalence of intermittent smoking increased from 4.8% to 5.4% ($p < 0.001$) and proportion of study participants who had stopped smoking increased from 33.7% to 35.1% ($p < 0.001$). The majority of baseline intermittent smokers (59.9%) remained intermittent smokers, while 15.9% became daily smokers and 19% quit smoking completely. During the follow-up period, snus[66] use was higher in all intermittent smoking categories, intermittent/daily, intermittent/intermittent, and intermittent/stopped; suggesting an association between intermittent smoking and snus use. Notably, more than 90% of intermittent smokers were not snus users; therefore, it was unclear if smoking cessation could be attributed to either the snus use or their intermittent smoking behavior. The authors considered intermittentand occasional smoking to be transitional stages for many smokers; either an uptake phase of smoking or preparation for smoking cessation. The authors further suggested that several psychosocial characteristics such as socioeconomic position, extent of nicotine addiction, and social participation may contribute to intermittent use patterns compared to daily cigarette smoking. According to the authors, intermittent smokers differ from daily smokers; they tend to be younger, more highly educated, have higher socioeconomic status, and are less addicted to nicotine (Lindstrom and Isacsson 2002b).

A prospective study examined patterns of tobacco use among VIP cohort participants, adults aged 30, 40, 50 and 60 years, with a ten-year follow-up (Lundqvist et al. 2009). In this cohort, 34% of men and 20% of women who quit smoking started to use snus; however, a majority of the smokers quit smoking without switching to snus. More specifically, among male smokers (n = 1,104), 25.9% quit smoking completely compared to 13.6% who switched to snus. Among female smokers (n = 1,914), it was four times more common to stop smoking without snus than to switch to snus (33% vs. 8.2%). The smoking cessation rate in this cohort was 4% over the 10-year period. The authors noted that this percentage is lower than cessation rates reported in other studies with shorter follow-up periods and suggested that the lower cessation rates might reflect the increasing risk for relapse over time. The authors also noted that sustained snus use over the follow-up period was common for both males and females, however, it was more common to remain nicotine free than to switch to cigarette smoking for those who were snus free at follow-up. Lundqvist et al. (2009) suggested that the sustained use of snus over the follow up period

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[66] The study refers to snus as "snuff."

suggested a prolonged state of nicotine addiction; Norberg et al. (2011) have also suggested that snus use may prolong nicotine addiction.

Furberg et al. (2008a) assessed the smoking habits and the association between smoking cessation in ever regular smokers and their history of snus use in the Swedish Twins (SALT) cohort, by estimating the probability of having used STPs in a lifetime and being a former regular smoker. The authors investigated 12 correlates of smoking cessation, including known predictors such as marital status, education, SES and nicotine dependence. Based on their model, the authors concluded that snus use was associated with being a former regular smoker (HR=2.7; 95%CI: 2.3 – 3.2), and reported that snus use was the strongest independent correlate of smoking cessation.

Cross Sectional Analyses: The results from cross-sectional analyses support snus use as a smoking cessation tool, especially among adult Swedish men (Furberg et al. 2005; Furberg et al. 2006; Gilljam and Galanti 2003; Lund et al. 2010; Lund et al. 2011; Ramström and Foulds 2006; Scheffels et al. 2012). Adult males participating in the prospective Swedish SALT survey, who were regular snus users were three times more likely to be former smokers than current smokers at the cross-sectional analyses (Furberg et al. 2005; Furberg et al. 2006). In a retrospective study conducted among former and current Swedish adult smokers, Gilljam and Galanti (2003) reported an increased probability of being a former smoker among ever snus user rather than being a current smoker (OR= 1.72; 95% CI: 1.30 – 2.28) or current snus use (OR=1.81; 95% CI: 1.31 – 2.53) when age, education and use of NRTs were considered. The authors also found mean duration of abstinence to be longer among former smokers who were never snus users than among those who were ever snus users. They also reported that having used snus at the latest quit attempt increased the probability of being abstinent by about 50% (OR= 1.54; 95% CI: 1.09 – 2.20). Their results suggest that Swedish male smokers who used snus may increase their overall chances of abstinence, even though snus may not be a necessary component of smoking cessation at the population level (Gilljam and Galanti 2003).

Two cross-sectional studies published by the Norwegian Institute for Alcohol and Drug Research and UK Centre for Tobacco Control Studies and University of Nottingham surveyed a large sample of Norwegian adults for smoking cessation methods and outcome of last attempt to quit smoking (Lund et al. 2010; Lund et al. 2011). Among former (n = 1,775) and current smokers (n = 1,808), snus use (17%) was reported as the most common method for quitting smoking compared to other medicinal nicotine products, such as nicotine patches (4%), nicotine chewing gum (10%), and Zyban (3%). For all quitting methods surveyed, the proportion of unsuccessful quitters (current smokers) was greater than the proportion of successful quitters (former smokers); however, the ratio of successful to unsuccessful quitters was higher for snus than the other smoking cessation methods (Lund et al. 2010). In addition, total abstinence at time of survey was significantly higher for snus use-only than for any other methods of quitting (OR= 2.66, $p<0.001$). Among smokers who reported using snus to quit (n = 671), 62.4% reported still using snus at time of survey, while 9.5% of smokers who had used nicotine chewing gum or patch still used these nicotine replacement products. Of those still using snus, 75% reported at least some reduction in the amount smoked.

Similar findings were reported by the same researchers in a meta-analysis of seven cross-sectional studies among Norwegian former/current smokers (Lund et al. 2011). The meta-analysis combined studies that provided usable information for calculating the quit ratio for smoking (number of former daily smokers as a proportion of ever smokers in a population), among Norwegian adults, aged 16- 74 years. Quit ratios for the individual studies varied, ranging from 32.2% in a nationally representative sample, among those aged 16-20 years to 67.4% in a student population in Oslo. In general, the quit ratio for smoking was significantly higher for daily snus users than for never snus users (6 out of 7 studies), although the quit ratio for smoking among those who used snus occasionally was significantly lower compared to never snus users. Overall, former smokers formed the largest group of snus users (6 out of 7 studies) and daily snus use was associated with former smoking. Occasional snus use was less likely to be associated with being a former smoker (Lund et al. 2011). Another pooled analysis by the same researchers, combined studies conducted among Norwegian adults who were surveyed as part of Statistics Norway, reached similar conclusions (Scheffels et al. 2012). The authors compared smoking cessation with snus use to other nicotine replacement therapies and showed that snus was the most common method for quitting smoking among male participants, while women were more likely to use nicotine replacement therapies. These studies showed that snus was the most prevalent smoking cessation aid among all categories of smokers and former smokers (Lund et al. 2010; Lund et al. 2011; Lund and Lindbak 2007).

Ramstrom and Foulds (2006) conducted a retrospective analysis of a cross-sectional survey among adult Swedish smokers and found that, among male primary smokers (n = 1,226), approximately one-third started secondary daily snus use. Eighty-eight percent of those secondary snus users had ceased daily smoking completely by the time of the survey as compared with 56% of those primary daily smokers who never became daily snus users (OR= 5.7; 95% CI: 4.9 - 8.1). When considered as the only cessation aid, the authors also reported that snus was the most commonly used cessation aid among men who made attempts to quit smoking. When used in conjunction with other cessation aids (i.e., nicotine chewing gum, spray, tablets, inhaler, and bupropion tablets), snus was the third most common cessation therapy, following nicotine chewing gum and the patch. A success rate of 66% was observed among men who had used snus as a single aid to smoking cessation compared to a success rate of 47% observed among nicotine gum users and 32% for those using the nicotine patch. The likelihood of remaining a daily smoker at the time of the survey was significantly higher for those without a history of daily snus use as compared to those with a history of daily snus use (OR=4.4; 95% CI: 3.2 to 5.9).

Youth Behaviors: Although no clinical trials have been conducted among adolescent tobacco users, several cohort studies evaluate youth tobacco use behaviors. In general, the gradual transitioning from smoking to snus observed in adults was not as apparent among adolescents. The experimentation with snus and smoking was common through teenage years, without an inclination towards a tobacco type, although boys were more likely to be snus users and girls were more likely to be cigarette smokers as young adults. Galanti and colleagues (2001) reported that the prevalence of cigarette smoking and snus use in the BROMS cohort of adolescents in Sweden increased among students age 11 to 12 years followed from grades 5 to 6 by gender.

Experimentation with both tobacco products was far more frequent among boys than among girls and cigarette smoking often marked the onset of tobacco use. The authors reported that, at 1-year follow-up, 4 in 10 boys with initial experience of oral snuff (i.e., snus) use had experimented with cigarette smoking, while only 2 in 10 smokers had experimented with oral snuff. Overall, both cigarette only and snus only users at baseline were more likely to remain in their baseline category or become a mixed user (Galanti et al. 2001). In another study of male youth, Grotvedt et al (2013) examined patterns of tobacco use among 16-year old Norwegian students (n = 1,440) followed for three years. In this cohort, baseline smokers were more likely to remain smokers or become dual users at follow-up, while the likelihood of switching from smoking only to snus only were not significant (OR=1.53; 95% CI: 0.71 - 3.31).

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

Causal inferences are not possible from the cross-sectional studies cited above. The temporality of exposure and cessation outcome is unknown and, in most cases, data on smoking cessation were self-reported and not biologically verified. In addition, the definition of tobacco-use categories varies across studies making it difficult to measure success rates for smoking cessation. Moreover, several authors have discussed the importance of psychosocial contributions to smoking cessation and their impact on an individual's decision to quit tobacco.

6.2.6. Likelihood that consumers will use the product as intended or designed

Understanding the frequency, amount, and duration of snus use and the degree of variability among individual and trends over time is an important part of examining STP use and the potential health effects of snus. However, there are inconsistencies among the studies as to the manner of information collection, the units of time, and the frequency of use. For example, surveys of snus use have measured lifetime snus use (i.e., ever users versus never users) or current snus use (i.e., as compared to former users and never users). Daily snus users may be compared to occasional users and never users, and units for individuals may be reported as daily or weekly, or alternatively, as grams, cans, or tins of snus or other STP. Notwithstanding these inconsistencies, the resulting data provide some insight into snus use behaviors.

The most common method of snus use is to deposit one to two grams of loose product or a pouch of pre-portioned packaged snus in the vestibular area inside the upper lip (Andersson 1991); Digard and colleagues (2009) reported that 96% of pouched users and 99% of loose snus users placed the snus at that site, though approximately one-third of pouched users and one-fifth of loose snus users move the portion around the mouth during use. Additional exposure estimates that may include the number of pouches, packages or grams used per day or week, the amount of time that snus is left in the mouth, as well the number of years of snus use are described below, in **Table 6-53** and in **Table 6-54** (note: the latter table can be found after the Reference List for this section). For ease in comparison, one can of loose snus in Sweden is generally assumed to contain 50 grams (Eliasson et al. 1995; Lewin et al. 1998; Schildt et al. 1998).

The most recent and comprehensive assessment of Swedish snus exposure patterns was reported by Digard and colleagues (2009). The authors conducted a telephone survey of daily snus users to quantify tobacco consumption among 2,914 snus users between the ages of 18 and 72 years (Table 1) and reported that female snus users (n=359) were more likely to use pouched snus (92.8%) than loose snus (6.4%) and 0.8% used both. Snus use among males (n=2,555) was more evenly distributed, as 54% reported pouched snus use, 42.1% used loose snus and a minority reported use of both. There was an increase in the prevalence of the use of packaged snus in this study compared to a 1992 report (date of data collection unknown) which indicated that 73% of snus users consume only loose snus, 13% only snus pouches, and 14% use both (Svenska Tobaks AB, Basdata om tobakskonsumtion 1992, TEMO AB, reported by Andersson et al. 1994). These differences reflect an increase in pouched snus use since its introduction in the late 1970s.

Table 6-53: Recent Patterns of Snus Use in Sweden (Digard et al. 2009) (means)

Pouched Snus	**Male**	**Female**
Packages per day	0.54	0.49
Portions per day	12.0	10.4
Consumption per day (g) from packages	12.4	9.3
Consumption per day (g) from portions	11.8	8.5
Time per day (hrs.)	13	7.7
Length of time in mouth (min)	69.7	47.3
Loose Snus		
Packages per day	0.59	0.58
Portions per day	12.3	13.5

Table 6-53: Recent Patterns of Snus Use in Sweden (Digard et al. 2009) (means)		
Consumption per day (g) from packages	29.3	29.0
Consumption per day (g) from portions	32.1	33.8
Time per day (hrs.)	12.7	14.6
Length of time in mouth (min)	69.6	56.1

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

Additional studies that provide some information about the frequency, intensity and/or duration of snus use in Scandinavia are summarized in **Table 6-54**. Many of these studies were conducted prior to the consumption study by Digard and colleagues, have smaller sample sizes, and some were conducted specifically among heavy users (Rosenquist et al. 2005; e.g., Wedenberg et al. 1996). The amount of snus use reported in these studies is highly variable, though the results are generally consistent with those observed more recently by Digard et al (2009). For example, on average, snus users in these studies consumed less than 50 grams of snus per day and fewer than four cans per week. There was variability in the number of hours that snus users reported using between studies ranging from 11 to 13 hours, but this was similar to the findings reported by Digard and colleagues (2009).

6.2.7. Swedish snus and dependence, with a review on clinical studies of nicotine absorption and pharmacokinetics.

Most forms of tobacco use may result in dependence, probably because of their nicotine content, and STPs such as Swedish snus are no exception (Boyle et al. 1995; Ebbert et al. 2006; Hukkanen et al. 2005; Mushtaq and Beebe 2012; SCENIHR 2008; USDHHS 1986). Reported incidences estimate that perhaps half of all users of tobacco (including STP) may be classified as "dependent" (Ferketich et al. 2007; Hughes et al. 2006), with considerable evidence now emerging of profound genetic influences on dependence (Drgon et al. 2009; Lessov-Schlaggar et al. 2008; Li and Burmeister 2009; NCI 2009; Pergadia et al. 2010; Ramoni et al. 2009), including both in smokers and Swedish snus users (Modig et al., 2011).

The broad range of different methods used to assess "dependence" in products containing

tobacco (and therefore nicotine), along with a paucity of such studies in users of smokeless tobacco products (STP) such as Swedish snus (Boyle et al., 1995), make an overall conclusion on "Swedish snus and dependence" quite difficult. Data reviewed herein (including data from animal studies) would indicate that, for a number of technical reasons (e.g., "fewer behavioral components"), dependence in Swedish snus users may well be considerably less than the dependence reported for other tobacco products. There is probably a "continuum of dependence" from cigarettes (high dependence) to pure nicotine (NRT: very low dependence, if any) (West et al., 2000). The dependence for Swedish snus is probably intermediate between the two (Fagerström and Eissenberg, 2012). An opposing view might be that use of Swedish snus results in dependence that is similar to that produced in users of other tobacco products (Holm et al., 1992; Post et al., 2010), with a question about NRT.

Clinical trials illustrate that Swedish snus products generally are associated with a faster absorption of nicotine than that from pharmaceutical gum, and a corresponding faster onset of subjective symptoms (e g "head rush"). In contrast, the estimated mean extracted amount of nicotine, as well as the area under the plasma concentration-time curve (AUC), was higher from a 4 mg piece of gum compared to a 1.0 g snus pouch, despite a lower maximal plasma concentration (C_{max}). There was a high inter-individual variation in nicotine extraction and uptake from Swedish snus which was not linear with pouch size. The data suggest that surface area, saliva penetration, and diffusion factors may be equally or even more important determinants of nicotine absorption from Swedish snus than pouch weight.

The more rapid nicotine delivery from Swedish snus compared to the selected NRT comparators may help to explain why many smokers have quit cigarettes completely by switching to Swedish snus, why Swedish snus is the most frequently reported cessation aid among male smokers in both Sweden and Norway, and why Scandinavian population surveys of the success rate with different quitting aids for smokers suggest that Swedish snus may be superior to NRT.

6.2.7.1. Defining "Dependence"

There are several definitions in the literature for "dependence", "nicotine dependence", and "tobacco dependence", with few attempts at defining "smokeless tobacco dependence" (DiFranza et al., 2011) and even fewer for "dependence in Swedish snus users" (Benowitz 2011; Holm et al. 1992). Various "dependence scales" have been published, with occasional comparisons made between scales ("concordance") (Agrawal et al. 2011; Carpenter et al. 2010; Etter 2008; Hughes et al. 2004; Okuyemi et al. 2007).

The most commonly used tobacco dependence measures (Piper et al., 2006) are the Fagerström Tolerance Questionnaire (FTQ) (Fagerström, 1978) and the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). A recent addition to the list of "dependence scales" termed the "Autonomy over Tobacco Scale" claims considerable improvement over the FTND (DiFranza et al., 2012).

6.2.7.1.1. Fagerström Tolerance Questionnaire

The FTQ was designed in 1978 to assess the physical dependence on nicotine. However, each of the 8 questions in the FTQ applies to smoking only:

1. How many cigarettes a day you smoke?
2. What brand do you smoke?
3. Do you inhale?
4. Do you smoke more during the morning than during the rest of the day?
5. How soon after you wake up do you smoke your first cigarette?
6. Which cigarette would you hate to give up?
7. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, at the library, cinema etc?
8. Do you smoke if you are so ill that you are in bed most of the day?

6.2.7.1.2. Fagerström Test for Nicotine Dependence

The FTND was modified to reflect criticism that question #5 above was the dominant driver of the score. Nevertheless, the 6 questions in the FTND scale are very similar to those in the FTQ, because the only changes that were applied were to those questions on nicotine rating and inhalation. Revised scoring was the main change:

1. How soon after you wake up do you smoke your first cigarette?
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc?
3. Which cigarette would you hate most to give up?
4. How many cigarettes/day do you smoke?
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
6. Do you smoke if you are so ill that you are in bed most of the day?

6.2.7.1.3. DSM-IV / 5

Another common set of criteria used to assess dependence is the Diagnostic and Statistical Manual of Mental Disorders (DSM) scale originally developed for alcohol abuse (Grant et al., 2007; West et al., 2006). The basic DSM criteria for nicotine dependence (DiFranza and Ursprung 2010) are as follows:

> A maladaptive pattern of substance use, leading to clinically significant impairment or stress, as manifested by three (or more) of the following, occurring at anytime in the same 12-month period:
>
> 1. There is a persistent desire or unsuccessful efforts to cut down or control substance use

2. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
3. Withdrawal, as manifested by either of the following: (a) the characteristic withdrawal for the substance (see below), or (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
4. Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of the same amount of the substance
5. The substance is often taken in larger amounts or over a longer period than was intended
6. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances, use the substance (e.g. chain-smoking), or recover from its effects
7. Important social, occupational, or recreational activities are given up or are reduced because of substance use.

The DSM diagnostic criteria for nicotine withdrawal are:

- *Criterion A:* Daily use of nicotine for several weeks; and

- *Criterion B:* Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed by four (or more) of the following signs: irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain, dysphoric or depressed mood, and insomnia; and

- *Criterion C:* The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; and

- *Criterion D:* The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

A review of moderate-to-heavy smokers with the DSM-IV criteria (Donny and Dierker, 2007) found that "*approximately 39.4% of daily smokers never reached nicotine dependence*." Updates of the DSM-IV criteria (as DSM-5) are now available (Baker et al., 2012; Chung et al., 2012)

6.2.7.1.4. International Classification of Diseases

WHO produced a set of criteria similar to the DSM criteria termed the International Classification of Diseases (ICD) (WHO 1992). The two sets of criteria are so similar that the suggestion has been made that "*the differences between the DSM fourth edition (DSM-IV) and the ICD tenth edition (ICD-10) versions are minimal and could be resolved*" (Saunders, 2006).

The ICD-10 criteria (DiFranza and Ursprung, 2010) are as follows:

Dependence Syndrome
Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than one month, then they have occurred together repeatedly within a twelve month period.

- A strong *desire* or sense of compulsion to take the substance.

- Impaired capacity to control substance-taking behavior in terms of onset, termination or level of use, as evidenced by: the substance being often taken in larger amounts or over a longer period than intended, or any unsuccessful effort or persistent desire to cut down or control substance use.

- A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.

- Evidence of tolerance to the effects of the substance, such that there is a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or that there is a markedly diminished effect with continued use of the same amount of the substance.

- Preoccupation with substance use, as manifested by: important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain the substance, take the substance, or recover from its effects.

- Persisting with substance use despite clear evidence of harmful consequences, as evidenced by continued use when the person was actually aware of, or could be aware of, or could be expected to have been aware of the nature and extent of the harm.

Withdrawal state
- Clear *evidence* of recent cessation or reduction of substance use after repeated, and usually prolonged and/or high-dose use of that substance.

- Symptoms and signs compatible with the known features of a withdrawal state (see below) from the particular substance or substances.

- Not accounted for by a medical disorder unrelated to substance use, and not better accounted for by another mental or behavioral disorder.

Nicotine withdrawal state
The general criteria for withdrawal state are met where any two of the following symptoms and signs are present:

- Craving for tobacco (or other nicotine-containing products)
- Malaise or weakness
- Anxiety
- Dysphoric mood
- Irritability or restlessness
- Insomnia
- Increased appetite
- Increased cough
- Mouth ulceration
- Difficulty concentrating

6.2.7.1.5. Other Dependence "Scales"

Other dependence scales have been presented elsewhere (Costello et al. 2007; Difranza et al. 2007; Difranza et al. 2012; Etter et al. 2003; Kellogg et al. 2003; Nonnemaker et al. 2004; Piper et al. 2006; Shiffman and Sayette 2005); they will not be discussed further here as they are generally not as well documented or extensively used as the Fagerström or DSM scales.

6.2.7.1.6. Dependence Scales for STP

Probably one of the very earliest published scales for dependence in STP users included 10 questions (scale 1) and 9 questions (scale 2), respectively (Boyle et al., 1995):

Scale 1

1. After a normal sleeping period, do you use smokeless within 30 min of waking?
2. Is it difficult for you not to use smokeless where its use would be unsuitable or restricted?
3. Do you use smokeless when you are sick or have mouth sores?
4. What brand of smokeless do you use?
5. How long does a tin / can last you?
6. On average, how many minutes do you keep a fresh dip or chew in your mouth?
7. Do you intentionally swallow tobacco juices?
8. Do you keep a dip or chew in your mouth almost all the time?
9. Do you experience strong cravings for a dip / chew when you go for more than 2 hr without one?

10. On average, how many dips / chews do you take each day?

Scale 2

1. How soon after waking do you have your first chew?
2. Do you find it difficult to refrain from chewing in situations where it would be inappropriate?
3. Do you chew when you are so ill you remain in bed?
4. Nicotine content of snuff or chew.
5. Number of tins used per week.
6. How often do you swallow your tobacco juice rather than spit?
7. Do you chew more in the morning than the rest of the day?
8. Which chew would be the hardest to give up?
9. What is the length of the dipping day?

A subsequent study in STP users (Thomas et al., 2006) used criteria that were identical to Scale 2 of the first study, with 9 questions.

A 2006 study of dependence in STP users had 6 questions (Ebbert et al., 2006):

1. How often after you wake up do you place you first dip?
2. How often do you intentionally swallow tobacco juice?
3. Which chew would you hate to give up most?
4. How many cans / pouches per week do you use?
5. Do you chew more frequently during the first hours after awakening than during the rest of the day?
6. Do you chew if you are so ill that you are in bed most of the day?

Very similar questions were posed in the set of questions to STP users posed by Ferketich et al (2007):

1. How many tins / pouches of smokeless tobacco do you typically use each week?

2. How often do you use smokeless tobacco?

3. Do you intentionally swallow tobacco juices?

4. Do you use smokeless tobacco when you are sick or have mouth sores?

5. How soon after awakening from you normal sleeping period do you use chewing tobacco or snuff?

6. Do you use cigarettes?

7. Is it difficult for you not to use smokeless tobacco where its use is restricted or not allowed?

The latest set of STP questions (Mushtaq and Beebe 2012) consists of 15 questions divided into 3 categories: withdrawal (1-4), heaviness of use (5-13), and compulsion(14-15):

1. Use after waking up
2. Strong cravings
3. Heaviness of use in morning
4. Hardest ST use to give up
5. No. of tins / week
6. No. of days a tin lasts
7. No. of days / week ST use
8. No. of dips / day
9. Swallow juices
10. Keep dip all the time
11. Length fresh dip kept
12. Length of dipping day
13. Nicotine contents / Brand of ST
14. Difficulty refraining
15. Use when ill

6.2.7.2. Dependence in Swedish Snus Users

The literature on dependence in Swedish snus users is quite limited (Edwards et al. 2011; Holm et al. 1992; Post et al. 2010).

The first of these studies of 27 Swedish snus (called snuff) users and 35 smokers was designed to obtain data on the absorption of nicotine in Swedish snus users, with a secondary aim to "*gather questionnaire measures of dependence in snuff users*." Both aspects were then used to compare Swedish snus users with cigarette smokers. The questionnaire was relatively simple: unpleasantness of abstaining for an hour or two, self-perceived addiction, craving for tobacco

when without it, difficulty of giving up for a month, and enjoyment of snuffing / smoking. Responses were on 3-point (enjoyment), 4-point (addiction, unpleasantness, difficulty giving up) and 5-point (craving) scales.

Plasma nicotine concentrations were very similar in both groups; the ratings for dependence were also very similar. Differences included the fact that "*the snuff users found their habit much more enjoyable*", whereas smokers were "*significantly more likely to have their first cigarette of the day before tea or coffee than were the snuffers*."

Another study (Post et al., 2010) of 466 exclusive smokers and 209 exclusive snus users (average age less than 18 years) used 9 (nine) items from three of the scales reviewed above. The following questions (administered by a mailed questionnaire) were asked of subjects "who have smoked or used snus at least 10 times in your lifetime":

1. How soon after waking up in the morning do / did you smoke your first cigarette of take / took your first snus dip?
2. Which cigarette or snus / dip is / was hardest to give up?
3. Do / did you find it difficult not to smoke or use snus inside places where it is forbidden?
4. Do / did you use tobacco (snus or cigarettes) even if you were so ill that you are / were in bed most of the day?
5. Was there a time when you often had such a strong desire to smoke or use snus that you couldn't keep yourself from it, or found it difficult to think of anything else?
6. Did you ever have times when you smoked / used snus even though you decided not to?
7. Did you ever have a period when you gave up or greatly reduced important activities (e.g. sports, time spent with friends) so you could smoke or use snus?
8. Have you ever tried to quit smoking or using snus but failed?
9. Have you ever felt like you were addicted to tobacco?

The study concluded that "smokeless tobacco in adolescence has a potential to induce nicotine dependence which is at least as high as for cigarette smoking." The study raises several technical questions including the young age of the subjects and, thus, the applicability of the data obtained to other groups. Virtually all of the subjects were unemployed and living with their parents; 78% of the cigarette smokers and 7% of snus users were female . The authors point out that "the development of instruments to assess nicotine dependence among smokeless tobacco users is still underway" yet, despite other published work (Ebbert et al., 2006; Ferketich et al., 2007) they used an arbitrary combination of three scales that had not been used previously with smokeless tobacco.

Edwards et al. (2011) published a population-based twin study (SALT: Swedish Screening Across the Lifespan Twin). Evaluation of dependence was not the primary endpoint of the study. Rather, one of the study's goals was to assess whether there are "differences between genetic and environmental influences on cigarette use versus Swedish snus use and corresponding measures of nicotine dependence" Analyses were based on approximately 28,000

same-sex twins of known zygosity. The authors used structural equation modeling to examine the relationships between major depression, regular tobacco use, and nicotine dependence given regular tobacco use.

For males only, the heritabilities of regular Swedish snus use and regular cigarette use were similar. However, Swedish snus-based nicotine dependence was more highly heritable than that for regular cigarette use. The genetic liability shared between major depression and tobacco use was higher for Swedish snus use than for cigarette smoking. The authors concluded that "results presented are suggestive of population differences in how major depression and tobacco use inter-relate."

6.2.7.3. "Continuum of Dependence"

A recent update (Fagerström, 2012) to the studies described above has suggested that "quitting smokeless tobacco, which has fewer behavioral components and is a more solitary thing than smoking, is easier than stopping smoking" (Fagerström et al., 2010). The authors also concluded that "there is no evidence for the abuse of pure nicotine" (Fagerström, 2012), as suggested previously (West et al., 2000) for different forms of NRT. It has subsequently been suggested that, for dependence "with each type of product used for nicotine self-administration, a new measure may be needed" (Fagerström and Eissenberg, 2012). Similar to the concept of a "continuum of risk" for different tobacco products (Levy et al. 2006; Sweanor et al. 2007), there may also exist a "continuum of dependence" (Fagerstrom and Eissenberg 2012; Tiffany et al. 2004), that would range from high in cigarettes, to low (if any) in pure nicotine, as used for example in NRT (West et al., 2000). The dependence for Swedish snus is probably intermediate between the two (Fagerström and Eissenberg, 2012).

Nicotine dependence "in users of smokeless tobacco might have different characteristics compared with the nicotine dependence of smokers" (Fagerström et al., 2010). For example, users of Swedish snus might "have been less resistant to cessation than corresponding populations of smokers, who have long been under pressure to quit" (Fagerström et al., 2010). A recent study of discordant twins suggests that the nature of the dependence in users of Swedish snus is different from that in cigarette users (Edwards et al., 2011). Delivery of nicotine in an extract of a smokeless tobacco product appeared to have fewer effects than nicotine alone, in both rats (Harris et al., 2012) and mice (Marti et al., 2011).

6.2.7.4. Nicotine absorption

In cigarette smokers, the transfer of nicotine from the inhaled smoke to the brain has been reported to be extremely rapid (Benowitz 2008; Hukkanen et al. 2005), reflecting the blood flow directly from the lungs to the brain. In users of STP, nicotine absorption occurs orally and thus is affected by the "first pass" concept, producing much slower delivery to the brain (Benowitz, 1997). Nonetheless, nicotine supplementation in the form of NRT is associated with a modest increase of cessation rates among smokers motivated to quit. It has been hypothesized that the relatively low level of efficacy observed in controlled clinical trials and population studies is related to the nicotine delivery profile of currently available NRT products which may produce

insufficient reductions of craving and urges to smoke. The rates of absorption of nicotine from different products have been compared graphically (Foulds et al., 2003), and are presented below.

In Scandinavia, Swedish snus is the most commonly reported quitting aid among males, and appears to be associated with a higher success rate than NRT or counseling among both males and females. These circumstances make it reasonable to study the nicotine pharmacokinetics and subjective effects of Swedish snus, particularly in relation to commonly used NRT products.

As shown in **Figure 6-4** below, Holm *et al* reported two studies examining nicotine intake in users of loose Swedish snus (Holm et al., 1992). Absorption from a single pinch (2 g) in ten users after overnight abstinence was fairly rapid. The increment in plasma nicotine concentrations averaged 9.9 ng/ml after ten minutes and peaked at 14.5 ng/ml at 30 minutes. Among groups of habitual Swedish snus users (n=27) and cigarette smokers (n=35), peak blood nicotine levels were similar (mean 36.6 ng/ml and 36.7, respectively), but there was a trend to higher cotinine levels among the Swedish snus users (399.2 ng/ml versus 306.3 ng/ml). The Swedish snus users and cigarette smokers reported similar levels of subjective dependence on tobacco.

Figure 6-4. Nicotine Intake in Users of Loose Swedish Snus

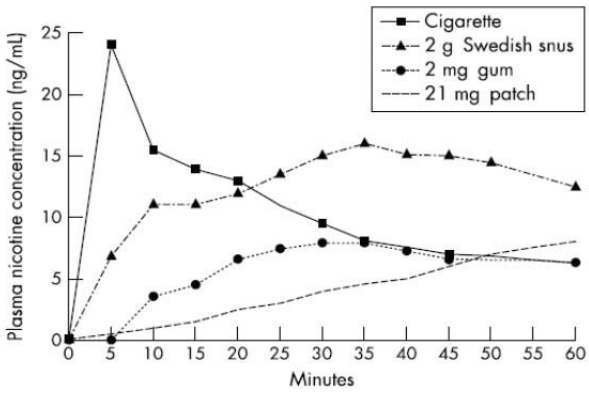

Figure 1 Venous blood concentrations in nanograms of nicotine per millilitre (ng/ml) of plasma as a function of time for various nicotine delivery systems; all plasma nicotine concentrations have been reconfigured such that the pre-absorption level starts at 0 ng/ml (that is, to take out the baseline differences). Cigarette, and 2 mg nicotine gum, adapted from Russell *et al*,[24] and 21 mg patch adapted from Stratton *et al*,[3] page 100. Swedish snus plasma nicotine concentrations in 10 Swedish snus users from a single 2 g pinch of loose snus adapted from Holm *et al*.[21]

In a study of oral mucosal changes among users of smokeless tobacco, the authors found that the average steady-state saliva cotinine concentration was about 300 ng/ml both for users of loose Swedish snus (n=22) and users of pouched Swedish snus (n=23), levels were similar to those reported among smokers (Andersson et al., 1994). A randomized, open-label, crossover

clinical trial including 63 smokers found that, during a two week test period, Swedish snus was superior to a 4 mg piece of nicotine gum in terms of reducing urges to smoke compared to baseline, although the decrease in the total craving score was not statistically significant for either product (Caldwell et al., 2010). Both Swedish snus and nicotine gum enabled subjects to reduce their smoking significantly compared to baseline. At the end of the test period participants were asked to rank their preferred purpose for using the products if they could use them long term. Subjects could choose from three possible uses: "short term to quit smoking", "to reduce smoking", or "long term instead of smoking". Swedish snus were ranked higher than the gum in all three dimensions; with a statistically significant difference for the "quit" and "reduce" dimensions.

6.2.7.5. Abuse Liability

6.2.7.5.1. Studies of the Nicotine Pharmacokinetics of Swedish Snus

It is widely accepted that nicotine is the main dependence-producing constituent in tobacco and that rate of delivery is an important determinant of abuse potential (SCENIHR 2008). Nicotine contributes significantly to the difficulty many tobacco users experience in attempting to quit. NRTs cannot produce the rapid, high peaks of nicotine in arterial blood to the brain that is typically associated with cigarette smoking. However, randomized trials have illustrated that NRTs can increase cessation rates among some smokers (Silagy et al. 2007). It has been hypothesized that the relatively modest efficacy seen with NRTs when used as prescribed is related to poor nicotine delivery which, in turn, may result in insufficient reduction of craving and urges to smoke.

In Scandinavia, many smokers have quit completely by switching to snus. In both Sweden and Norway snus is the most commonly reported quitting aid among males and appears to be associated with a higher success rate than NRT or counseling (Ramström and Foulds 2006; Scheffels et al. 2012). In contrast, there is no non-prescription drug available that has been shown to increase quit rates among snus users motivated to quit tobacco use. Results from studies of NRT among users of smokeless products have generally been negative (Ebbert et al. 2011). These circumstances make it reasonable to study the nicotine pharmacokinetics and subjective effects of snus, particularly in relation to commonly used NRT products.

Very few studies have examined the nicotine pharmacokinetics and/or subjective effects of Swedish snus. Slightly more studies have investigated other types of smokeless tobacco, including American moist snuff. Yet because of differences in product characteristics that are relevant for nicotine uptake such as pH, moisture, and the raw tobacco, such data may not be relevant to snus.

In 1992, Holm et al (1992) reported two studies examining nicotine intake in users of loose Swedish snus. Absorption from a single pinch (2 g) in ten users after overnight abstinence was fairly rapid. The increment in plasma nicotine concentrations averaged 9.9 ng/ml after ten minutes and peaked at 14.5 ng/ml at 30 minutes. Among groups of habitual snus users (n=27)

and cigarette smokers (n=35) peak blood nicotine levels were similar (mean 36.6 ng/ml and 36.7, respectively), but there was a trend to higher cotinine levels among the snus users (399.2 ng/ml versus 306.3 ng/ml). The snus users and cigarette smokers reported similar levels of subjective dependence on tobacco.

In a study focused on oral mucosal changes among users of smokeless tobacco, Andersson et al (Andersson et al. 1994) found that the average steady-state saliva cotinine concentration was about 300 ng/ml both for users of loose snus (n=22) and users of pouched snus (n=23), and similar to that reported among smokers. A randomized, open-label, crossover clinical trial including 63 smokers found that, during a two week test period, snus was superior to a 4 mg piece of nicotine gum in terms of reducing urges to smoke compared to baseline, although the decrease in total craving score was not statistically significant for either product (Caldwell et al. 2010). Both snus and nicotine gum enabled subjects to reduce their smoking significantly compared to baseline. At the end of the test period participants were asked to rank their preferred purpose for using the products if they could use them long term. Subjects could choose from three possible uses: "short term to quit smoking", "to reduce smoking", or "long term instead of smoking". Snus was ranked higher than the gum in all three dimensions, and the difference was statistically significant for the "quit" and "reduce" dimensions.

6.2.7.5.2. Swedish Match Snus Nicotine Studies

Because of the relative paucity of data on nicotine pharmacokinetics of snus, Swedish Match sponsored three separate studies (collectively, the "Snus Nicotine Studies") that compared different types of Swedish snus manufactured according to the GOTHIATEK® standard with either nicotine gum (2 or 4 mg), or nicotine lozenges (3x2 mg).

6.2.7.5.2.1. Governance of the Studies

There is currently no internationally accepted governance structure specific to the clinical studies of tobacco products. Because the Snus Nicotine Studies included different types of pharmaceutical nicotine as comparators, Swedish Match applied the standards for governance and conduct of the trials applicable to clinical trials of pharmaceutical products or medical devices. This decision included the following elements:

- Study protocols were developed in collaboration between Swedish Match and an external principal investigator (one of Sweden's leading experts on nicotine pharmacology) according to internationally accepted guidelines.

- Studies were performed in accordance with Swedish laws, ICH guidelines, and the guidelines of the Declaration of Helsinki.

- Written, full informed consent was obtained from all study participants.

- The conduct of the study was approved by an appropriately constituted, independent research ethics committee.

- The trials were conducted according to full ICH-GCP.

- Approval of the protocol and all study procedures was obtained from the Swedish Medical Products Agency (Läkemedelsverket).

- Management of all clinical and other study-related information, including monitoring, was conducted by a well-reputed external contractor with extensive experience of nicotine pharmacology studies (CROel AB, Lund, Sweden).

- All data handling and statistical analyses were conducted by the external contractor (CROel AB).

- The studies were registered prospectively in EudraCT, the European clinical trials database, except that the SM WS 02-study is not registered as it was initiated before such registration was mandated.

- Swedish Match committed to publish study results in peer-reviewed scientific journals according to the CONSORT guidelines.

- Swedish Match committed to make individual study data available for systematic reviews and/or meta-analyses.

6.2.7.5.2.2. SM WS 02-Study

The Swedish Match WS 02-study (Lunell and Lunell 2005) evaluated the pharmacokinetics, including steady state nicotine plasma levels, following one day's regular use of four different types of Swedish snus compared to a 2 mg piece of nicotine chewing gum (Nicorette®). The study documents (e.g., protocol, full study report, etc.) are attached as Appendix 2I.

Material and Methods

The study used an open-label, partly randomized cross-over design and comprised five 12-hour sessions. A total of twelve (12) healthy male non-smoking regular users of snus aged 18-23 years were randomly given 12 hourly repeated doses of four different types of snus. The participants tested the nicotine gum during a separate session. With a period of at least five days between the sessions. The products were administered as multiple doses every hour. The snus pouches were used under standardized conditions for 30 minutes. The nicotine gum was chewed every two seconds for 30 minutes (using a metronome for standardization). Non-compliance with these standardized procedures led to exclusion of data from the statistical analysis. Participants were instructed to abstain from any nicotine-containing products from 8:00 pm the evening before each session. A baseline nicotine plasma concentration exceeding 4 ng/ml was interpreted as a

protocol violation and the participant's data were excluded. The pharmacokinetic variables were estimated based on data from 11 subjects, and the ratios versus the nicotine gum on ten subjects.

Tested snus products included 1.0 and 0.5 g pouches of traditional brands with a pH around 8.5, moisture around 50%, and slightly varying nicotine content (approximately 7-9 mg/g). One of the 1.0 g products and the 0.5 g product had a moist (brown) pouch material, and the other 1.0 g product came in non-moistened (white) pouch. The fourth snus product was a 0.3 g pouch of a novel brand with a lower pH (7.3) and lower moisture content (approximately 30%) than the traditional brands, and came in a white pouch.

Serial samples of venous blood were drawn at baseline, and 1, 2, 4, 6, 8, 10, 11, and 12 hours, and at the five 10-min intervals between the 11- and 12-hour time points. Determination of nicotine was performed at ABS Laboratories (London, U.K.) using capillary gas chromatography with a nitrogen-selective detector after a single liquid-liquid extraction of a basified plasma sample.

Residual nicotine in the used snus pouches was analyzed to estimate extracted dose. The mean nicotine content of ten unused pouches of each product was used for comparison in these calculations. The nicotine analyses used to estimate extracted dose were conducted at the Swedish Match CAL using gas chromatography.

Pharmacokinetic calculations were done using the WinNonlin Pro computer system for pharmacokinetic data analysis (Pharsight Corp., Mountain View, CA). The ratios of pharmacokinetic parameters for snus versus the 2 mg gum were calculated for each participant.

Results

The estimated mean nicotine extraction from the snus products ranged from 22-44%, and showed a large inter-individual variation. The mean nicotine extraction from the gum was estimated at 44%, also with a large inter-individual variation.

For the traditional snus products the mean C_{max} obtained in the last dosing interval ranged from 24-29 ng/ml with 1.0 g pouches, and was 21 ng/ml with the 0.5 g pouch product. The corresponding C_{max} with the novel, drier 0.3 g product and with the nicotine gum was substantially lower, 11 ng/ml, and 13 ng/ml, respectively. The mean AUC of the last dosing interval showed similar differences between the products. The median T_{max} in the last dosing interval was approximately 30 minutes for all tested products.

The snus products were well tolerated and accepted. No adverse events were reported. Adverse events were reported by some when testing the nicotine gum. They were generally mild, and included hiccups, headache, irritated throat, abdominal discomfort, cough, and nausea.

Discussion

The mean plasma nicotine concentration time-curves for the traditional snus products was substantially higher than for the nicotine gum with AUC and C_{max} about 2-2.5 times higher with

the 1.0 g products, and about two times higher with the 0.5 g product. The nicotine uptake was comparable for the nicotine gum and the novel, drier 0.3 g snus product. The two latter products produced nicotine blood levels comparable to those associated with moderate cigarette smoking (7-10 cigarettes/day), whereas the levels observed with the traditional snus products were comparable to those among heavier smokers. One of the 1.0 g traditional products produced steady state nicotine levels comparable to those reported previously for 2.0 g pinches of loose snus.

6.2.7.5.2.3. SM WS 06-Study

The Swedish Match WS 06-study (Lunell and Curvall 2011) evaluated pharmacokinetics and subjective effects following administration of single doses of two different types of traditional Swedish snus compared to a 4 mg nicotine chewing gum (Nicorette®). The study documents (e.g., protocol, full study report, etc.) are attached as Appendix 2J.

Material and Methods

The study used an open-label, randomized three-way cross-over design. A total of fifteen (15) healthy, daily smokers (9 males, 6 females) aged 19-49 years who smoked an average of 15.3 cigarettes per day were included. Ever-users of smokeless tobacco products or nicotine gum were not eligible for inclusion. Subjects were fasting and abstinent from smoking overnight (minimum 12 hours). Non-smoking status was checked by CO level in exhaled air at baseline with an accepted upper level of 11 ppm. One subject was excluded due to a baseline nicotine plasma concentration exceeding 4 ng/ml.

The study products were given as a single oral administration on three separate occasions separated by at least six days. Tested snus products included 1.0 g non-moistened pouches of traditional brands with a pH of approximately 8.7, moisture approximately 50%, and slightly varying nicotine content (approximately 9-10 mg/g). The comparator product was a 4 mg piece of nicotine chewing gum (Nicorette®). Study products were administered for 30 minutes and under the same standardized conditions those used in the SM WS 02-study. Coffee and carbonated beverages were not permitted because they may affect oral absorption of nicotine.

Serial samples of venous blood were drawn at baseline, and 2, 4, 8, 16, 24, 30, 45, 60 minutes, 1.5, 2, 4, 6, and 8 hours after administration of each product. Determination of nicotine in plasma was performed using capillary gas chromatography with nitrogen phosphorous detection after a single liquid-liquid extraction of a basified plasma sample. Pharmacokinetic calculations were done using the WinNonlin Pro computer system for pharmacokinetic data analysis (Pharsight Corp., Mountain View, CA). C_{max}, T_{max}, and AUC_{inf} were defined as primary, pharmacokinetic outcome variables.

Resting, supine heart rate was measured at baseline, and after 10, 20, and 30 minutes. Each subject's rating of subjective effects was recorded using a 100 mm Visual Analogue Scale ("VAS") anchored with "not at all" to "extremely". VAS scores were collected at baseline, and after 5, 10, 20, and 30 minutes. The scores concerned the following dimensions:

- Overall "product strength" (head rush, "buzz", "hit", feeling alert)

- Craving intensity/urges to smoke
- Increased salivation
- Burning sensation in mouth and/or throat

Residual nicotine in the used snus pouches was analyzed to estimate extracted dose. The mean nicotine content of six unused pouches of each product was used for comparison in these calculations. The nicotine analyses used to estimate extracted dose was done at the Swedish Match CAL in Stockholm, Sweden, using gas chromatography.

Results

The estimated mean nicotine extraction from the snus products ranged from 21-25%, and showed large inter-individual variation. The mean nicotine extraction from the gum was estimated at 67%. The estimated absolute amount of extracted nicotine was statistically significantly larger ($p<0.05$) from the gum (mean 2.56 mg) than from the snus products (mean 2.12 mg, and 2.18 mg).

The rise of the nicotine plasma concentration during the first minutes after administration was faster with both snus products than with the gum. At eight minutes, for instance, the mean concentration with the snus products was 7.0-7.2 ng/ml compared to 4.9 ng/ml with the gum. The mean nicotine concentration at 30 minutes (just after stopping dosing) was also higher with both snus products than with the gum. The mean C_{max} with the two types of snus was 14.8 ng/ml, and 13.7 ng/ml, respectively, compared to 12.8 ng/ml with the gum. The mean time to C_{max} was also shorter with snus than with the gum (37 vs 46 minutes) and mean AUC_{inf} was estimated at 3,190 ng x min/ml with the gum vs 3,062 and 2,829 ng x min/ml with the two types of snus

The rating of head rush, salivation, and mouth/throat burn during the first 20 minutes was higher with the snus products than with the gum, reaching statistical significance ($p<0.05$) for the snus product with the higher nicotine content (10 mg/g) for head rush at 20 minutes, and salivation and mouth/throat burn at 5 minutes. Rating of craving/urges to smoke decreased similarly with snus compared to gum.

No subject withdrew from the study due to an adverse event. Two subjects experienced hiccups for about ten (10) minutes during the gum session. One subject experienced coughing during the gum session, and light headache during one of the snus sessions. No subject experienced nausea, dizziness or other systemic effects during any of the sessions.

Discussion

This study demonstrated a faster absorption of nicotine from the tested snus products, and a corresponding faster rise of the score for head rush compared with the 4 mg nicotine gum. Head rush reflects the pharmacological effect in the brain's "reward system", and is central to a smoker's liking of a nicotine-containing product, as well as for the product's abuse potential.

The subjective rating of craving/urges to smoke decreased similarly with snus and gum. The observed discrepancy between the subjective response for head rush and craving may perhaps be explained by the absence of provocative cues. Most smokers easily recognize the head rush from

a cigarette. Craving/urges to smoke, the main acute nicotine withdrawal symptom, constitute a more complex sensation that may not as easily be recognized, particularly in a clinical setting.

The estimated mean extracted amount of nicotine was statistically significantly higher with the gum and the AUC_{inf} slightly higher than with the snus products. The lower C_{max} despite the larger AUC_{inf} may be explained by a slower and more prolonged absorption from the gum.

6.2.7.5.2.4. SM WS 12-Study

This Swedish Match study WS 12 evaluated nicotine pharmacokinetics following administration of different types of snus compared to a nicotine lozenge (Nicorette® Microtab). The study documents (e.g., protocol, full study report, etc.) are attached as Appendix 2K.

Several considerations form the rationale for this study:

- Currently available NRTs, when used as prescribed, typically deliver less nicotine and at a slower rate than snus. This has been cited as one possible reason for their relatively limited efficacy for tobacco cessation purposes.

- Population-based surveys indicate that 10-15% of habitual users of pouched snus often administer two pouches simultaneously, and the pinch size among users of loose snus is typically larger than 1.0 gram (Digard et al. 2009).

- Previous studies have indicated that only a portion of the total nicotine in a snus pouch is extracted and absorbed by the user.

- Extraction of nicotine from snus does not appear to be linear with pouch size, which suggests that surface area, saliva penetration, and diffusion factors may be more important determinants of nicotine absorption than pouch weight.

- It is not known if nicotine uptake from snus is linear with nicotine concentration.

- Consumer surveys and results from controlled clinical trials (Joksic et al. 2011) illustrate that many smokers who switch to snus prefer small, less conspicuous pouches, but small pouches may not deliver enough nicotine to effectively decrease craving/urges to smoke.

Materials and Methods

The study uses an open-label, randomized five-way cross-over design. A total of sixteen (16) healthy, non-smoking, daily snus users aged 18-50 years were included. Non-smoking status during 24 hours before clinical visits will be checked by CO level in exhaled air with an accepted upper level of 10 ppm.

Tested snus products included a brand with a nicotine content of 8 mg/g (1.0 g pouch, and simultaneous use of two 1.0 g pouches), and a brand with a nicotine content of 16 mg/g (1.0 g

pouch and 0.5 g pouch). The comparator product was Nicorette® Microtab nicotine lozenge (3 simultaneous 2 mg tablets). Administration of snus products was for 30 minutes and under the same standardized conditions described for the SM WS 03 study. Coffee and carbonated beverages were not permitted as they may affect oral absorption of nicotine.

Serial samples of venous blood were collected at baseline and at regular time intervals up to 6 hours after administration of each product. Determination of nicotine in plasma was performed using capillary gas chromatography with nitrogen phosphorous detection after a single liquid-liquid extraction of a basified plasma sample. Pharmacokinetic calculations were done using the WinNonlin Pro computer system for pharmacokinetic data analysis (Pharsight Corp., Mountain View, CA). C_{max}, T_{max}, and AUC_{inf} were defined as primary, pharmacokinetic outcome variables.

Residual nicotine in the used snus pouches was analyzed to estimate extracted dose.

Resting, supine heart rate was measured at baseline and during the first 30 minutes. Each subject's rating of subjective effects was recorded using a 100 mm VAS anchored with "not at all" to "extremely." VAS scores collected at baseline and during the first 30 minutes addressed the same dimensions as in the SM WS 06-study, namely:

- Overall "product strength" (head rush, "buzz", "hit", feeling alert)
- Craving intensity/urges to smoke
- Increased salivation
- Burning sensation in mouth and/or throat

Results

As in the previous two studies, the inter-individual extraction efficiency for the snus products showed quite high variability, from 10-57%, although the variability between the different brands was small and intra-individual variability was also small. The relationships between the AUC_{inf} and the in vivo-extracted dose per kg body weight or body surface area showed fairly good linearity. This suggests that amount of nicotine extracted from different brands of pouched snus provides a good prediction of the systemic exposure to nicotine when the humidity and pH of the products are the same. Nicotine was absorbed more slowly from the Nicorette® Microtabs sublingual nicotine lozenges, but systemic exposure was comparable to that for the snus products.

All products, including the nicotine lozenges, increased "head rush" and reduced craving over the first 30 minutes. The effect was the strongest for those allocated to test two 1.0 g snus pouches, but the difference compared to those testing the nicotine lozenges was not statistically significant.

Discussion

The main strengths of the Swedish Match nicotine uptake studies were that they used randomized, cross-over designs, highly standardized administration of products, and state-of-the-art methods for the chemical and pharmacokinetic analyses. They were also conducted under a

governance structure which was the same as that for controlled clinical trials of pharmaceutical products, which was appropriate in light of the fact that different NRT products (gum, lozenge) were used as comparators in all three studies.

Although administration of products was under standardized conditions, there was considerable inter-individual variation in the nicotine uptake from the tested snus products. In addition, extraction of nicotine from snus did not appear to be linear with pouch size, which suggests that surface area, pouch geometry, saliva penetration, and diffusion factors may be equally or even more important determinants of nicotine absorption than pouch weight. It was not possible to assess the relevance of product pH as nearly all tested products had the same pH. The only product with a different, lower pH, the novel product tested in the SM WS 02-study, also differed with respect to other features that could be relevant for nicotine uptake, such as, pouch weight and humidity.

No currently available NRT or smokeless tobacco product can compete with cigarettes in terms of rapid nicotine delivery to the brain. A pulmonary as opposed to oral/gastrointestinal route of administration will always result in quicker and higher nicotine levels in the arterial blood that reaches the brain. This may have implications for a product's dependence-producing effects. It has been suggested that use of smokeless tobacco in general is associated with less dependence than smoking (SCENIHR 2008), as evidenced by higher quit rates among the placebo controls in randomized cessation trials including smokers versus trials including users of smokeless tobacco (Fagerstrom and Eissenberg 2012). In particular, the long-term, continued (9-26 weeks) quitting rate among the placebo controls in a controlled trial of varenicline for tobacco cessation among users of Swedish snus was 33.5% which is much higher than quitting rates typically seen among placebo controls in tobacco cessation trials including cigarette smokers (Fagerstrom et al. 2010).

The pharmacological effects of nicotine on the brain's "reward system" are possibly central to a smoker's liking of nicotine-delivering alternatives to cigarettes, and putatively an important determinant of a product's efficacy for smoking cessation purposes. Slow nicotine delivery and relatively modest success rates with currently available NRTs among smokers who want to quit have been cited as important reasons to develop novel products with a more rapid nicotine delivery (Caldwell et al. 2010). The clinical studies of Swedish snus demonstrate that Swedish snus manufactured according to the GOTHIATEK® standard can deliver nicotine more rapidly than some commercially available NRT products. This may help to explain why many smokers in Scandinavia have been able to quit smoking completely by switching to snus, that snus is the most frequently reported cessation aid in Sweden and Norway, particularly among males, and why success rates with snus appear to be higher among both male and female smokers compared to other quitting aids (Ramström and Foulds 2006; Scheffels et al. 2012).

It is noteworthy that, in the SM WS 06 study, the total amount of nicotine extracted from a 4 mg gum and AUC_{inf} were larger than with the comparator 1.0 g pouch snus products, despite a lower C_{max} with the gum. This suggests that total nicotine exposure among users of at least some types of currently available NRTs is comparable to that among snus users.

A very recent study (Digard et al., 2012) examined many of the same variables addressed in the

three Swedish snus studies discussed above comparing four (4) different snus-like STPs, a cigarette, and nicotine gum. An open-label, randomized, 6-way cross-over study was performed involving 20 healthy Swedish snus and cigarette users. The four snus-like products consisted of 2 pouched ("Lucky Strike Original Brown" and "Lucky Strike Bold") and 2 loose styles ("Granit", 1 or 2.5 g). The cigarette used was "Lucky Strike Red"; the nicotine gum was Nicorette®. The percentage of nicotine extracted from the products was highest for the nicotine gum, with 63% extracted. For the snus-like products, the mean extraction during use was between and 24 and 32%, similar to the data presented for Swedish snus.

Blood nicotine concentrations were ranked according to the total nicotine content of the product. As shown in **Figure 6-5** below, the AUC and C_{max} values ranged from 26.9 to 13.1 ng.h/ml and 17.9 to 9.1 ng/ml, respectively, across all of the products. The authors concluded that "nicotine was absorbed more rapidly from the cigarette but systemic exposure was within the range of the smokeless tobacco products." Absorption kinetics were dependent on quantity of tobacco by weight and total nicotine, rather than by product form. (Digard et al. 2012).

Figure 6-5. Mean Plasma Nicotine Concentrations Following Single Use of Different Tobacco Products and Nicotine Gum

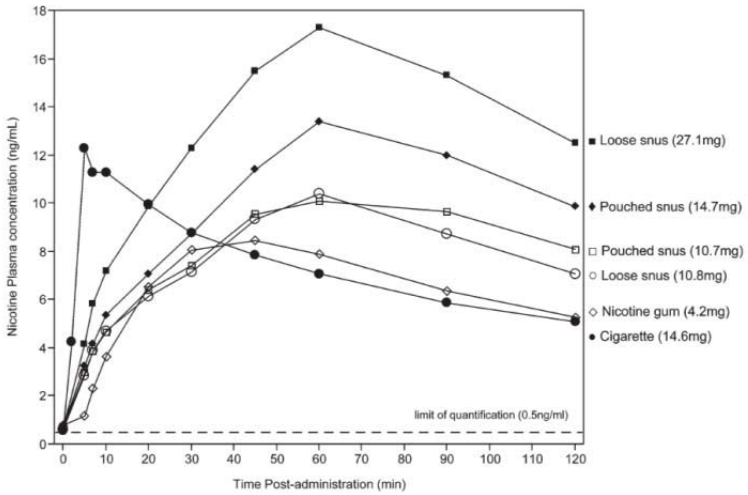

Figure 1. Mean plasma nicotine concentrations at each time point following single use of the different tobacco products and nicotine gum. Products (nicotine content): • Cigarette (14.6 mg); □ Pouched snus (10.7 mg); ○ Loose snus (10.8 mg); ♦ Pouched snus (14.7 mg); ■ Loose snus (27.1 mg); ◊ Nicotine gum (4.2 mg). The dashed line represents the limit of quantification (0.5 ng/ml).

Conclusions

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

dependence in users in Swedish snus is probably less than the dependence to cigarettes.

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

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

6.2.8. References

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Table 6-54. Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
Grams per day/week			
	Grams of smokeless tobacco per day		(1993) (Bolinder 1997; Bolinder and de Faire 1998)
27 (35-60 year old) firefighters in Stockholm	Mean (std dev): 27 (15) Median (25^{th}, 75^{th} percentile): 21 (14, 36)		
	Mean (std) grams per day		(1992-1993) (Ibrahim et al. 1996)
15 male patients in Göteborg, Sweden who were suspected to have snuff-induced oral lesions	36.1 (17.6)		
Current users (n=31)	Consumption (g/day)		People in the southern healthcare region of Sweden with no previous cancer diagnosis (controls only), 2000-2004 (Rosenquist et al. 2005)
	1-14	>14	
	68%	32%	
Portion snus (n=23)	Mean (std) g/day	g/day range	Healthy men who used snus but not other tobacco for >= 3 months, subset of sample used by (Andersson 1991), chewing tobacco users were a subset from (Andersson et al. 1994)
	14.4 (7.1)	5.8-32.8	
Loose moist snus (n=22)	20.8 (15.5)	6.7-82.4	
Chewing tobacco (n=9)	7.2 (4.0)	1.9-12.7	
	Grams per day (mean=22.5 g day)		Swedish construction workers' cohort males, 1978-1993

Table 6-54. Patterns of Snus Use in Scandinavia					
	Intensity of Use				Data source (Reference)
	<12.5	12.5-24.9	25.0-50	>50	(Hergens et al. 2008b; Hergens et al. 2008a)
Current users (n=32,973)	21.8%	45.0%	22.8%	10.4%	
	Grams per day				Ice-hockey players and students in Värmland (Rolandsson et al. 2005)
	<50	50	>50		
	78%	18%	5%		
Snuff users (n=92)	Mean (95% CI) g snuff use/day				Males in Northern Swedish MONICA sample (1990) (Eliasson et al. 1995)
	22.9 (20.7, 25.0)				
	Mean (std) g per day				(subsample of Axel 1976 sample) with degree 3 or 4 lesions (Andersson and Warfvinge 2003)
20 habitual non-smoking users of loose snus	36 (17) g/day				
	Mean (std) g per day				(Wedenberg et al. 1996)
15 regular snuff users who did not smoke and had snuff induced lesions	36.1 (17.6)				
	Mean (range) grams per day				(Axell et al. 1976)
114 male snuff dippers who underwent biopsy	13.8 (4 - 50)				
	Average consumption of snus per day				(Svenska Tobaks AB, Basdata om tobakskonsumtion 1992,

Table 6-54. Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
Loose snus:	15.7 g/day		TEMO AB, reported by Andersson et al. 1994)
Portion snus:	9.3 g/day		
	Median daily consumption		Controls in a case-control study (Schildt et al. 1998)
Controls selected from the National Population Registry and National Registry for Causes of Death	2 packages (100 grams)		
Grams per week			
Daily snuff users in southern Sweden (9 nonsmokers, 1 smoked on weekends) (n=10)	Average weekly snuff consumption (g)		(Holm et al. 1992)
Regular snuff users, not current smokers, hospital workers (n=27)	160		
	152		
Current users (n=48)	Median grams per week (range)		18-75 year olds in Göteborg (Gyllen et al. 2004)
	88 (12 to 525)		
n=91	Grams per week		Controls: 40-79 year olds in Stockholm and southern Sweden (1988-1991) (Lewin et al. 1998)
	<=50 g/week	>50 g/week	
	63%	37%	
	Mean (std dev) current consumption (g/week)		Male who did not use tobacco, used >=1 can (50 g) snuff per

Table 6-54. Patterns of Snus Use in Scandinavia				
	Intensity of Use			**Data source (Reference)**
n=21	146 (60)			week for 2 years or smoked >= 10 cigarettes per day for 2 years (Eliasson et al. 1991; Eliasson et al. 1993)(Ellingsen et al. 2009)(Ellingsen et al. 2009)
	Grams of snuff used per week Mean Range			Blue-collar workers in southern Norway (Ellingsen et al. 2009)
Snuff only users (n=11)	75	2-200		
Smokers who use snuff (n=2)	2.6	0-50		
Pinches/quids per day/week				
13 boys who regularly used snuff	Mean consumption (pinches per day)			Schoolchildren in Huddinge (outskirts of Stockholm) (Modeer et al. 1980)
	5			
Snus users	Quids per week in past 2 years			Controls (<80 year olds, 1995-1997) who used >= 1 quid per week for >= 6 months (Lagergren et al. 2000)
	1-14	15-35	>35	
n=124	36%	27%	36%	
Regular users (n=28)	Mean pinches per week			Subsample of the BROMS cohort (Post et al. 2005)
	31			
Cans/boxes per day/week				

Table 6-54. Patterns of Snus Use in Scandinavia							
	Intensity of Use						Data source (Reference)
Tobacco use	Average cans/week (1 can = 24–50 g)						18-80 year olds in Northern Sweden (1998) (Aro et al. 2010)
Snus only	3.2						
Snus and cigarettes	2.2						
Snus use	≤ 4 cans/week				> 4 cans/week		Males in Twin registry (Hansson et al. 2009)
Former (1,456)	81.7%				18.3%		
Current (2,661)	77.0%				23.0%		
Gender	≤ 4 cans/week				> 4/cans per week		Vasterbotten Intervention Programme 30-50 year old current snus users (1990-1994 - baseline, 10-year follow-up) (Norberg et al. 2006)
Males (n=7,692)							
Baseline	77%				23%		
Follow-up	74%				26%		
Females (n=8,880)							
Baseline	88%				12%		
Follow-up	87%				13%		
n=33	Boxes/week						Non-smoking male 19-year-olds living in the community of Goteborg, Sweden (Monten et al. 2006)
	1	2	3	4	5	>=6	
	21%	45%	12%	6%	12%	3%	

Table 6-54. Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
	Mean boxes per week: 2.6 (std dev = 1.5)		
	Current # of snus boxes per week		(Persson et al. 2000)
2,599 males born between 1938-1957, living in Stockholm, oversampled men with a strong family history of diabetes	<2	>=3	
	48%	52%	
	Mean (95% CI) cans of snuff/week		Males in Northern Swedish MONICA sample (1990) (Eliasson et al. 1995)
Snuff users (n=92)	3.2 (2.9, 3.5)		
Snuff users who smoke (n=38)	2.5 (2.2, 2.9)		
Snus user (did not smoke, used snus >= once/week)	Mean: 3.5 cans per week		Males in a small municipality in rural southwest Sweden, 2001-2003. (Sundbeck et al. 2009)
	Packages (1 package = 14 g) of chewing tobacco used per day		(Axell et al. 1992)
	Mean # days per package	Range of packages per day	
20 users of a non-fermented Swedish brand of chewing tobacco	4.2	1.5-10	
Hours/Times per day			
	Hours per day using snus		(Sweden) (Wallstrom et al. 2010)
	Mean (std dev)	Range	

Table 6-54. Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
50 non-smoking daily snus users who use > 2 cans/week (>100 g snus) for ≥10 years	15.2 ± 2.1	7 to 22	
	Mean (std) # hours per day with snuff in mouth		(Wedenberg et al. 1996)
15 regular snuff users who did not smoke and had snuff induced lesions	13.1 (3.8)		
	mean (std) hours per day of snuff use		(1992-1993) (Ibrahim et al. 1996)
15 male patients in Göteborg, Sweden who were suspected to have snuff-induced oral lesions	13.1 (3.8)		
	Mean (range) hours per day		(Axell et al. 1976)
114 male snuff dippers who underwent biopsy	6.8 (1 - 24)		
	Mean (std) hours/day	hours/day range	Healthy men who used snus but not other tobacco for >= 3 months, subset of sample used by (Andersson 1991) chewing tobacco users were a subset from (Andersson et al. 1994)
Portion snus (n=23)	13.1 (3.1)	8.0-20.0	
Loose moist snus (n=22)	12.3 (3.6)	6.0-16.0	
Chewing tobacco (n=9)	13.0 (4.0)	7.5-17.0	

Table 6-54. Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
20 users of a non-fermented Swedish brand of chewing tobacco	Hours per day using chewing tobacco Mean: 10.7 Range: 3.5-22		(Axell et al. 1992)
	Times per day		(Luomanen et al. 1997)
	Range	Mean	
11 moist snuff users in Finland	4-10	8	
	Times per day		Case-control study, 40-79 year olds, born in Sweden, living in 1 of 5 counties in northern or central Sweden (1989-1995), controls selected from population registers (Ye et al. 1999)
	<=5	>5	
Current users (n=191)	59%	41%	
Total consumption			
	Total consumption (kg)		Controls: 40-79 year olds in Stockholm and southern Sweden (1988-1991) (Lewin et al. 1998)
	<125	>=125	
n=91	69%	31%	
	Mean (std dev) cumulative tobacco consumption (kg)		(Eliasson et al. 1991; Eliasson et al. 1993)
21 males who used >=1 can (50 g) snuff per week for 2 years or smoked >= 10	52.2 (35.1)		

Table 6-54. Patterns of Snus Use in Scandinavia						
	Intensity of Use					**Data source (Reference)**
cigarettes per day for 2 years						
	Median lifetime consumption among controls					Controls in a case-control study (Schildt et al. 1998)
Controls from the National Population Registry and National Registry for Causes of Death	156.0 kg					
	Used >= 5 can-years (average # of cans per week *year used snuff)					31-40 year olds Stockholm residents born in 1945-1954 (Wickholm et al. 2004)
Current snuff users (n=122)	78%					
Former snuff user (n=31)	60%					
Type of snus						
Gender and frequency of snus use	Snus product used often					16- to 20-year-olds living in Norway (Wiium and Aaro 2011)
Males Males	Traditional loose snus	Portion snus	Mini portion snus	Loose and portion	Don't know	
Occasional (n=94)	21.3%	60.6%		16%	2.1%	
Weekly (n=40)	27.5%	70.0%		2.5%	0%	
Daily (n=260)	44.6%	40.4%		15%	0%	
Total (n=394)	37.3%	48.2%		14.0%	0.5%	

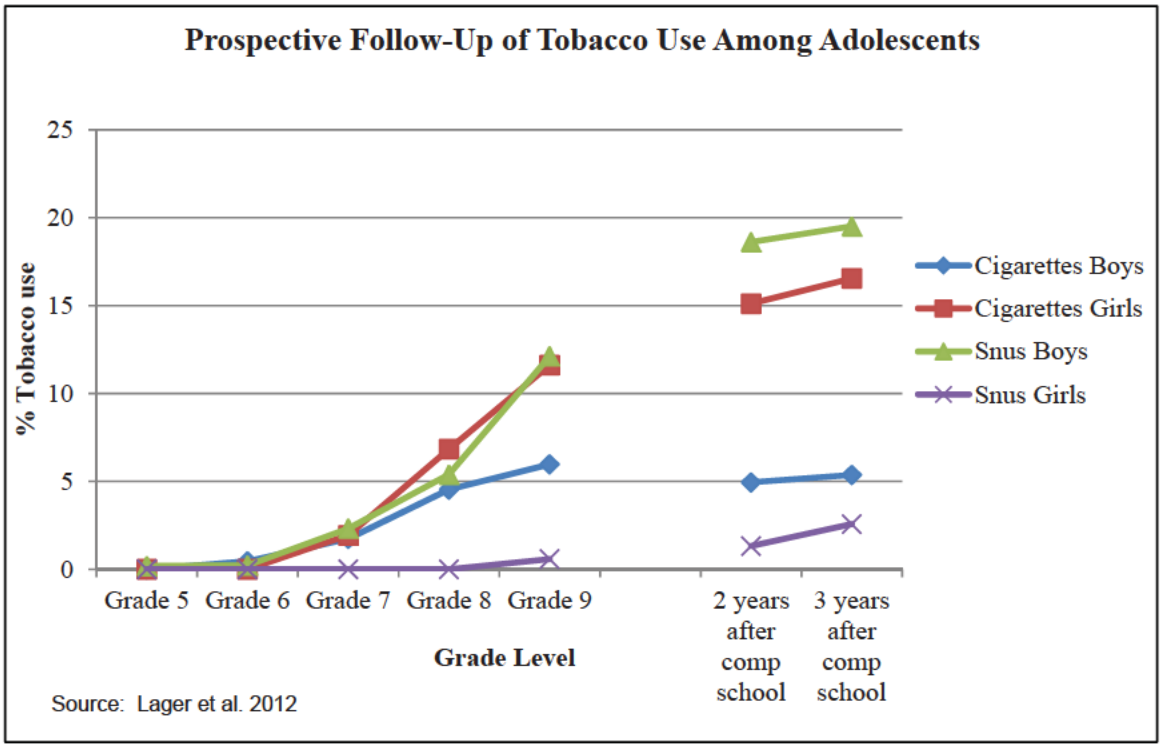
Table 6-54. Patterns of Snus Use in Scandinavia						
	Intensity of Use					Data source (Reference)
Females						
Occasional (n=107)	4.7%	59.8%	25.2%	4.7%	5.6%	
Weekly (n=29)	0%	65.5%	27.6%	6.9%	0%	
Daily (n=59)	5.1%	78.0%	11.9%	5.1%	0%	
Total (n=195)	4.1%	66.2%	21.5%	5.1%	3.1%	

6.3 Effect on Tobacco Use Initiation among Non-Users

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

Several studies have focused on snus uptake, some of which focus specifically on adolescents (Edvardsson et al. 2009; Galanti et al. 2001; Galanti et al. 2008; Ramström and Foulds 2006). Tobacco uptake is often initiated at an early age. Smoking is generally initiated between 10 and 13 years of age, with a rapid increase occurring between the ages of 14 through 15 years (Edvardsson et al. 2009; Furberg et al. 2008b; Galanti et al. 2008). Adolescent males surveyed as part of the BROMS cohort initiated snus at the median age of 15 years; while females exhibited snus use at 18 years (Galanti et al. 2008). Overall, snus uptake seems to occur between ages 15 through 18 years (Furberg et al. 2008b; Post et al. 2010; Wiium and Aaro 2011).

Figure 6-6. Prospective Follow-Up of Tobacco Use Among Adolescents



The proportion of adults over age 18 who use snus in both Sweden and Norway vary by age (**Table 6-55**, which appears after the reference list to this section). Those younger than about age 60 years are more likely to use snus than older adults. According to data from the Swedish Council for Information on Alcohol and Other Drugs (CAN) (as reported by Hvitfeldt and Gripe 2009), daily snus use was highest among males aged 16 – 29 years old, followed by 30-44 year olds, 45 -64 year olds and those 65 years or older, 22%, 21%, 19% and 9% respectively. This pattern was observed in other national surveys in both Sweden and Norway (Lund and Lindbak 2007; Statistics Sweden 2007).

Among adolescents, daily snus use was higher among those in higher grades compared to the lower grades (Lund and Lindbak 2007). Galanti and colleagues conducted six follow-up assessments on tobacco use behaviors among adolescents in the BROMS cohort, which followed students from fifth grade (approximately age 11 years old) to three years after compulsory school (approximately age 19 years old)) (Galanti et al. 2001; Galanti et al. 2008; Lager et al. 2012). The figure below shows the prevalence of use at the different follow-up periods for cigarette smoking and snus use among adolescent boys and girls in this cohort. Among girls, daily snus use was low in compulsory school (1-2%) and was still low two to three years after compulsory school (2-3%). Cigarette use among school-age girls increased from 7th through 9th grades from approximately 3% to 12%; with the increasing trend continuing two to three years following completion of compulsory school, 15% to 17%. Among school-aged boys, daily snus use increased from 7th to 9th grades from about 3% to 13%. Two to three years after compulsory school, daily snus use had increased, and was reported by 18 to 20% of these boys. Cigarette use among boys, typically followed a similar trend, with an increase from 2% to 6%, from 7th through 9th grade. Two to three years post compulsory school, cigarette use remained steady, at approximately 5-6%. One-year follow-up revealed that among male baseline non-tobacco users (n=1,114), 1.7% became oral snuff users, 12.3% became cigarette smokers, and 5.7% became dual users by follow-up in the 6th grade. Among female non-tobacco users (n=1,185) by one-year follow-up, 1% became oral snuff users, 15.5% initiated cigarette smoking and 1.8% became dual tobacco users (Galanti et al. 2001). For both male and female non-tobacco users, snus-only initiation was lower than for smoking. Overall, compared with never users, ever users of tobacco at baseline had a higher risk of continuing to smoke or to be smokeless tobacco users at the end of follow-up.

Galanti and colleagues (2001) also measured susceptibility to tobacco use as a lack of firm intention not to smoke or use oral snuff (snus) in the near future among never tobacco users at baseline (i.e., not strongly opposed to starting). Adolescent non-tobacco users classified as "susceptible" to smoking at baseline were more likely to have experimented with smoking a year later, OR= 3.6; 95% CI: 2.7 – 4.8 (Galanti et al. 2001). Overall, the relative likelihood of snus use for susceptible boys were comparable to that of smoking (OR= 6.1 vs. 6.2). Susceptibility to snus was not assessed among female students given their low prevalence of oral snus (Galanti et al. 2001). The authors further reported that tobacco initiation was gender-dependent. A higher proportion of snus starters were boys (15.5%) compared to girls (6.8%) and a higher proportion of cigarette starters were girls (82%) compared to boys (57.3%). (Galanti et al. 2008).

Among adult Swedes, almost all daily smoking (91%) had been initiated by age 22 years, while initiation of daily snus use continued throughout all age ranges (Ramström and Foulds 2006). In addition, fewer than 10% of Swedish daily male smokers started smoking after age 22, whereas a third of snus users started after age 22 years, regardless of their tobacco use status. Daily snus use was most common among participants aged 25 to 44 years, while daily smoking is most common in ages 45–64 years (Ramström and Foulds 2006).

Three studies assessed population trends in tobacco use among adults in Sweden and Norway (Lundqvist et al. 2009; Norberg et al. 2011; Rodu et al. 2003). Lundqvist and colleagues

(2009)conducted a population trend survey among middle-aged adults n=4327 males, n=6288 females) in Northern Sweden and found that, at follow-up, among tobacco-free participants at baseline, 328 women (5%) and 368 men (7.8%) initiated tobacco use during the 10-year period, some of whom were former tobacco users (ex-smokers) that had relapsed, 2.2% and 3.2% respectively. Overall, males were more likely to initiate snus use compared to females; while females were more likely to initiate cigarette smoking (Lundqvist et al. 2009; Norberg et al. 2011). Rodu et al. (2003) assessed tobacco patterns among adult men and women in the MONICA project survey. In the follow-up of five to thirteen years, never users of tobacco were the most stable group (98%) compared to tobacco users. Snus use or cigarette initiation was more common among those already using tobacco compared to never users or ex-tobacco users (Rodu et al. 2003).

Summary: In Sweden and Norway, uptake of snus occurred across all age categories compared to cigarette uptake which appeared to occur more frequently at a younger age. In addition, tobacco initiation was shown to be gender-dependent, as males were more likely to initiate snus while females more likely to initiate cigarette smoking. Studies in Sweden and Norway have shown that snus initiation was more prevalent among former cigarette smokers than among non-tobacco users (Furberg et al. 2005; Furberg et al. 2006; Lund et al. 2010; Lund et al. 2011). In addition to this evidence in the published literature, additional evidence that non-tobacco users are not likely to initiate snus use or purchase based on modified risk claims comes from the Swedish Match Consumer Perception Study (discussed in detail in Section 6.4). In this study, modified risk product claims did not encourage non-users of tobacco to either use snus or influence their decision to buy snus.

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

Using the Swedish Level of Living Survey (ULF) survey from 1988/9 and 1996/7, Stenbeck et al. (2009) examined whether the use of snus in1988/9 was associated with smoking in 1996/7. Participants were stratified by age, with a younger (16 – 44 year olds) and an older sub-group (45 – 84 year olds) to account for tobacco habits established at younger ages. The authors found that, compared to non-snus users at baseline, younger participants who were considered "snus beginners" and those who were consistent snus users were more likely to stop smoking compared to smoking initiation. Among older participants and compared to non-snus users, those who began snus use in the follow up period had nearly equal odds of either initiating or quitting cigarette smoking (OR 8.2 vs. 6.6). Among older participants, consistent snus users were no different from the non-snus users in initiating or quitting cigarette smoking. Among the younger cohorts, those who quit snus use during the follow-up period were more likely to initiate smoking (~6% of the snus users), although, the authors noted that "the overall net effect was small, as this group represented very few people." In sum, the authors concluded that 1990s snus use was associated with a greater incidence of smoking cessation than smoking initiation. Smokers who started using snus were much more likely than non-snus using smokers to quit smoking.

Several cross-sectional studies on the relationship between snus use and cigarette smoking support some of the findings observed in the longitudinal studies (Furberg et al. 2005; Ramström and Foulds 2006). Furberg et al. (2005) evaluated the association between snus use and subsequent smoking initiation among adult males as part of the Swedish SALT twins study. Men who had used snus before they started smoking were compared to men who had never used snus in relation to any lifetime smoking while adjusting for age and other variables associated with smoking initiation. Results from this study suggested that "regular" and "now and then" snus use was inversely associated with smoking initiation.

Ramstrom and Foulds (2006) analyzed retrospective data from a cross-sectional survey completed by adult males participating in the Sweden Your Country and Your Life national survey. Among male primary snus users, 20% reported that they started daily smoking. This is compared to non-primary snus users, among whom more than twice as many (47%) reported that they started daily smoking. Thus, male primary snus users had a decreased likelihood of initiating smoking compared to non-snus users (OR= 0.28; 95% CI: 0.22 - 0.36). The authors concluded that the likelihood of initiating daily smoking was significantly lower for those who had started using snus than for those who had not. Among primary snus users who started secondary smoking (potential gateway subjects), 74% later ceased daily smoking, 56% returned to exclusive daily snus use and 18% had, by the time of the survey, quit tobacco use altogether.

Youth Behaviors: Galanti and colleagues (2001; 2008) assessed tobacco initiation among adolescents between the ages of 11 and 18 years in 5th grade through three years post-compulsory school (n = 2,938). At one-year follow-up (6th grade), the authors reported that 36% of baseline snus (called snuff) users (n=52) had also smoked while the others remained snus-only users; among baseline cigarette smokers (n=419), 18% used snus at follow-up (Galanti et al. 2001). In the longer follow-up at 3-years post-compulsory school, a more established pattern was observed. The authors reported that, compared to non-tobacco users, baseline snus users were not more likely to become cigarette smokers at follow-up (OR= 1.95; 95% CI: 0.96 – 3.8); and that exclusive cigarette users (OR= 2.89; 95% CI: 2.25 – 3.71) and mixed starters (OR= 4.81; 95% CI: 3.09 – 7.5) were more likely to smoke cigarettes at the end of follow-up. The likelihood of being a current smoker at end of follow up was higher, but not significantly so, for cigarette starters compared with snus starters (OR=1.42; 95% CI: 0.98 - 2.1), and those who were mixed starters (cigarette and snus) were more likely to smoke at follow-up (OR=2.54; 95% CI: 1.68 – 3.91) (Galanti et al. 2008). Due to the low rates of snus initiation and smoking progression among snus starters, the authors concluded that "at most 6% of the final smoking prevalence in this cohort could theoretically be attributable to the gateway effect of snus." The results demonstrated that initiating tobacco use with both snus and cigarettes was a stronger predictor of being a current smoker by the end of follow up. Snus starters had a lower risk of being a current tobacco user at follow up when compared to those who had experimented with both products at the earlier time point. Thus, the authors concluded that, "[p]rogression of tobacco use in adolescence is not predicted by onset with snus or cigarettes, but rather by initiation with both tobacco types close in time and/or at young age. The proportion of adolescent smoking prevalence attributable to a potential induction effect of snus is likely small" (Galanti et al. 2008).

Grotvedt and colleagues (2013) assessed smoking initiation among 16-year old Norwegian males (n = 1,440) and followed them for three years. The authors reported that baseline snus use was not associated with increased likelihood of smoking only at follow-up (OR= 0.86; 95% CI: 0.40 - 1.81); after adjusting for "previous smoking" experience. However, baseline snus users were more likely to be dual users, defined as occasional smokers and daily snus users (OR= 1.88; 95% CI: 1.06 - 3.33). There were no trends of switching from use of snus alone to cigarettes alone. Furthermore, baseline smokers were most likely to remain smokers (OR= 13.31; 95% CI: 8.2 - 21.6) or become dual users (OR= 10.74; 95% CI: 6.56 - 17.57). In addition, adolescents using snus only at baseline were more likely to be tobacco free (24%) at follow-up than smokers and dual users (14% and 15%, respectively). The authors concluded that snus use at baseline increased the risk of being a dual tobacco user.

Haukkala and colleagues conducted a 3-year longitudinal study among students participating in their schools' (n = 27) smoking prevention program in Helsinki, Finland (Haukkala et al. 2006). Because the prevalence of snus (called "oral snuff") experimentation was low among girls, the authors' examined the impact of snus experimentation upon later smoking among boys at three time points, 8th grade, and start and end of 9th grade. In predicting the impact of snus experimentation on later smoking, they compared those who had at least tried snus to those who had never tried. Those who had tried snus but were not regular smokers in 7th grade (baseline) had a higher risk for regular smoking in the 8th grade (OR= 6.21; 95% CI: 3.20 – 12.06). In a similar model, 8th grade snus experimentation predicted weekly smoking at the start of 9th grade (OR= 4.38; 95% CI: 2.82 – 6.80). Similarly, boys who were regular smokers at baseline had a higher risk of snus use at one year follow-up (OR= 7.26; 95% CI: 7.26 – 14.67). The impact of snus experimentation upon later smoking experimentation was smaller than vice versa which the authors attributed to the greater prevalence of smoking experimentation than snus experimentation.

6.3.3. Likelihood that former users of tobacco products will re-initiate use with the tobacco product.

As discussed above, three clinical trials in which snus was used as a cessation aide to smoking reduction have been published (Fagerstrom et al. 2012; Joksic et al. 2011; Sharp et al. 2008); as well as a pooled analysis of the two randomized controlled trials (Rutqvist et al. 2013).

A 48-week randomized, double-blind, placebo-controlled clinical trial of the use of snus as a smoking reduction and cessation aid was conducted in 319 smokers in Serbia from January 2008-March 2010 (Joksic et al. 2011). The study assessed the reduction in smoking by 50% during the first 24 weeks of the trial, and eventual smoking cessation (weeks 24-48). Smoking cessation using carbon monoxide (CO) measurements was verified at 12-week intervals. Although the proportion of participants who achieved the ≥50% reduction in smoking was equivalent in the two groups, a higher proportion of participants in the snus group achieved extreme reduction (≥ 75%) in smoking after 24 weeks compared to the placebo group (snus group: 15/158, 9.5% vs. 4/161, 2.5%). The proportion of participants who achieved 24 week cessation by the end of trial was higher in the snus group (5.7%) compared to the placebo group (1.9%), with an odds ratio of 3.3 (95% CI: 0.9 - 12.5, p=0.08).

A double-blind, placebo-controlled trial in which snus was tested for smoking cessation was conducted at five U.S. trial sites from February 2009 to March 2010 (Fagerstrom et al. 2012). Smoking cessation using CO measurements was verified at weeks 6, 10, 16 and 28. The continuous abstinence rate at end of trial (cumulative for weeks 6-28, or 23 weeks total) in the snus and placebo groups, each with 125 participants, were 4.0% and 1.6% respectively; with an odds ratio of 2.5 (95% CI: 0.4 - 27, p=0.45), which was not statistically significant.

The data from these two placebo-controlled clinical trials using snus as a cessation aid were combined into a pooled analysis (Rutqvist et al. 2013). The single estimate of cessation at 23 or 24 weeks (6 months), pooled from the two studies, was 2.83 (95% CI: 1.03 – 7.75, exact p=0.06, chi squared p=0.03). Although neither of the individual studies achieved statistical significance, and the pooled estimate is of borderline significance, the point estimates of the likelihood of achieving smoking cessation using snus compared to a placebo are consistent with other nicotine replacement modalities, reported by Silagy et al. (2004) and Stead et al. (2012).

Three studies assessed population trends in tobacco use among adults in Sweden and Norway (Lundqvist et al. 2009; Norberg et al. 2011; Rodu et al. 2003). Lundqvist and colleagues conducted a population trend survey among middle-aged adults in Northern Sweden and found that, among tobacco-free participants at baseline, 5% (328) of women and 7.8% (368) of men initiated tobacco use during the 10-year follow up period, 2.2% and 3.2% respectively of whom were former tobacco users (ex-smokers) that had relapsed. Among male smokers (n = 1,104), 25.9% quit smoking completely compared to 13.6% who switched to snus. Among female smokers (n = 1,914), it was four times more common to stop smoking without snus than to switch to snus (33% vs. 8.2%). The smoking cessation rate in this cohort was 4% over the 10-year period; the authors noted that this percentage is lower than cessation rates in other studies with shorter follow-up periods which, they suggested, might reflect the increasing risk for relapse over time. Overall, males were more likely to initiate snus use compared to females, while females were more likely to initiate cigarette smoking (Lundqvist et al. 2009; Norberg et al. 2011). The authors also noted that, although sustained snus use over the follow-up period was common for both males and females, it was more common for those who were snus free at follow-up to remain nicotine free than to switch to cigarette smoking. Lundqvist et al. (2009) suggested that the sustained use of snus over the follow up period suggested a prolonged state of nicotine addiction, and Norberg et al. (2011) have also suggested that snus use may prolong nicotine addiction.

Rodu et al. (2003) assessed tobacco use patterns among adult men and women in the MONICA project survey. In the follow-up of five to thirteen years, never users of tobacco were the most stable group (98%) compared to tobacco users. Former dual users (concurrent use of both snus and cigarettes) were much less stable than former users of either cigarettes or snus. The authors reported that ex-dual users who were using tobacco again at follow-up chose snus over cigarettes by a three to one margin. Snus use or cigarette initiation was more common among those already using tobacco compared to never users or ex-tobacco users (Rodu et al. 2003).

Although it is difficult to draw conclusions from the cross-sectional analyses, they nonetheless support snus uptake as a smoking cessation tool, especially among adult Swedish men (Furberg

et al. 2005; Furberg et al. 2006; Gilljam and Galanti 2003; Lund et al. 2010; Lund et al. 2011; Ramström and Foulds 2006; Scheffels et al. 2012).

Among adult males participating in the Swedish twins (SALT) survey, discussed as a prospective study in section 6.2, men who were regular snus users were three times more likely to be former smokers than current smokers at the cross-sectional analyses (Furberg et al. 2005; Furberg et al. 2006). Furberg et al. (2008a) assessed the association between smoking cessation in ever regular smokers and their history of snus use in the SALT cohort, and found that snus use was associated with being a former regular smoker (HR=2.7; 95% CI: 2.3 – 3.2). In a retrospective study conducted among former and current Swedish adult smokers, Gilljam and Galanti (2003) found that there was an increased likelihood of being a former smoker than a current smoker among ever snus users (OR= 1.72; 95% CI: 1.30 – 2.28) or current snus users (OR=1.81; 95% CI: 1.31 – 2.53), considering age, education and use of nicotine replacement therapy.

Gilljam and Galanti (2003) found that the mean duration of abstinence was longer among former smokers who were never snus users than among those who were ever snus users. The authors further reported that having used snus at the latest quit attempt increased the probability of being abstinent by about 50% (OR= 1.54; 95% CI: 1.09 – 2.20). Their results suggested that Swedish male smokers who used snus may increase their overall chances of abstinence, but that snus may not be a necessary component of smoking cessation at the population level (Gilljam and Galanti 2003).

Two cross-sectional studies published by the Norwegian Institute for Alcohol and Drug Research and UK Centre for Tobacco Control Studies and University of Nottingham surveyed a large sample of Norwegian adults for smoking cessation methods and outcome of last attempt to quit smoking (Lund et al. 2010; Lund et al. 2011). Among former (n = 1,775) and current smokers (n = 1,808), snus use (17%) was reported as the most common method for quitting smoking compared to other medicinal nicotine products, such as nicotine patches (4%), nicotine chewing gum (10%), and Zyban (3%). For all quitting methods surveyed, the proportion of unsuccessful quitters (current smokers) was greater than the proportion of successful quitters (former smokers); however, the ratio of successful to unsuccessful quitters was higher for snus than for the other smoking cessation methods (Lund et al. 2010). In addition, total abstinence at time of survey was significantly higher for snus use-only than for any other methods of quitting (OR= 2.66, $p<0.001$). Among smokers who reported using snus to quit (n = 671), 62.4% reported still using snus at time of survey, while only 9.5% of smokers who had used nicotine chewing gum or patch still used these nicotine replacement products; however, 75% of those who were still using snus reported at least some reduction in the amount smoked.

Similar findings were reported by the same researchers in a meta-analysis of seven cross-sectional studies among Norwegian former/current smokers (Lund et al. 2011). The meta-analysis combined studies that provided usable information for calculating the quit ratio for smoking (number of former daily smokers as a proportion of ever smokers in a population), among Norwegian adults, aged 16- 74 years. Quit ratios for the individual studies varied, ranging from 32.2% in a nationally representative sample, among those aged 16-20 years to 67.4% in a student population in Oslo. In general, the quit ratio for smoking was significantly

higher for daily snus users than for never snus users (6 out of 7 studies), although, the quit ratio for smoking among those who used snus occasionally was significantly lower compared to never snus users. Overall, former smokers formed the largest group of snus users (6 out of 7 studies). Daily snus use was associated with former smoking but occasional snus use was less likely to be associated with being a former smoker (Lund et al. 2011). Another pooled analysis by the same researchers, combining studies conducted among Norwegian adults who were surveyed as part of Statistics Norway, reached similar conclusions (Scheffels et al. 2012). The authors compared smoking cessation with snus to other nicotine replacement therapies. The study results showed that snus was the most common method for quitting smoking among male participants, while women were more likely to use nicotine replacement therapies. These studies showed that snus was the most prevalent method used among all categories of smokers and former smokers (Lund et al. 2010; Lund et al. 2011; Lund and Lindbak 2007).

Summary: The clinical trials in which snus use was specifically used for smoking cessation support resulted in a success rate roughly equivalent to other NRTs. However, since there was no long term follow-up beyond the 6-month trial, relapse rates are unknown. Data from Scandinavian cohorts have further shown that being a former smoker is common among snus users (Lund et al. 2010; Lund et al. 2011; SCENIHR 2008; Scheffels et al. 2012), although there is some suggestion that there are low rates (5%) of relapse among former smoking snus users (Lundqvist et al. 2009). Additional evidence that former tobacco users are not likely to re-initiate tobacco use or purchase products based on modified risk claims comes from the Swedish Match Consumer Perception Study (discussed in detail in Section 6.4). In this study, modified risk product claims did not encourage former tobacco users to re-initiate use of this tobacco product or motivate them to purchase snus. As with the other non-users of tobacco, the modified risk claims were less likely to deter former users from using or purchasing snus.

6.3.4. References

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Table 6-55: Snus Users in Scandinavia by Age and Sex							
	Males			Females			Data source (reference)
Scandinavian National Surveys							
Age (years)	Daily		Occasionally	Daily		Occasionally	Swedish National Institute of Public Health 2011
16-29	17%		10%	5%		9%	
30-44	21%		9%	4%		4%	
45-64	21%		4%	3%		2%	
65-84	11%		2%	2%		0%	
Column percents	Daily	Weekly	Occasionally	Daily	Weekly	Occasionally	Snus using 16- to 20-year-olds living in Norway 2007 (Wiium and Aaro 2011)
Age began using snus (years)							
9–11	2.3%	0%	2.1%	1.7%	3.4%	0	
12–14	28.5%	35.0%	17.0%	13.6%	3.4%	11.2%	
15–17	62.7%	50.0%	66.0%	72.9%	75.9%	66.4%	
18–20	6.5%	15.0%	14.9%	11.9%	17.2%	22.4%	
Age began using snus regularly (years)							

Table 6-55: Snus Users in Scandinavia by Age and Sex							
	Males			Females			Data source (reference)
9–11	0.8%	0%	3.2%	-	-	-	
12–14	11.9%	15.0%	10.6%	5.1%	0%	7.5%	
15–17	67.7%	57.5%	64.9%	66.1%	58.6%	57.9%	
18–20	19.6%	27.5%	21.3%	28.8%	41.4%	34.6%	
2007	Daily			Daily			Sweden (Hvitfeldt and Gripe 2009)
16-29	22%			5%			
30-44	21%			4%			
45-64	19%			4%			
65-84	9%			1%			
2005	Daily or Occasional Snus Use						Population data, Norway. (Lund and Lindbak 2007)
Grade 8	5%						
Grade 9	15%						
Grade 10	29%						
2004-2006	Daily		Occasional				
16-24	17%		17%				
25-34	19%		9%				
35-44	11%		4%				

Table 6-55: Snus Users in Scandinavia by Age and Sex				
	Males		Females	Data source (reference)
45-54	6%	5%		
55-64	2%	4%		
65-74	1%	--		
Studies in the peer-reviewed literature				
40 year olds (n=12,341)	28.1%		11.8%	Data from the Sweden Vasterbotten Intervention Programme, 2002 - 2007 (Norberg et al. 2011)
50 year olds (n=13,046)	23.8%		6.2%	
60 year olds (n=13,023)	17.5%		2.5%	
Age (years)	OR (95% CI) for current daily snus use versus non-use, adjusted for age, occupational class, disposable income and education		OR (95% CI) for current daily snus use versus non-use, adjusted for age, occupational class, disposable income and education	Stockholm Public Health Survey, 18-84 year olds in Stockholm County (2006) (Engstrom et al. 2010)
18-24	1.00		1.00	
25-34	0.92 (0.74, 1.14)		0.63 (0.43, 0.92)	
35-44	0.85 (0.69, 1.06)		0.72 (0.50, 1.04)	
45-54	0.58 (0.46, 0.72)		0.59 (0.40, 0.86)	
55-64	0.31 (0.25, 0.39)		0.22 (0.15, 0.35)	
65-74	0.18 (0.14, 0.24)		0.14 (0.08, 0.25)	
75+	0.07 (0.05, 0.11)		0.02 (0.00, 0.12)	

Table 6-55: Snus Users in Scandinavia by Age and Sex					
	Males		**Females**		**Data source (reference)**
	Snus use (results not stratified by gender)				18-80 year olds in Northern Sweden, 1998 (Aro et al. 2010)
Age (years)	Current	Former	Never		
20-34 (n=94)	25%	7%	68%		
35-49 (n=266)	12%	7%	81%		
50-64 (n=375)	14%	6%	80%		
>=65 (n=254)	5%	7%	89%		
Maternal age (years)			% used snus during pregnancy		Women born in Sweden, Norway, Denmark, Finland, Iceland, had singleton infant in Sweden at >=28 weeks gestation during 1999-2006, (Wikstrom et al. 2010)
<=19 (n=8,982)			1.8%		
20–24 (n=66,367)			1.7%		
25–29 (n=184,163)			1.3%		
30–34 (n=205,933)			1.0%		
>=35 (n=104,927)			1.7%		
Age (years)	Ever Tried	Currently Use	Ever Tried	Currently Use	Swedish 13, 15 and 17 year olds, 2003 (Nilsson et al. 2009)
13	18%	2%	8%	0%	
15	41%	10%	20%	0%	

Table 6-55: Snus Users in Scandinavia by Age and Sex							
	Males			Females		Data source (reference)	
17	52%		19%	40%	4%		
	Current (n=2,661)	Former (n=1,456)	Never (n=12,525)			Twin registry (Hansson et al. 2009)	
Mean age (years)	52.5	53.5	56.9				
	Current Snus Use (n=10,473)			Current Snus Use (n=16,754)		Malmo Diet and Cancer Cohort, 1991-1996 (Janzon and Hedblad 2009)	
	Yes	No		Yes	No		
Mean age (years)	56.8	59.2		54.6	57.4		
Age group (years)	Snus User (did not smoke and used snus >= once/week)					Males in a small municipality in a rural area in southwest Sweden, 2001-2003 (excluded current dual users) (Sundbeck et al. 2009)	
	Yes	No					
30-49	28%	72%					
50-76	10%	90%					
Age group (years)	Used Snus Daily			Used Snus Daily		Jonkoping (Sweden) 15-70 years old 2003 – latest year available (Hellqvist et al. 2009)	
15	7%			0%			
20	26%			0%			

Table 6-55: Snus Users in Scandinavia by Age and Sex											
	Males					Females					Data source (reference)
30	29%					0%					
40	23%					6%					
50	22%					2%					
60	16%					0%					
70	5%					0%					
Age (years)	n	None	Occasional	Every Week	Every day	n	None	Occasional	Every Week	Every day	16-20 year olds randomly sampled from the Norwegian Population Registry, 2004 (Wiium et al. 2009)
16	253	80.2%	7.9%	5.5%	6.3%	243	94.2%	4.9%	0.4%	0.4%	
17	251	67.7%	13.5%	5.2%	13.5%	235	90.6%	6.4%	1.7%	1.3%	
18	245	69.0%	11.4%	4.9%	14.7%	231	90.5%	6.1%	1.3%	2.2%	
19	240	66.3%	11.3%	5.0%	17.5%	232	91.4%	6.9%	1.7%	0.0%	
20	240	60.4%	19.6%	4.2%	15.8%	229	92.6%	4.4	1.3	1.7	
Age at cohort entry (years)	Ever used snus (regardless of smoking)										Males, Construction Industry's Organization for Working Environment Safety and Health, "Bygghälsan" (1978-1993) (Carlens et al. 2010)
< 24 (n=78,377)		38%									
25-34 (n=72,289)		33%									

Table 6-55: Snus Users in Scandinavia by Age and Sex									
	Males				Females				Data source (reference)
35-44 (n=59,025)		25%							
45-54 (n=37,404)		18%							
>=55 (n=30,684)		18%							
Age (years)	Daily								10th graders in Oslo county participating in Health Study 2000 – 2001 (Grotvedt et al. 2012)
16 year old	7%								
Age (years)	n	Daily	Occas-ional	None	n	Daily	Occas-ional	None	10th graders in 6 counties in Norway, 2000-2004 (Grotvedt et al. 2008)
14.5-15.6	1,888	5.6%	15.5%	78.9%	1,991	0.3%	3.3%	96.4%	
15.6-15.9	1,901	6.4%	15.3%	78.3%	1,974	0.1%	3.5%	96.4%	
15.9-16.1	1,956	5.3%	15.8%	79.0%	1,915	0.0%	3.6%	96.4%	
16.1-18.4	1,988	5.6%	15.9%	78.5%	1,872	0.0%	3.2%	96.9%	
Grade	(n=1,494)				(n=1,444)				BROMS cohort (baseline in 1998) (Galanti et al. 2008)
	Ever used snus		Currently use snus		Ever used snus		Currently use snus		
5	8.0%		0.2%		3.2%		0.0%		

Table 6-55: Snus Users in Scandinavia by Age and Sex					
	Males		Females		Data source (reference)
9	54.6%	18.2%	32.3%	1.9%	
3rd year post-compulsory (18 years old)	71.5%	25.0%	55.9%	5.6%	
Grade (n=4,098)	Tried snus	Currently use snus	Tried snus	Currently use snus	Survey of Norwegian lower secondary students,13-15 year olds, 1995 (Braverman et al. 2001)
9th grade	40.1%	19.7%	15.5%	4.2%	
8th grade	26.0%	11.5%	8.3%	2.0%	
7th grade	15.8%	4.5%	4.0%	1.3%	
Age (years)	Use Snus Daily				Swedish Survey of Living Conditions (ULF, 1988–89), 16 to 74 year old males (Haglund et al. 2007)
16-24 (n=1,000)	23.2%				
25-44 (n=2,113)	22.1%				
45-64 (n=1,392)	10.1%				
65-74 (n=497)	9.5%				
Age (years)	% Use Snus (male and female combined)				Cohort in Northern Sweden (baseline: 1996)
12-13	3.2%				

Table 6-55: Snus Users in Scandinavia by Age and Sex					
	Males		**Females**		**Data source (reference)**
14-15	9.9%				(Hedman et al. 2007)
Age (years)	Daily snus user				Born in 1942 or 1952, Orebro and Ostergotland, Sweden 2002 (Halling et al. 2007)
50 (n=2,606)	20%				
60 (n=2,755)	12%				
Age (years)	Use Snus Daily		Use Snus Daily		Your Country and Your Life (Sweden, 2001-2002) (Ramström and Foulds 2006)
16-24	24%		2%		
25-44	31%		4%		
45-64	19%		2%		
65-79	8%		0%		
Age (years)	Occasional or Daily Use	Experimented	Occasional or Daily Use	Experimented	Finnish Adolescent Health and Lifestyle Survey, 2003 (Huhtala et al. 2006)
12 (n=758)	0.3%	0.8%	0%	0%	
14 (n=2,337)	1.3%	8.7%	0.5%	3.5%	
16 (n=2,299)	7.1%	30.4%	0.6%	12.0%	
18 (n=1,367)	8.5%	44.0%	0.9%	17.6%	

Table 6-55: Snus Users in Scandinavia by Age and Sex				
	Males		**Females**	**Data source (reference)**
Age (years)	Snuff Use			14 to 19 year olds in public dental clinics in Göteborg, 1986 (Hirsch et al. 1991)
14 (n=137)	4%			
15 (n=394)	6%			
16 (n=385)	7%			
17 (n=393)	8%			
18 (n=520)	14%			
19 (n=316)	11%			
	Mean (std) age (years)	Age range (years)		Healthy men who used snus but not other tobacco for >= 3 months, subset of sample used by (Andersson 1991), chewing tobacco users were a subset from (Andersson et al. 1994)
Portion snus (n=23)	40.8 (8.7)	21-57		
Loose moist snus (n=22)	38.8 (13.8)	22-75		
Chewing tobacco (n=9)	50.4 (9.6)	38-68		
	Age started using snus (years)			Case-control study, 40-79 year olds, born in Sweden, living in 1 of 5 counties in
	16-20 (n=77)		>=21 (n=114)	

Table 6-55: Snus Users in Scandinavia by Age and Sex			
	Males	**Females**	**Data source (reference)**
191 current users	40%	60%	northern or central Sweden (1989-1995), controls selected from population registers (Ye et al. 1999)

Table 6-56: Patterns of Snus Use in Scandinavia					
	Intensity of Use				Data source (Reference)
Grams per day/week					
	Grams of smokeless tobacco per day				(1993) (Bolinder 1997; Bolinder and de Faire 1998)
27 (35-60 year old) firefighters in Stockholm	Mean (std dev): 27 (15) Median (25^{th}, 75^{th} percentile): 21 (14, 36)				
	Mean (std) grams per day				(1992-1993) (Ibrahim et al. 1996)
15 male patients in Göteborg, Sweden who were suspected to have snuff-induced oral lesions	36.1 (17.6)				
Current users (n=31)	Consumption (g/day)				People in the southern healthcare region of Sweden with no previous cancer diagnosis (controls only), 2000-2004 (Rosenquist et al. 2005)
	1-14		>14		
	68%		32%		
Portion snus (n=23)	Mean (std) g/day		g/day range		Healthy men who used snus but not other tobacco for >= 3 months, subset of sample used by (Andersson 1991), chewing tobacco users were a subset from (Andersson et al. 1994)
	14.4 (7.1)		5.8-32.8		
Loose moist snus (n=22)	20.8 (15.5)		6.7-82.4		
Chewing tobacco (n=9)	7.2 (4.0)		1.9-12.7		
	Grams per day (mean=22.5 g day)				Swedish construction workers' cohort males, 1978-1993 (Hergens et al. 2008b; Hergens et al. 2008a)
	<12.5	12.5-24.9	25.0-50	>50	
Current users (n=32,973)	21.8%	45.0%	22.8%	10.4%	

Table 6-56: Patterns of Snus Use in Scandinavia				
	Intensity of Use			**Data source (Reference)**
	Grams per day			Ice-hockey players and students in Värmland (Rolandsson et al. 2005)
	<50	50	>50	
	78%	18%	5%	
Snuff users (n=92)	Mean (95% CI) g snuff use/day			Males in Northern Swedish MONICA sample (1990) (Eliasson et al. 1995)
	22.9 (20.7, 25.0)			
	Mean (std) g per day			(subsample of Axel 1976 sample) with degree 3 or 4 lesions (Andersson and Warfvinge 2003)
20 habitual non-smoking users of loose snus	36 (17) g/day			
	Mean (std) g per day			(Wedenberg et al. 1996)
15 regular snuff users who did not smoke and had snuff induced lesions	36.1 (17.6)			
	Mean (range) grams per day			(Axell et al. 1976)
114 male snuff dippers who underwent biopsy	13.8 (4 - 50)			
	Average consumption of snus per day			(Svenska Tobaks AB, Basdata om tobakskonsumtion 1992, TEMO AB, reported by Andersson et al. 1994)
Loose snus:	15.7 g/day			
Portion snus:	9.3 g/day			
	Median daily consumption			Controls in a case-control study

Table 6-56: Patterns of Snus Use in Scandinavia		
	Intensity of Use	**Data source (Reference)**
Controls selected from the National Population Registry and National Registry for Causes of Death	2 packages (100 grams)	(Schildt et al. 1998)
Grams per week		
Daily snuff users in southern Sweden (9 nonsmokers, 1 smoked on weekends) (n=10) Regular snuff users, not current smokers, hospital workers (n=27)	Average weekly snuff consumption (g) 160 152	(Holm et al. 1992)
Current users (n=48)	Median grams per week (range) 88 (12 to 525)	18-75 year olds in Göteborg (Gyllen et al. 2004)
n=91	Grams per week <=50 g/week | >50 g/week 63% | 37%	Controls: 40-79 year olds in Stockholm and southern Sweden (1988-1991) (Lewin et al. 1998)
n=21	Mean (std dev) current consumption (g/week) 146 (60)	Male who did not use tobacco, used >=1 can (50 g) snuff per week for 2 years or smoked >= 10 cigarettes per day for 2 years (Eliasson et al. 1991; Eliasson et al. 1993)(Ellingsen et al. 2009)(Ellingsen et al. 2009)
	Grams of snuff used per week Mean Range	Blue-collar workers in southern Norway (Ellingsen et al. 2009)

Table 6-56: Patterns of Snus Use in Scandinavia				
	Intensity of Use			**Data source (Reference)**
Snuff only users (n=11)	75	2-200		
Smokers who use snuff (n=2)	2.6	0-50		
Pinches/quids per day/week				
13 boys who regularly used snuff	Mean consumption (pinches per day)			Schoolchildren in Huddinge (outskirts of Stockholm) (Modeer et al. 1980)
	5			
Snus users	Quids per week in past 2 years			Controls (<80 year olds, 1995-1997) who used >= 1 quid per week for >= 6 months (Lagergren et al. 2000)
	1-14	15-35	>35	
n=124	36%	27%	36%	
Regular users (n=28)	Mean pinches per week			Subsample of the BROMS cohort (Post et al. 2005)
	31			
Cans/boxes per day/week				
Tobacco use	Average cans/week (1 can = 24–50 g)			18-80 year olds in Northern Sweden (1998) (Aro et al. 2010)
Snus only	3.2			
Snus and cigarettes	2.2			
Snus use	≤ 4 cans/week	> 4 cans/week		Males in Twin registry (Hansson et al. 2009)
Former (1,456)	81.7%	18.3%		
Current (2,661)	77.0%	23.0%		

Table 6-56: Patterns of Snus Use in Scandinavia							
	Intensity of Use						Data source (Reference)
Gender	≤ 4 cans/week					> 4/cans per week	Vasterbotten Intervention Programme 30-50 year old current snus users (1990-1994 - baseline, 10-year follow-up) (Norberg et al. 2006)
Males (n=7,692)							
Baseline	77%					23%	
Follow-up	74%					26%	
Females (n=8,880)							
Baseline	88%					12%	
Follow-up	87%					13%	
n=33	Boxes/week						Non-smoking male 19-year-olds living in the community of Goteborg, Sweden (Monten et al. 2006)
	1	2	3	4	5	>=6	
	21%	45%	12%	6%	12%	3%	
	Mean boxes per week: 2.6 (std dev = 1.5)						
	Current # of snus boxes per week						(Persson et al. 2000)
2,599 males born between 1938-1957, living in Stockholm, oversampled men with a strong family history of diabetes	<2					>=3	
	48%					52%	
	Mean (95% CI) cans of snuff/week						Males in Northern Swedish MONICA sample (1990) (Eliasson et al. 1995)
Snuff users (n=92)	3.2 (2.9, 3.5)						
Snuff users who smoke (n=38)	2.5 (2.2, 2.9)						

Table 6-56: Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
Snus user (did not smoke, used snus >= once/week)	Mean: 3.5 cans per week		Males in a small municipality in rural southwest Sweden, 2001-2003. (Sundbeck et al. 2009)
	Packages (1 package = 14 g) of chewing tobacco used per day		(Axell et al. 1992)
	Mean # days per package	Range of packages per day	
20 users of a non-fermented Swedish brand of chewing tobacco	4.2	1.5-10	
Hours/Times per day			
	Hours per day using snus		(Sweden) (Wallstrom et al. 2010)
	Mean (std dev)	Range	
50 non-smoking daily snus users who use > 2 cans/week (>100 g snus) for ≥10 years	15.2 ± 2.1	7 to 22	
	Mean (std) # hours per day with snuff in mouth		(Wedenberg et al. 1996)
15 regular snuff users who did not smoke and had snuff induced lesions	13.1 (3.8)		
	mean (std) hours per day of snuff use		(1992-1993) (Ibrahim et al. 1996)
15 male patients in Göteborg, Sweden who were suspected to have snuff-induced oral lesions	13.1 (3.8)		
	Mean (range) hours per day		(Axell et al. 1976)

Table 6-56: Patterns of Snus Use in Scandinavia			
	Intensity of Use		**Data source (Reference)**
114 male snuff dippers who underwent biopsy	6.8 (1 - 24)		
	Mean (std) hours/day	hours/day range	Healthy men who used snus but not other tobacco for >= 3 months, subset of sample used by (Andersson 1991) chewing tobacco users were a subset from (Andersson et al. 1994)
Portion snus (n=23)	13.1 (3.1)	8.0-20.0	
Loose moist snus (n=22)	12.3 (3.6)	6.0-16.0	
Chewing tobacco (n=9)	13.0 (4.0)	7.5-17.0	
20 users of a non-fermented Swedish brand of chewing tobacco	Hours per day using chewing tobacco Mean: 10.7 Range: 3.5-22		(Axell et al. 1992)
	Times per day		(Luomanen et al. 1997)
	Range	Mean	
11 moist snuff users in Finland	4-10	8	
	Times per day		Case-control study, 40-79 year olds, born in Sweden, living in 1 of 5 counties in northern or central Sweden (1989-1995), controls selected from population registers (Ye et al. 1999)
	<=5	>5	
Current users (n=191)	59%	41%	
Total consumption			
	Total consumption (kg)		Controls: 40-79 year olds in Stockholm and southern Sweden

Table 6-56: Patterns of Snus Use in Scandinavia						
	Intensity of Use					Data source (Reference)
	<125			>=125		(1988-1991) (Lewin et al. 1998)
n=91	69%			31%		
	Mean (std dev) cumulative tobacco consumption (kg)					(Eliasson et al. 1991; Eliasson et al. 1993)
21 males who used >=1 can (50 g) snuff per week for 2 years or smoked >= 10 cigarettes per day for 2 years	52.2 (35.1)					
	Median lifetime consumption among controls					Controls in a case-control study (Schildt et al. 1998)
Controls from the National Population Registry and National Registry for Causes of Death	156.0 kg					
	Used >= 5 can-years (average # of cans per week *year used snuff)					31-40 year olds Stockholm residents born in 1945-1954 (Wickholm et al. 2004)
Current snuff users (n=122)	78%					
Former snuff user (n=31)	60%					
Type of snus						
Gender and frequency of snus use	Snus product used often					16- to 20-year-olds living in Norway (Wiium and Aaro 2011)
Males Males	Traditional loose snus	Portion snus	Mini portion snus	Loose and portion	Don't know	
Occasional (n=94)	21.3%	60.6%		16%	2.1%	

Table 6-56: Patterns of Snus Use in Scandinavia						
	Intensity of Use					Data source (Reference)
Weekly (n=40)	27.5%	70.0%		2.5%	0%	
Daily (n=260)	44.6%	40.4%		15%	0%	
Total (n=394)	37.3%	48.2%		14.0%	0.5%	
Females						
Occasional (n=107)	4.7%	59.8%	25.2%	4.7%	5.6%	
Weekly (n=29)	0%	65.5%	27.6%	6.9%	0%	
Daily (n=59)	5.1%	78.0%	11.9%	5.1%	0%	
Total (n=195)	4.1%	66.2%	21.5%	5.1%	3.1%	

6.4 Effect of Marketing on Consumer Understanding and Perceptions

6.4.1. Knowledge, Attitudes and Beliefs of Smoking Tobacco and Alternative Tobacco Products among Users

This section of the Application summarizes the available scientific literature describing studies that assessed current consumer awareness of and knowledge about Swedish snus. Swedish Match has identified a total of thirteen (13) published product-specific studies in which the knowledge, attitudes, and beliefs of adults and adolescents in Swedish and other Scandinavian populations were assessed (see also ENVIRON KAB Report 2014, attached as Appendix 6D).

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

Only one study has specifically addressed consumers' ability to understand modified risk claims for Swedish snus. Borland and colleagues (2012) investigated the impact of providing factual information on the relative harms of STPs and NRTs compared to smoked tobacco using a pre- and post-test comparison of knowledge about harms. The study was conducted in several locations worldwide (i.e., Australia, United Kingdom, and the United States), including among smokers in Sweden. After administration of the Fact Sheet, the authors observed that the knowledge on the mechanisms of tobacco-related harms became more accurate among smokers in Sweden, which was observed in the other countries investigated. Participants who read all or at least some of the Fact Sheet believed, post-survey, that STPs were less harmful. Given the pre-test low levels of knowledge that smokers had about the harmfulness of different nicotine delivery products, the authors concluded that the provision of information may be an effective means to educate smokers on alternative nicotine delivery products such as STPs and NRTs. Increased knowledge levels on the relative harmfulness of STP/NRT compared to cigarettes increased participants' interests in using NRT as a cessation aid and/or trying STPs as a substitute for cigarette smoking.

Rolandsson and Hugoson (2000) conducted an intervention study among male ice-hockey players, aged 12-19 years (n=252). The intervention entailed administering tobacco-related information: over-head pictures on the harmful effects of tobacco in general and from the view of oral health. The questionnaires collected information on personal characteristics, socio-economics, behavior and knowledge of tobacco products. Questionnaires were administered three times on two separate occasions; the first two were provided at baseline, administered immediately before and after a 15-minute anti-tobacco information session conducted by two dental hygienists. The third questionnaire was provided three weeks later. Post intervention, the authors noted that knowledge of tobacco and its harmful effects increased significantly; however, in spite of knowledge, tobacco use habits remained the same. Also, with regards to differences between tobacco use groups, no significant difference could be observed among those snus users and non-users concerning their knowledge of the harmful effects of tobacco (there was only one smoker in this study).

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

Five cross-sectional studies investigated the perception of health risks related to snus use among adults (Bolinder et al. 2002; Borland et al. 2012; Lund and Scheffels 2012; Lund and Scheffels 2013; Lund 2012). These studies reported that Scandinavians had an exaggerated perception of the health risks associated with snus use. Lund and Scheffels (2013) investigated the differences in perceptions of the relative risk of some cancers from tobacco use, including lung cancer and cardiovascular diseases among Norwegian adults who were either current or former tobacco users. They reported that, for all diseases except lung cancer, a majority of smokers believed snus users had a higher or equal risk. Although, none of the tobacco users believed the risk of lung cancer or CVD was far higher for snus, some participants perceived the risks to users of either tobacco type to be fairly similar. Lund (2012) reached similar conclusions, both former and current adult smokers inaccurately reported that the harm from snus and cigarettes were more or less equal or that snus was only somewhat less risky. However, smokers with a history of snus use were more likely to correctly predict that daily snus use was far less risky than daily cigarette smoking. Correct beliefs of differential risks between the two products were positively correlated with the willingness to use snus in future quit attempts or having used it for smoking cessation. Borland and colleagues (2012) investigated the impact of providing factual information on the relative harms of STP/NRT compared to smoked tobacco using a pre- and post-test comparison of knowledge about harms. The study was conducted in several locations worldwide (Australia, United Kingdom and the US), including among smokers in Sweden. After administration of the Fact Sheet, the authors observed that the knowledge on the mechanisms of tobacco-related harms became more accurate among smokers in Sweden, which was observed in the other countries investigated. Participants who read all or at least some of the Fact Sheet believed, post-survey, that STPs were less harmful. Given the pre-test low levels of knowledge that smokers had about the harmfulness of different nicotine delivery products, the authors concluded that the provision of information may be an effective means to educate smokers on alternative nicotine delivery products such as STPs and NRTs. Increased knowledge levels on the relative harmfulness of ST/NRT compared to cigarettes increased participants' interests in using NRT as a cessation aid and/or trying STPs as a substitute for cigarette smoking.

Two of the five studies observed that a significant percentage of the medical community hold beliefs that are in conflict with scientific consensus on the health risks of snus (Bolinder et al. 2002; Lund and Scheffels 2012). Bolinder and colleagues (2002) reported that half of the doctors surveyed believed that snus use probably increases the risk of oral cancer, hypertension, and some heart diseases. Lund and Scheffels (2012) observed that, among Norwegian general practitioners, snus was the least preferred smoking cessation aid. Some doctors reported that they never or seldom recommended snus as a cessation aid (Bolinder et al. 2002; Lund and Scheffels 2012).

With regards to perceptions of relative risk of nicotine addiction, exclusive smokers were significantly more prone to believe that smokers had a higher risk of addiction. Among Norwegian snus users and cigarette smokers, a majority believed that snus users and smokers were more or less at the same risk of becoming addicted to nicotine, but there was a statistically significant difference between the groups regarding the distribution of perceptions of addiction risks. Compared to other tobacco user groups, current dual users believed that snus users ran the highest risk to be addicted to nicotine (Lund and Scheffels 2013).

Certain factors were found to be correlated with the belief that snus was less harmful than cigarettes. Males and adults under 30 years of age tended to answer questions on the relative risks of snus more accurately than females and those over 60 years of age; females were more likely to be concerned with safety (Wikmans and Ramstrom 2010). A higher proportion of those with a history of snus use correctly believed that daily snus use was "far less risky" than daily cigarette smoking compared to participants without history of snus use (Lund 2012). A belief that smokeless tobacco was less harmful than cigarettes was also associated with interest in trying the product (Borland et al. 2012; Lund 2012). Those with a higher nicotine dependency, and those who had used snus in quit attempts, were more likely to have an accurate knowledge of the relative harmfulness of snus (Wikmans and Ramstrom 2010).

Youth Behaviors: Seven studies examined tobacco-related knowledge, attitudes and beliefs among adolescents and/or young adults. Four were cross-sectional in design, two were prospective studies and one was an intervention study.

Rolandsson and Hugoson (2000) conducted an intervention study among male ice-hockey players, aged 12-19 years (n=252). Intervention entailed administering tobacco-related information and questionnaires collected information on personal characteristics, socioeconomics, behavior and knowledge of tobacco products. Questionnaires were administered three times on two separate occasions; the first two were provided at baseline immediately before and after a 15-minute anti-tobacco information session conducted by two dental hygienists. The third questionnaire was provided three weeks later. Post intervention, the authors noted that knowledge of tobacco and its harmful effects increased significantly; however, in spite of this knowledge, tobacco use habits remained the same. Also, with regards to differences between tobacco use groups, no significant difference could be observed among snuff users and non-users regarding their knowledge of the harmful effects of tobacco, as there was only one smoker in this study.

Prospectively, Rosendahl and colleagues (2005; 2008) evaluated knowledge of use behaviors and its impact on subsequent tobacco use. In the 2005 study, participants completed a self-administered questionnaire to assess knowledge of tobacco effect (aesthetic and health) and were then surveyed annually from the sixth through ninth grade. Knowledge items included nicotine dependence, health concerns and popularity of tobacco advertisements. The authors reported that acquired knowledge often did not predict future tobacco use. For instance, knowledge of the addictive properties of nicotine did not predict future cigarette smoking; on the other hand, a correct answer to the item on the addictive properties of snus was associated with a higher risk of snus use, either exclusively or in conjunction with cigarette smoking. A knowledge score was generated, but no association was observed between this score and subsequent tobacco use, and it did not predict future tobacco use. In the 2008 study, indicators of snus and cigarette use in the previous year were used to model the development of behavior between 11 and 18 years of age. The authors observed marked gender differences; rapid escalation for snus use was found only among males while high consumption of cigarettes was observed only among females. Dual users showed a trajectory of steeper and more prolonged increase in tobacco consumption than exclusive users of either snus or cigarettes.

Four cross-sectional studies evaluated knowledge, attitudes and beliefs among Scandinavian adolescents and young adults (Nilsson et al. 2009; Overland et al. 2008; Wiium et al. 2009; Wiium et al. 2011). Subjective attractiveness (e.g., coolness factor, sexiness) and perceived trendiness (e.g., popularity) were evaluated among Norwegian adolescents (Wiium et al. 2009; Wiium et al.

2011). Both cigarette smoking and snus use were considered to be unattractive; however, snus was reported to be trendier than smoking. Males generally considered snus use to be more attractive and trendier than did females, and use was more common among males than females. According to a cross-sectional study conducted by Nilsson et al. (2009), a majority of Swedish adolescents (85%) expected their parents to try to make them stop using snus, suggesting that these adolescents on some level consider snus use to be a habit of which their parents would not approve.

With regards to youths' perception of harmfulness of different tobacco types and substitutes, participants aged 16-20 years old were asked to rank tobacco products in order of harm, including snus, NRTs and cigarettes (Overland et al. 2008). As observed among adult participants, adolescents overrated the harmfulness of snus. Cigarettes were generally rated as more harmful than snus, but 41% still rated snus as equally or more harmful than cigarettes, while NRTs were perceived as least harmful among substitutes and other tobacco types.

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

Among adult smokers, Borland and colleagues (2012) assessed the likelihood of using NRT on their next quit attempt and the likelihood of trying smokeless tobacco. The authors reported that the knowledge levels on the relative harmfulness of STPs or NRTs compared to cigarettes increased participants' interests in using either NRTs or STPs as a substitute for cigarette smoking. In a national survey among Norwegian adults, Lund (2012) observed that the correct perception of the relative risk of snus and cigarettes correlated positively with having used snus when quitting smoking.

Norwegian general practitioners who completed a mail-in questionnaire believed that snus was much less harmful than cigarettes. Nevertheless medical professionals were most likely to recommend other NRTs and cessation medications such as varenicline and were least likely to recommend snus as a cessation tool (Lund and Scheffels 2012).

6.4.1.2. Conclusions

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

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

Most of the studies were conducted among tobacco users. One drawback of the available studies is the limited information on tobacco-related knowledge and beliefs among non-smokers and non-

users of tobacco. Also, only one of the identified studies was a prospective design (among adolescents) to examine changes in perceptions and tobacco-related behaviors over time, and perceptions on tobacco harmfulness did not appear to predict future tobacco use.

6.4.2. Swedish Match's Consumer Perception Study of the Swedish Match Snus Products in this Application

6.4.2.1. Study Overview

Swedish Match conducted a Consumer Perception Study (the "Study") to assess the effects on current tobacco users and non-users of the modifications to the Snus Products' warning labels proposed in this Application. The Study assessed the effect of the proposed modifications on subjects' tobacco use behavior and their understanding and perception of the health risks associated with the Snus Products as a result of exposure to test and control warning labels. In particular, the study evaluated the following label modifications:

1. Removal of the statement "WARNING: This product can cause mouth cancer."

2. Removal of the statement "WARNING: This product can cause gum disease and tooth loss."

3. Replacement of the statement "WARNING: This product is not a safe alternative to cigarettes" with the statement(s) "WARNING: No tobacco product is safe, this product presents substantially lower risks to health than cigarettes."

4. Retaining the statement "WARNING: This product is addictive."

Consistent with Subsections 911(g)(1)(B) and 911(g)(2)(B)(vi) of the Act and Section VI.A of the MRTP Guidance, the Study assessed the effect of marketing the Snus Products with a modified warning label on the following populations and behaviors:

- Tobacco use behavior among current tobacco users;
- Tobacco use initiation behavior among non-users;
- Consumer understanding and perceptions of the product;
- The population as a whole; and
- Certain demographic groups.

Consistent with these research objectives, the Study results provide diagnostic learning about the intended use of the Snus Products among current tobacco users and non-users; assess the potential for the proposed modified warning labels to produce unintended negative consequences to the population as a whole and to particular subgroups of interest; and assess whether the proposed modified warning label is misleading.

Swedish Match's MRTP Advisory Panel reviewed the study protocol before the Study was conducted, and it was discussed with CTP at several pre-submission meetings. Suggestions and recommendations from both CTP and the MRTP Advisory Panel were incorporated into the final protocol which is attached at Appendix 6E. The study protocol was subject to oversight by (b) (4) IRB and, it was determined that (b) (4)

(b) (4) . The study was conducted by (b) (4) .

The Consumer Perception Study was conducted as (b) (4)

Data collection took place from November 21, 2013, to December 29, 2013. The total sample was 13,203 subjects with completed interviews for current tobacco users (n=6,593) and non-users of tobacco (n=6,610). Sample demographics included analyzable imminent quitter, former smoker, minority, low income, and youth users and non-users of tobacco products from various geographic regions of the United States.

(b) (4)

(b) (4)

The Consumer Perception Study generated important and extensive data related to (i) the intended use of the Snus Products among current users of tobaccos and non-tobacco users; (ii) the proposed

warning labels' potential to produce unintended negative consequences to the population as a whole, as well as to demographic subgroups of interest; and (iii) subjects' comprehension and understanding of the proposed warning labels to assess whether they are misleading.

Swedish Match's MRTP Advisory Panel has reviewed and provided their input regarding the Study results. They acknowledged the long-term significance of the results which expand the knowledge base regarding consumer tobacco use behaviors and perceptions and may provide the basis for several scientific publications. Swedish Match intends to facilitate use of the data by the scientific community in further investigations and publications.

6.4.2.2. Study Demographics

There were 13,203 total participants in the Consumer Perception Study. The population included 6,593 current users and 7,658 ever users of tobacco. Of the current tobacco users 3,809 were male and 2,784 were female, 1,611 were between the ages of 18 and 24 years, 4,711 were minorities (defined to include African-American, Hispanic, Asian, Native American, Other, and Hawaian or other Pacific Islander), and 6,570 had an income below $45,000. The current tobacco users included 1,556 daily smokers and 1,171 daily snus users. Thirty eight percent (38%) of the cigarette smokers and 42% of the snus users reported that they would definitely or most likely attempt to quit within the next month (Slide 56, SM Label Eval. 2014), and 42% of cigarette smokers and 46% of snus users reported that they would definitely or most likely attempt to reduce their consumption within the next month (Slide 57, SM Label Eval. 2014).

The study population also included 6,610 current non-users of tobacco. Of the current non-users, 3,736 were male, 2,874 were female, 2,026 were between the ages of 18 and 24, 1,997 were minorities, and 3,206 had an income below $45,000. Seventeen percent (17%) of the current non users of tobacco reported that were they had used tobacco products in the past (Slide 146, SM Label Eval. 2014).

6.4.2.3. Summary of Results

The data from the Consumer Perception Study address four of the five key areas of investigation required to support an MRTP order: (1) the effect on tobacco use behaviors among current users; (2) the effect on tobacco use initiation among non-users; (3) the effect of marketing on consumer understanding and perceptions; and (4) the effect on the population as a whole. The results of this research are specific to the Snus Products which are the subject of this Application, and further supplement the extensive preclinical, toxicology and epidemiology data related to the effects and use of Swedish snus as compared to traditional cigarettes.

The presentation of the full study data prepared by (b) (4) is included at Appendix 6F. The following sections summarize some of the highlights of the study results. The following sections describe the results of the two modified risk warnings: (a) No tobacco product is safe, this product presents substantially lower risks to health than cigarettes and (b) No tobacco product is safe, this product presents a lower risk to health than cigarettes, as compared to the four warnings currently required for smokeless tobacco products by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Act: (a) This product can cause mouth cancer; (b) This product can cause gum disease and tooth loss; (c) This product is not a safe alternative to cigarettes; and (d) This product is addictive.

6.4.2.3.1. The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Behavior Among Current Tobacco Users

Current Tobacco Users - Likelihood to Use and Motivation to Purchase Snus: A total of 6,593 current tobacco users participated in the study, of whom 1,556 smoked cigarettes daily and 1,171 used snus daily. Overall, the modified risk claims result in a modest increase in the likelihood that current smokers would use or purchase snus. Among current tobacco users, only 20% of those exposed to the modified risk claim that snus presents "substantially lower risks" than cigarettes reported that the modified warning was likely to extremely likely (top 2 Box) to cause them to use snus. While this was a significantly greater percentage than reported by those exposed to any of the four claims currently required for smokeless tobacco products (which ranged from 12-14%) (Slide 61, SM Label Eval. 2014), it was still substantially lower than the likelihood to use a tobacco product seen in research studies previously conducted to assess consumers' interest in a tobacco product. Of those exposed to the "lower risk" modified claim, 16% reported that they were likely to extremely likely to use snus (Slide 61, SM Label Eval. 2014). This was not significantly greater than what was reported by those exposed to any of the four current claims (Slide 61, SM Label Eval. 2014). The current users of tobacco exposed to either of the modified risk claims reported significantly greater motivation (17% and 16%) to purchase snus than those exposed to any of the four current claims (8-11%) (Slide 71, SM Label Eval. 2014).

Dual Use: Dual use of cigarettes and snus is marginally more likely among current smokers exposed to the modified risk warnings. Among the current smokers who reported that they were likely or extremely likely to use snus, 24% of those exposed to the "substantially lower risks" claim reported that they were likely or extremely likely to try both snus and cigarettes. This was significantly higher than that reported by those exposed to the addiction and mouth cancer warnings (16% each) but not significantly higher than what was reported by those exposed to the gum disease and the not a safe alternative warnings (17% each), although it is noteworthy that the addiction warning will be an alternate warning for the modified risk product. There was no significant difference in the likelihood of dual use among current smokers likely to use snus exposed to the "lower risk" claim (Slide 62, SM Label Eval. 2014). A majority of current smokers likely to use both snus and cigarettes who were exposed to the modified risk claims (65 and 61%) reported that they would use snus to reduce or quit smoking, although this was not significantly different than those exposed to the control warnings (Slide 63, SM Label Eval. 2014).

Imminent Quitters: Thirty-eight (38%) and forty-two (42%) percent of the current smokers reported that they were definitely or most likely to quit or reduce their consumptions of cigarettes within the next month. Of these imminent quitters, 21% of those exposed to the "substantially lower risks" and 18% of those exposed to the" lower risk" modified risk claims reported that they would be likely or extremely likely to use snus. These results were greater than for those exposed to any of the current claims (14-15%), and significantly so for those exposed to the "substantially lower risks" claim 49 (Slide 249, SM Label Eval. 2014). Similarly, significantly more of the imminent quitters exposed to the modified risk claims (18 and 17%) reported that they would be motivated to purchase snus and significantly less likely to be discouraged from purchasing snus (12 and 13%) compared to those exposed to the current warnings (28-45% motivated and 20-38% discouraged). However, imminent quitters were significantly more likely to report that the modified risk claims would have no impact on their decision (47 and 43%) compared to those exposed to the gum disease (33%) and mouth cancer (32%) warnings and similar to those exposed

to the addiction and not a safe alternative warnings (47% each) (Slide 259, SM Label Eval. 2014). Among those imminent quitters who reported that they were likely to use snus, 25% indicated that they would likely use both snus and cigarettes (Slide 250, SM Label Eval. 2014). Of those potential dual users exposed to the modified risk claims, most (65 and 68%) reported that they would use snus to quit or reduce the use of cigarettes (Slide 251, SM Label Eval. 2014).

In sum, the modified risk claims resulted in a modest increase in the likelihood that current tobacco users would use or purchase snus, and a minimal increase in the likelihood that they would engage in dual use of both cigarettes and snus. The modified risk claims also increased the likelihood that imminent quitters and reducers would be more likely to use, more motivate to buy, and less likely to be discouraged from using snus. A quarter (25%) of the imminent quitters who were likely to use snus reported that they were likely to be dual users of snus and cigarettes, and most of those reported that they would use snus to reduce or quit cigarettes.

6.4.2.3.2. The Effect of Marketing Swedish Snus with a Modified Warning Label on Tobacco Use Initiation Behavior Among Non- users

Current Non-Users of Tobacco - Likelihood to Use and Motivation to Purchase Snus: A total of 6,610 non-users of tobacco participated in the study. Most (61% and 66%) of the non-users exposed to the modified risk claims reported that they were not at all likely or unlikely to use snus. This was lower than the percentage of those exposed to the current warnings (67-74%), and significantly so for those exposed to the "substantially lower risks" claim. Those exposed to the "lower risk" claim were significantly less likely (66%) to report that they were not at all likely or unlikely to use snus than those exposed to the current gum disease (70%) and mouth cancer (74%) claims.

The percentages of those reporting that they were likely or extremely likely to use snus were approximately the same for those exposed to the modified risk claims (8% and 6%) as those exposed to the current warnings (6-9%) (Slide 113, SM Label Eval. 2014). Similarly, the modified risk claims did not increase the motivation for non-users of tobacco to buy snus. Five percent (5%) and 4% of those exposed to the modified risk claims reported that those claims would motivate them to purchase snus compared to 3-4% for those exposed to the current claims. The modified risk claims were significantly less likely (42 and 48%) than the current warnings (58-74%) to discourage or somewhat discourage snus purchase. However, significantly more of the non-users (42 and 40%) reported that the modified risk claims would have no impact on their motivation to purchase snus compared to 18-30% of those exposed to the current claims (Slide 114, SM Label Eval. 2014).

Former Tobacco Users: Seventeen percent (17%) or 1,124 of the current non-users of tobacco reported that they used tobacco in the past (Slide 146, SM Label Eval. 2014). None of the claims were likely to influence these former tobacco users to use snus. Most of the former users exposed to the modified risk claims reported that they would not or were unlikely to use snus (65% for both), although this number was lower than for those exposed to the current claims (64-83%)and significantly so for those exposed to the gum disease warning (Slide 157, SM Label Eval. 2014). Similarly, none of the claims tested made former tobacco users likely or highly likely to use (2% modified risk; 1-6% current claims) or motivated to purchase snus (3 and 1% modified risk; 2% current claims). Moreover, 41 and 51% of former users reported that the modified risk claims

would discourage their purchase of snus. This was significantly lower than for those exposed to three of the four current claims (and similar to those exposed to the addiction claim) (49-76%). However, significantly more of those exposed to the modified risk (and addiction) warnings reported that the warning would have no impact on their decision to purchase snus (47 and 43% modified risk; 44% addiction) compared to those exposed to the gum disease (19%) and mouth cancer (18%) claims (Slide 158, SM Label Eval. 2014).

In sum, the modified risk claims were no more likely than the current claims to encourage non-users of tobacco to use or buy snus. Although, the current claims were more likely than the modified risk claims to deter snus use among non-users of tobacco, more of those exposed to the modified risk claims reported that the claims were not likely to impact their decision to buy snus. None of the claims were likely to influence former tobacco users to use or motivate them to purchase snus. As with the other non-users of tobacco, the modified risk claims were less likely to deter former users from using or purchasing snus, however significantly more reported that the claims would not impact their decision.

6.4.2.3.3. The Effect of Marketing Swedish Snus with a Modified Warning Label on Consumer Understanding and Perceptions of the Product

Understanding, Clarity and Credibility: Approximately two-thirds (66 and 65%) of the 13,203 total respondents (smokers and non-smokers) exposed to the modified risk claims reported that the claims were easy or very easy to understand. However, this is significantly lower than those who reported that each of the current claims was easy or very easy to understand (74-87%). While only 5% found the modified risk claims to be difficult or very difficult to understand, this was also significantly higher than what was reported by those exposed to the current claims (2-3%) (Slide 13, SM Label Eval. 2014). These results are similar to those reported by total respondents when asked about the clarity of the meaning of the claims. Of those exposed to the modified risk claims 56 and 57% reported that the claims were clear or very clear and 10 and 12% reported that they were vague or very vague. These results were also significantly different than those exposed to the current claims, of whom 70-86% reported that the claims were clear or very clear and 3-7% reported that they were vague or very vague (Slide 14, SM Label Eval. 2014). Only 45 and 43% of study participants exposed to the modified risk claims reported that the claims were very or extremely believable. This was significantly lower than those who found the current warnings to be very or extremely believable (68-77%) (Slide 17, SM Label Eval. 2014). This pattern was consistent though out all of the demographic sub-populations tested.

Current smokers (73 and 71%) were more likely than the total population to report that the modified risk claims were easy or very easy to understand and slightly less likely (4%) to report that they were difficult or very difficult to understand. These results remained significantly lower than those reported for the current claims. Significantly more smokers exposed to the current claims (81-88%) reported that the claims were easy or very easy to understand and fewer (1-3%) reported that they were difficult or very difficult to understand (Slide 59, SM Label Eval. 2014). The results relating to the clarity of the warnings were similar to those reported for ease of understanding. Although most (62 and 66%) of the tobacco users exposed to the modified risk claims rated them as clear or very clear, this was significantly lower than those (75-87%) reporting that the current claims were clear to very clear. Moreover, significantly more of the current tobacco users exposed to the modified risk claims (7 and 9%) reported that they were vague or very

vague compared to 1-5% of those exposed to the current claims (Slide 60, SM Label Eval. 2014). Those exposed to the modified risk claims were also significantly less likely to find the claims to be very or extremely believable (45 and 43%) than those exposed to the current claims (71-75%) (Slide 72, SM Label Eval. 2014).

Non-users of tobacco were less likely (59 and 58%) than the total population to report that the modified risk claims were easy or very easy to understand and more (7 and 6%) likely to report that they were difficult or very difficult to understand. As with smokers and the total population, these results differed significantly from those reported by non-users exposed to the current warnings (69-85% clear; 3-5% difficult) (Slide 111, SM Label Eval. 2014). The results for clarity of the claims followed the same pattern. Forty-nine percent (49%) of those exposed to the modified risk claims reported that the claims were clear or very clear, and 16% reported that they were vague or very vague. These results again differed significantly from those exposed to the current claims, 65-84% of whom reported that the current claims were clear or very clear and 3 to 9% reported that they were vague or very vague (Slide 112, SM Label Eval. 2014). Again, those exposed to the modified risk claims were significantly less likely to find the claims to be very or extremely believable (34 and 36%) than those exposed to the current claims (65-79%) (Slide 115, SM Label Eval. 2014).

Risk Perception: Prior to exposure to any of the claims, 15% of the total respondents reported that daily snus use presented a moderate risk, 30% reported that snus was extremely harmful and 27% "didn't know" (Slide 18, SM Label Eval. 2014). Following exposure to the claims, significantly more of the total respondents exposed to the modified risk claims (30 and 31%) reported that snus posed a moderate risk compared to 13 to 19% of those exposed to the current claims. Indeed, significantly more of those exposed to the current claims (39-58%) reported that snus was extremely harmful compared to 23 and 24% for the modified risk claims (Slide 19, SM Label Eval. 2014). Similarly, half (51 and 50%) of the total respondents exposed to the modified risk claims reported that snus was somewhat less harmful than cigarettes (Slide 21, SM Label Eval. 2014) compared to just 19% prior to exposure to the claims (Slide 20, SM Label Eval. 2014). This is significantly higher than what was reported by those exposed to the current claims. Approximately half of those exposed to the current claims (46-57%) reported that snus and cigarettes were equally harmful (which was significantly higher than reported by those exposed to the modified risk claims) (Slide 21, SM Label Eval. 2014). These results are similar to those comparing the risk perception of snus to that of quitting tobacco entirely. Significantly more of the total respondents exposed to the modified risk warnings (43 and 40%) reported that snus was somewhat more harmful than quitting compared to those exposed to the current warnings, and significantly more of those exposed to the current warnings (53-63%) reported that snus was much more harmful than quitting (Slide 30, SM Label Eval. 2014).

Prior to exposure to the claims, tobacco users generally reported that daily snus use posed a lower risk than what was reported by the total study population. Twenty-one percent (21%) of total tobacco users reported that snus presented a moderate risk, 18% reported that it was extremely harmful, and 27% reported that they didn't know (Slide 73, SM Label Eval. 2014). Following exposure to the modified risk claims, 37 and 35% of current tobacco users reported that snus posed a moderate risk compared to 17-22% of those exposed to the current warnings. Only 28% of the smokers exposed to the modified risk claims believed that every day use of snus would present a harmful to extremely harmful risk. This was significantly lower than what was reported by those exposed to each of the four control claims (42-60%) (Slide 74, SM Label Eval. 2014). Most of the current users of tobacco exposed to the modified risk claims also reported that snus was somewhat

less harmful than cigarettes (53 and 49%) compared to those exposed to the control claims (17-22%). In contrast, most of those exposed to the control claims (42-54%) reported snus and cigarettes to be equally harmful (Slide 76, SM Label Eval. 2014). The modified labels had no significant effect on tobacco users' rating of the harmfulness of snus compared to quitting tobacco completely (Slide 84 and 85, SM Label Eval. 2014), although more of those exposed to the modified risk claims reported that snus was somewhat more harmful than quitting compared to those exposed to the control claims, more of whom reported that snus was much more harmful than quitting (Slide 85, SM Label Eval. 2014).

With respect to current non-users of tobacco, prior to exposure to any of the warnings, 9% reported that snus presented a moderate risk, 50% reported that snus presented a harmful to extremely harmful risk, and 27% didn't know (Slide 116, SM Label Eval. 2014). Following exposure to the modified risk claims, 25 and 24% of the non-users rated daily snus use as a moderate risk and 38 and 40% reported that snus presented a harmful or extremely harmful risk. In contrast, significantly more of the non-users exposed to the current claims (55-74%) rated snus as harmful or extremely harmful and significantly fewer (8-15%) reported that snus use presented a moderate risk (Slide 117, SM Label Eval. 2014). As compared to cigarettes, approximately half (49 and 52%) of those exposed to the modified risk warnings reported that snus was somewhat less harmful than cigarettes, compared to 10-19% of those exposed to the current claims, most of whom (51-62%) reported that the health risk of snus and cigarettes are equal (Slide 119, SM Label Eval. 2014). Most (76 and 75%) of those exposed to the modified risk claim reported that snus was more harmful than quitting tobacco entirely, although this was significantly lower than those exposed to the gum disease and mouth cancer claims (85 and 87%) (Slide 128, SM Label Eval. 2014).

In sum, while most of the total respondents, current users and current non-users of tobacco found the modified risk claims to be understandable and clear, these results were significantly lower than those reported for the current warnings. This may be due to the greater concreteness of the current claims and consumers' greater familiarity with the currently mandated warning labels. Fewer than half of the total respondents, current users and current non-users considered the modified risk claims to be believable, while those rating the current claims as believable exceeded 60%.

Following exposure to the modified risk claims total respondents, tobacco users and non-users of tobacco were more likely to rate snus as posing a moderate risk and less likely to report that it was harmful or extremely harmful than they were prior to exposure to any of the claims. This contrasted with those exposed to the current claims, more of whom reported that snus was harmful or very harmful and fewer of whom reported that snus posed a moderate risk. A similar pattern was demonstrated in the results of the comparisons of snus to cigarettes. Significantly more of those exposed to the modified risk claim rated snus as somewhat less harmful than cigarettes compared to those exposed to the current claims, significantly more of whom reported that cigarettes and snus are equally harmful. These data suggest that the modified risk claims were somewhat successful in educating consumers about the actual and comparative risks of snus and cigarettes. The results are more consistent with the message conveyed regarding the actual risk as reflected in the clinical and epidemiology studies described in this Application.

6.4.2.3.4. The Effect of Marketing Swedish Snus with a Modified Warning Label on Certain Demographic Groups

6.4.2.3.4.1. Minorities

The study population included 4,711 minority participants of whom 42.4% were current users of tobacco and 57.6% were current non tobacco users.

Understanding, Clarity and Credibility: Most of the minority tobacco users exposed to the modified risk claims reported that they were easy or very easy to understand (73 and 71%) (Slide 303, SM Label Eval. 2014) and that they were clear or very clear (71 and 61%) (Slide 304, SM Label Eval. 2014). The understanding for both of the modified risk statements was comparable to that reported for the current addiction (79%) and not a safe alternative (75%) statements. However the modified risk claims were significantly less understandable than the current gum disease (84%) and mouth cancer (82%) warnings. Minority tobacco users exposed to the "substantially lower risks" modified risk statement reported a level of clarity (71%) comparable to that reported for understandability (Slide 303, SM Label Eval. 2014). However, only 61% of those exposed to the "lower risk" modified risk statement reported that the claim was clear or very clear. This was significantly lower than what was reported for any of the four current claims (73-79%) and well below that reported for the "substantially lower risks" modified risk claim (71%) (Slide 304, SM Label Eval. 2014). Again, those exposed to the modified risk claims were significantly less likely to find the claims to be very or extremely believable (50 and 48%) than those exposed to the current claims (66-73%) (Slide 308, SM Label Eval. 2014)

Consistent with the results reported by all current tobacco users and non-users, fewer minority non-users of tobacco reported that the modified risk claims were easy to very easy to understand (60%) (Slide 445, SM Label Eval. 2014) and clear or very clear (53 and 51%) (Slide 446, SM Label Eval. 2014). These results were also significantly lower than those reported for all of the current warnings (71-74% understanding and 65-80% clarity), except the "not a safe alternative warning" (60%) which was not significantly different than what was reported for the modified risk claims. Those exposed to the modified risk claims were again significantly less likely to find the claims to be very or extremely believable (32%) than those exposed to the current claims (59-77%) (Slide 457, SM Label Eval. 2014).

Likelihood to Use and Motivation to Purchase: Approximately a quarter of minority tobacco users exposed to the modified risk claims reported that they were likely or extremely likely to use (29 and 24%) (Slide 305, SM Label Eval. 2014) and motivated to purchase (26 and 24%) (Slide 307, SM Label Eval. 2014) snus. The likelihood of snus use was similar to that reported for all of the current claims (20-25%) (Slide 305, SM Label Eval. 2014). However, the motivation to buy snus based on the modified risk claims was higher than for all of the current warnings and significantly so for the gum disease (16%) and mouth cancer (14%) warnings (Slide 307, SM Label Eval. 2014).

Of those minority tobacco users who reported that they were likely to use snus, there was little difference between those exposed to the modified risk warnings and those exposed to the current warnings with respect to the likelihood that they would engage in the dual use of snus and cigarettes (Slide 306, SM Label Eval. 2014).

At least half of the minority non-users of tobacco exposed to the modified risk claims reported that they were unlikely to use (56 and 60%) snus. This was lower than for those exposed to the current claims (62-72%) and significantly lower for those exposed to the substantially lower risk modified risk claim compared to the current gum disease, addiction and mouth cancer claims (Slide 447, SM Label Eval. 2014). Half of those (50%) exposed to the modified risk claims reported that they were

unlikely to start using cigarettes based on the claims, although this was not significantly different from those exposed to the current claims (42-59%) (Slide 448, SM Label Eval. 2014). Most of the remainder reported that the claims had no impact on their decision to use (22 and 20%) snus (Slide 447, SM Label Eval. 2014) or to start using cigarettes (28 and 26%) (Slide 448, SM Label Eval. 2014).

Risk Perception: Prior to exposure to any of the warning statements, 21% of minority tobacco users reported that snus presented a moderate risk, 18% reported it to be extremely harmful and 23% didn't know (Slide 309, SM Label Eval. 2014). Following exposure to the claims, 31 and 32% of the minority tobacco users exposed to the modified risk claims reported that snus posed a moderate risk and 25 and 22% reported that it was extremely harmful. As with the other populations described above, this contrasted with the results reported by those exposed to the current warnings. Significantly fewer of those exposed to the current warnings (17-23%) reported that snus presented a moderate risk and significantly more (32-50%) reported it to be extremely harmful (Slide 310, SM Label Eval. 2014). Compared to cigarettes and quitting tobacco entirely, the results were similar. Significantly more of those exposed to the modified risk statements rated snus as somewhat more harmful than cigarettes (46 and 48%) (Slide 312, SM Label Eval. 2014) and quitting tobacco entirely (51 and 50%) (Slide 321, SM Label Eval. 2014) than those exposed to the current claims, significantly more of whom reported that snus and cigarettes presented equal risk (35-48%) and (with the exception of those exposed to the addiction claim) that snus use was much more harmful than quitting tobacco entirely (43-57%).

The results for minority non-users of tobacco were similar. Prior to exposure to any of the claims 10% reported that snus presented a moderate risk, 37% rated it extremely harmful and 29% didn't know (Slide 458, SM Label Eval. 2014). Exposure to the modified risk and current claims resulted in a pattern similar to that described for the other populations above. Of those exposed to the modified risk claims significantly more (23 and 24%) reported that snus posed a moderate risk and significantly fewer rated it as extremely harmful (27% for both). Again, this was in contrast to those exposed to the current claims. Significantly fewer (10-17%) of those exposed to the current claims (except the addiction claim) reported that snus posed a moderate risk and significantly more (48-69%) reported that snus was extremely harmful (Slide 459, SM Label Eval. 2014). This pattern persisted in the risk perception of snus compared to cigarettes and to quitting smoking entirely. Significantly more of those exposed to the modified risk claims rated snus somewhat less harmful than cigarettes (42 and 48%) and significantly fewer reported that cigarettes and snus are equally harmful (26 and 23%). Those exposed to the current warnings reported the opposite pattern. Significantly fewer of those exposed to the current warnings reported that snus was somewhat less harmful than cigarettes (10-15%) and significantly more reported that snus and cigarettes are equally harmful (46-53%) (Slide 461, SM Label Eval. 2014). Similarly, significantly more of those exposed to the modified risk claims reported that snus was somewhat more harmful than quitting tobacco entirely while significantly more of those exposed to the current warnings reported that snus was much more harmful than quitting (Slide 470, SM Label Eval. 2014).

In sum, the results for minority users and non-users of tobacco are similar to those for the total user and non-user populations and do not appear to raise unique issues or concerns for the minority populations. Most of the minority users and non-users found the modified risk claims to be understandable and clear. As with the total population and smokers and non-smokers generally, these results were significantly lower than what was reported for the current claims. Following exposure to the claims, the risk perception patterns for minority respondents followed a pattern

similar to that reported for total respondents, users and non-users. Again, those exposed to the modified risk claims more likely to report that snus posed a moderate risk and less likely to report that it posed an extremely harmful risk than those exposed to the current claims. The results further suggest that that modified risk claims are unlikely to motivate minority non-users to use or buy snus.

6.4.2.3.4.2. Low Income

The study population included 6,750 low income participants having an income below $45,000, of whom 52.5% were current users of tobacco and 47.5% were current non tobacco users

Understanding, Clarity and Credibility Most (71 and 74%) of the low income tobacco users exposed to the modified risk claims reported that those claims were easy or very easy to understand (Slide 353 SM Label Eval. 2014) and 66 and 63% reported that the claims were clear or very clear (Slide 352, SM Label Eval. 2014). These results are again significantly lower than those reported by low income tobacco users exposed to the four current claims (83-89% understanding; 75-90% clarity). As with the populations described above, fewer of the low income non-users of tobacco exposed to the modified risk claims reported that they were easy or very easy to understand (59 and 61%) (Slide 498, SM Label Eval. 2014) and that the claims were clear or very clear (48 and 52%) (Slide 499, SM Label Eval. 2014). Likewise, these results were significantly lower than the results reported by low income users exposed to the current claims (73-86% understanding; 68-85% clarity). Similarly, both low income users and non-users exposed to the modified risk claims were significantly less likely to find the claims to be very or extremely believable (42 and 41% users; 31 and 36% non-users) than those exposed to the current claims (72 and 79% users; 67-78% non-users) (Slide 356 users and Slide 510 non users, SM Label Eval. 2014).

Likelihood to Use and Motivation to Purchase: Fourteen percent (14%) of the low income current tobacco users exposed to the "substantially lower risks" modified risk claim reported that they were likely or extremely likely to use snus. This was significantly higher than those exposed to the current gum disease, addiction and mouth cancer warnings (8% each). There was no significant difference in the likelihood of use among those exposed to the "lower risk" modified risk claim (10%) and any of the current claims (8-11%) (Slide 353, SM Label Eval. 2014). Similarly, there was no significant difference among those who were motivated to purchase snus based on either of the modified risk (10 and 11%) or the four current (5-8%) claims (Slide 355, SM Label Eval. 2014) . Among low income smokers likely to use snus, 22% of those exposed to the "substantially lower risks" modified risk claim reported that they were likely or extremely likely to use both cigarettes and snus. This was significantly higher than those exposed to the current gum disease (9%) and addiction claims (7%) (Slide 354, SM Label Eval. 2014).

Very few of the low income non-users of tobacco exposed to the modified risk claims reported that they were likely or very likely to use (6%) (Slide 493, SM Label Eval. 2014) or motivated to purchase (4%) (Slide 509, SM Label Eval. 2014) snus. These results were not significantly different from the results reported by those exposed to the current warnings. Moreover, among low income non-users of tobacco who reported that they were likely to use snus, exposure to the modified risk and current warnings resulted in no significant difference with respect to the likelihood of initiating cigarette use (Slide 501, SM Label Eval. 2014).

Risk Perception: Before exposure to the claims, 19% of low income users of tobacco reported that

snus presented a moderate risk, 21% rated snus as extremely risky and 31% didn't know (Slide 357, SM Label Eval. 2014). Following exposure to the modified risk claims, just over one-third (35 and 39%) reported that snus posed a moderate risk which was higher than, but not significantly so, for those exposed to the current claims (14-21%). Those exposed to the current warnings were significantly more likely to rate snus as harmful or extremely harmful (47-64%) compared to those exposed to the modified risk warnings (27 and 28%) (Slide 358, SM Label Eval. 2014). Those exposed to the modified risk claims were also significantly more likely to report that snus was somewhat more harmful than cigarettes (52 and 45%) (Slide 360, SM Label Eval. 2014) and somewhat more harmful than quitting tobacco entirely (47 and 43%) (Slide 369, SM Label Eval. 2014) compared to those exposed to the current warnings (6-10% cigarettes; 23-33% quitting). Conversely, those exposed to the current warnings were significantly more likely to rate snus and cigarettes as equally harmful (59-68%) (Slide 360, SM Label Eval. 2014) and much more harmful than quitting tobacco (42-63%) (Slide 369, SM Label Eval. 2014) than those exposed to the current warnings (41 and 48% cigarettes; 28 and 31% quitting).

Prior to exposure to any of the claims, 9% of low income non-users of tobacco reported that snus presented a moderate risk, 41% rated it as extremely risky and 29% didn't know (Slide 511, SM Label Eval. 2014). Following exposure to the warnings, significantly more of those exposed to the modified risk claims reported that snus posed a moderate risk (24 and 26%) compared to those exposed to the current claims (10-14%). Conversely, significantly more of those exposed to the current claims reported that snus was extremely harmful (47-66%) compared to those exposed to the modified risk claims (28 and 29%) (Slide 512, SM Label Eval. 2014). Similarly, compared to cigarettes, significantly more of those exposed to the modified risk warnings reported that snus was somewhat less harmful than cigarettes (44 and 52%) compared to those exposed to the current warnings (8-17%). Again, those who were exposed to the current warning were significantly more likely to report that snus and cigarettes were equally harmful (50-60%) compared to those exposed to the modified risk claims (28 and 22%) (Slide 514, SM Label Eval. 2014). Thirty four (34%) and thirty one (31%) percent of the low income non-users of tobacco exposed to the modified risk claims reported that snus was somewhat more harmful than quitting tobacco entirely, and 41 and 43% reported that snus was much more harmful than quitting. These results were generally significantly different than those exposed to the current claims, 17-26% of whom reported that snus was somewhat more harmful than quitting and 55-71% reported that snus was much more harmful than quitting (Slide 523, SM Label Eval. 2014).

In sum, the perception of clarity, understanding and credibility reported by low income users and non-users of tobacco are similar to what was reported by the total user and non-user populations Following exposure to the claims the risk perception patterns for minority respondents followed a pattern similar to, but less dramatic than, that reported for total respondents, users and non-users, with those exposed to the modified risk claims more likely to regard snus as a moderate risk and somewhat less harmful than cigarettes. The modified risk claims were also unlikely to cause or motivate low income non-users of tobacco to use or by snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for the low income population.

6.4.2.3.4.3. Youth (ages 18 to 24 years)

Understanding, Clarify and Credibility: Most of the tobacco users ages 18-24 years reported that the modified risk claims were easy or very easy to understand (74 and 75%) (Slide 399, SM Label Eval. 2014) and clear or very clear (63 and 61%) (Slide 400, SM Label Eval. 2014).

However, these results were again significantly lower than what was reported by those exposed to the current warnings (81-86% understandable; 73-83 clear). Tobacco users ages 18-24 years found the claims more understandable and clearer than non-tobacco users ages 18-24. Of the non-users of tobacco ages 18-24 exposed to the modified risk claims, 59 and 56% reported that the claims were easy or very easy to understand (Slide 551, SM Label Eval. 2014) and 44 and 45% classified the claims as clear or very clear (Slide 552, SM Label Eval. 2014). As with the other populations, these results were significantly lower than those exposed to the current claims (62-80% clarity; 74-84% ease of understanding except that the "not a safe alternative" claim (66%) was not significantly different than the modified risk claims.) Once again, significantly fewer of the users and non-users of tobacco between the ages of 18 and 24 years found the modified risk claims to be believable or very believable (43 and 45% users; 30 and 31% non-users) than those exposed to the current warnings (66-72% users; 58-71% non-users) (Slide 404 users and Slide 555 non users, SM Label Eval. 2014).

Likelihood to Use and Motivation to Purchase: Tobacco users ages 18-24 years exposed to the "substantially lower risks" modified risk claim were significantly more likely to use snus (25%) and significantly less likely to be discouraged from using snus (29%) than those exposed to the current gum disease (42% encouraged; 16% discouraged) and mouth cancer (43% encouraged; 14% discouraged) warnings. There was no significant difference in likelihood of use between the "lower risk" claim and any of the current warnings (Slide 401, SM Label Eval. 2014). Tobacco users ages 18-24 years exposed to the "substantially lower risks" claim were also significantly more likely to be motivated to purchase snus (22%) and significantly less likely to be discouraged from purchasing snus (15%) than those exposed to any of the current claims (8-12% motivated; 27-44% discouraged) (Slide 403, SM Label Eval. 2014). Of those likely to use snus, there was little difference in the likelihood of dual use among those exposed to any of the claims (Slide 401, SM Label Eval. 2014).

More than half (56%) of the non-users of tobacco ages 18-24 years exposed to the "substantially lower risks" modified risk claims reported that they were unlikely to use snus This was significantly lower than the percentage of those exposed to the current gum disease (63%), mouth cancer (72%) and not a safe alternative (68%) claims. However, there was no significant difference in the likelihood of use between those exposed to the "lower risk" modified risk claim and any of the current claims. Nor was there a significant difference among those exposed to any of the claims who reported that they were likely or extremely likely to use snus (Slide 553, SM Label Eval. 2014). Those exposed to the modified risk claims were also significantly less likely (46 and 47%) to be discouraged from buying snus than those exposed to the gum disease (68%), mouth cancer (68%) and not a safe alternative (62%) claims. However, there was no significant difference regarding the likelihood that any of the claims would to motivate non-users ages 18-24 to buy snus (Slide 554, SM Label Eval. 2014).

Risk Perception: Prior to exposure to any of the warning statements, 22% of tobacco users ages 18-24 classified daily snus use as a moderate risk, 21% classified it as extremely harmful and 19% didn't know (Slide 405, SM Label Eval. 2014). The movement in the perception of the risk of daily snus use was not as pronounced in this population as in others. Of those exposed to the modified risk warnings, 29 and 34% reported that snus posed a moderate risk which, for both modified risk claims, was significantly higher than only the mouth cancer warning (17%). The percentage of those exposed to the "lower risk" claim who classified snus as a moderate risk was also significantly higher than those exposed to the current gum disease and not a safe alternative

claims. The results for those who classified snus as extremely harmful were also mixed. Significantly more of those exposed to the gum disease (48%) and mouth cancer (47%) claims classified snus as extremely harmful compared to those exposed to both modified risk claims (28 and 20%). Those exposed to the "not a safe alternative claim" were also significantly more likely to classify snus as an extremely high risk (37%) compared to those exposed to the "lower risk" modified risk claim (Slide 406, SM Label Eval. 2014).

Those exposed to the modified risk claims were significantly more likely (50 and 42%) to consider snus somewhat less harmful than cigarettes than those exposed to the current claims (13-20%), who were significantly more likely to report that snus and cigarettes posed equal risk (36-46%) than those exposed to the "substantially lower risks" claim (20%). Only those exposed to the "not a safe alternative claim" were significantly more likely (46%) to consider snus and cigarettes as equally harmful than those exposed to the "lower risk" modified risk claim (29%) (Slide 408, SM Label Eval. 2014). Those exposed to the modified risk claims were significantly more likely to consider snus somewhat more harmful than quitting all tobacco use (50 and 55%) than those exposed to the current claims (27-39%) except that the difference between the "lower risk" modified risk claim and the current addiction claim was not significant. Similarly those exposed to all of the current claims except the addiction claim (51-59%; 34% addiction) were significantly more likely than those exposed to the modified risk claims (29 and 30%) to consider snus much more harmful than quitting (Slide 417, SM Label Eval. 2014).

Prior to exposure to any of the claims, 11% of the non-users of tobacco ages 18-24 years considered snus to pose a moderate risk, 38% classified it as an extremely harmful risk and 23% didn't know (Slide 556, SM Label Eval. 2014). Following exposure to the modified risk warnings, 25 and 27% reported that snus posed a moderate risk which was significantly higher than those exposed to all of the current claims (10-15%) with the exception of the addiction claim (18%). Conversely, those exposed to all of the current claims except the addiction claim were significantly more likely (51-61%; addiction 36%) than those exposed to either of the modified risk claims (23 and 27%) to rate snus as extremely harmful (Slide 557, SM Label Eval. 2014). Compared to cigarettes, significantly more of the non-users ages 18-24 exposed to the modified risk claims (55 and 58%) than to the current claims (11-23%) rated snus as somewhat less harmful than cigarettes, significantly more of whom rated snus and cigarettes as equally harmful (46-58%) compared to those exposed to the modified risk claims (22 and 25%) (Slide 560, SM Label Eval. 2014). This trend was repeated in the comparison of snus to quitting all tobacco. Significantly more of those exposed to the modified risk claims (36 and 38%) rated snus as somewhat more harmful than those exposed to the gum disease (24%), mouth cancer (23%%), and "not a safe alternative" (22%) claims, significantly more of whom (61, 61 and 69%, respectively) reported that snus was much more harmful than quitting tobacco compared to those exposed to the modified risk claims (42 and 39%). There were no significant differences in either parameter between those exposed to the modified risk claims and those exposed to the addiction warning (Slide 568, SM Label Eval. 2014).

In sum, the study did not raise concerns that the modified risk claims would have an adverse effect on youth ages 18 to 24 years. In general, this population found the claims to be clear and understandable. Their perception of the risk following exposure to the claims was similar to, but not as dramatic as, that reported by the total, user and non-user populations. Youth exposed to the modified risk claims were more likely to report that snus posed a moderate risk and a somewhat lower risk than cigarettes. The modified risk claims were also unlikely to cause or motivate non-

users ages 18 to 24 to use or buy snus or initiate cigarette use. Overall, the study does not appear to raise unique issues or concerns for youth ages 18 to 24.

6.4.2.3.5. The effect of Marketing Swedish Snus with a Modified Warning Label on the Population as a Whole

As was noted above, the Consumer Perception Study assessed the effects of the modified risk warnings on the total population, total users of tobacco products, total non-users of tobacco products, and minority, low income and youth users and non-users of tobacco. It also assessed tobacco users who reported being imminent quitters or reducers; dual users of snus and other tobacco products and current non-users who reported being former users of tobacco. The study did not reveal an adverse impact of the modified risk warnings on the population as a whole or on any of the foregoing subpopulations.

Most of the total users of tobacco products, total non-users of tobacco products, and minority, low income and youth users and non-users of tobacco reported that they understood the modified risk warnings and that the modified risk claims were clear. However, the percentages reporting that the modified risk claims were easy or very easy to understand were, in all cases, lower than for the current claims. These results were significantly lower than for the current claims except for the level of understanding reported by the minority users of tobacco. In general, a higher percentage of users than non-users in each category reported that the claims were easy or very easy to understand. The difference in understanding and clarity between the modified risk and the current claims may reflect the greater length and complexity of the modified claims and the greater familiarity of consumers with the current claims.

In general, fewer than half of the respondents in each category reported that the modified risk claims were credible, which was significantly lower than for the current claims. Credibility was generally lower among non-users than users in all categories, with the highest percentage of minority users of tobacco products reporting that the claims were credible (50%).

Following exposure to the modified risk warnings, all of the populations were more likely to rate snus as posing a moderate risk and less likely to report that it was harmful or extremely harmful than they were prior to exposure to any of the claims. For all categories, those exposed to the modified risk claims were significantly more likely to rate snus as a moderate risk compared those exposed to the current claims who were more likely to rate snus as presenting a significant risk. However, this pattern was less pronounced among low income and youth users of tobacco. The same trend was consistently reported in the comparison of the risks posed by snus and cigarettes. In all categories, those exposed to the modified risk claims were more likely to rate snus as somewhat less harmful than cigarettes and less likely to report that snus and cigarettes posed equal risk compared to those exposed to the current claims in whom the opposite trend was observed. These results suggest that the modified risk claims serve the important function of educating consumers about the demonstrated lower risk of snus as compared to cigarettes.

In general, fewer than a quarter of the tobacco users in each category exposed to the modified risk claims reported that they were likely to use or motivated to purchase snus. This percentage was generally slightly higher among those exposed to the modified risk claims than those exposed to the current claims. The percentage was highest among minority users and lowest among low income

users.

The majority of non-users in each category reported that they were unlikely to use or buy snus and generally fewer than 10% reported that they were likely to use or buy snus. These results were generally somewhat lower for those exposed to the modified risk claims compared to the current claims. Approximately two-thirds of former tobacco users exposed to the modified risk claims reported that they were unlikely to use snus and 3% or fewer reported that they were likely to use or motivated to purchase snus. Based on these results, the modified risk claims appear to be unlikely to motivate non-users of tobacco in any of the populations, including those who formerly used tobacco products, to try snus.

Current smokers who reported being imminent quitters or reducers exposed to the modified risk claims were more likely to try snus than those exposed to the current claims. Of those likely to try snus, a quarter indicated that they were likely to use both cigarettes and snus, with approximately two-thirds of those reporting that they would use snus to quit or reduce cigarette use. The likelihood of dual use among all current smokers likely to use snus was higher for those exposed to the modified risk claims than to the current claims with two-thirds of those also reporting that they would use snus to quit or reduce smoking, although this was not significantly different than what was reported by those exposed to the control claims.

6.4.2.3.6. Conclusion

The overall results of the Consumer Perception Study demonstrate that the proposed warning labels for the Snus Products are unlikely to produce unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study results demonstrate subjects' comprehension and understanding of the proposed warning labels and support the conclusion that the modified risk claims are not misleading, but rather promote a better understanding of the actual health risks of snus as compared to cigarettes. While the modified warning label changed consumers' perception of the harmfulness of snus, additional measures are perhaps needed to more substantially alter consumer risk perception to make it more consistent with the scientific evidence.

The Study provides several key insights related to intended use of the Snus Products by current users and non-users of tobacco products, and the results of this research supplement the extensive preclinical, toxicology and epidemiology data presented in this Application regarding the effects and use of snus as compared to cigarettes. In particular, study results significantly contributed to Swedish Match's decision to include the term "substantially" in the proposed label change for the Snus Products, that is "No tobacco product is safe, but this product presents *substantially* lower risks to health than cigarettes." The survey results were consistent with the scientific literature on relative risk perception of snus (Lund and Scheffels 2013), and the term "substantially" is supported by the voluminous product-specific scientific evidence presented in this Application.

6.4.3. References

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6.5 Effect on the Population as a Whole

Statistical models are useful tools for estimating the health effects expected to result from changes in the distribution of a harmful exposure in a given population. In the case of changes which result from a regulatory action, a population model allows direct comparison of the potential health impacts of alternative policies that might affect the distribution of the exposure in different ways, thereby supporting the selection of one policy over another (Levy et al. 2006). Desirable features of such a model include the clarity with which the underlying assumptions are stated, and the ability of the model to delineate the relationship between the estimates it produces and the assumptions underlying the model (Garrison 2003; Weinstein et al. 2003).

Swedish Match presents below the results of statistical modeling which demonstrate that Swedish snus, the proposed MRTP, is likely to benefit the health of the population as a whole, taking into account both users and non-users of the products. The model integrates information regarding the marketing of the MRTP, including its potential effects on health, tobacco use behavior and tobacco use initiation, to provide an overall assessment of the potential effect that Swedish snus may have on overall tobacco-related morbidity and mortality. For more details, see ENVIRON Tipping Point Analysis 2014 (attached as Appendix 6G).

Consistent with the MRTP Guidance, the model provides quantitative estimates of the effect of the proposed marketing of the Snus Products on the population as a whole. Swedish Match concludes that these data—when taken together with the data presented in Section 6.1 of the Application regarding the expected health benefits to individual consumers—establish that the issuance of a marketing authorization order under Section 911(g) of the Act is indeed "appropriate for the protection of the public health."

6.5.1. Dynamic Population Model (DPM)

To assist in the analysis of the effects of the proposed MRTPs, ENVIRON developed a comprehensive, flexible DPM which can be used to assess whether the introduction of an MRTP is likely to lead to or reduce harm at the population level. The DPM is a new tool which builds on approaches described by others (Hoogenveen et al. 2008; Kulik et al. 2012; Levy and Friend 2002; Tengs et al. 2001; Tengs et al. 2004; Tengs et al. 2005) but which provides additional flexibility not found in existing models. Importantly, the DPM permits the model user to define all parameters, and it significantly improves the validity of previous models by accounting for age- and time dependent changes in risks.

6.5.1.1. Funding Sources

Financial support for the DPM was provided through a contract between RJR and ENVIRON, with Swedish Match providing additional financial assistance. Neither Swedish Match nor RJR participated in the development or interpretation of the model, nor did either company provide or recommend any data used to validate the model. All work was completed independently by ENVIRON.

6.5.1.2. Methods

The DPM starts with a hypothetical birth cohort, (i.e., a population initially all of the same age), all of whom begin as never tobacco users. The DPM follows the population as it ages, distributing

subsets of the cohort into user-defined exposure categories (e.g., current and former smoking or MRTP use) and applying the correct, age- and exposure-specific mortality rate to each category. The model permits assessment of the effects of different transitions (e.g., switching between cigarettes and Swedish snus and, among former tobacco users, relapsing to prior use states), and compares the number of survivors in a base case which includes never, current, and former cigarette smokers, but no snus users, with the number of survivors in a counterfactual scenario that also includes never, current, and former snus users. In other words, the base case population has access to only one type of product, namely cigarettes. In the counterfactual exposure scenario, proportions of the population may use an alternative product with a different risk profile, namely Swedish snus. In this manner, the DPM estimates all-cause mortality in the hypothetical population under different exposure distributions, and compares the numbers of survivors expected under each exposure scenario.

The DPM user defines the size of the hypothetical population. The time variable is age (categorical), and the DPM user specifies the age at which to begin and end follow-up, as well as the age category widths. All age categories are required to have the same width.

6.5.1.2.1. Transitions between exposure states

The DPM distributes persons into age and exposure categories using age category-specific exposure transition probabilities entered by the DPM user. All cohort members begin as unexposed to both the base case and alternative products (**Figure 6-7**, left-hand box). As follow-up of the base case progresses (Figure 6-7, top row), individuals either remain as unexposed (curved arrow) or transition to current use of the base case product (top row, second box), shown by the forward arrow. Current users may remain current users (curved arrow) or became former users in the next follow-up interval. Subsequently, former users may restart the base case product and quit again.

Rows below the top in Figure 6-7 describe the additional possibility of exposure to the alternative product (in this case, Swedish snus, the proposed MRTP) in the counterfactual scenario. For example, unexposed cohort members (top left-hand box) may remain as unexposed (curved arrow) or transition to use of the alternative product (downward arrow). Current alternative product users may remain current users (curved arrow), switch to the base case product, become concurrent dual users of both cigarettes and Swedish snus, or quit use of the alternative product in the next follow-up interval. Subsequently, persons can remain in their exposure category (curved arrow) or move into other exposure categories (forward arrow).

The DPM user can define the probability of transitioning from one exposure state to another from available data, or the transition probabilities can be specified to address a particular question of interest. For example, assuming that the smoking initiation rate among US males aged 13-17 years in a particular year of interest is 11%, then the probability of transitioning from never tobacco user to smoker in age category 13-17 would be set by the DPM user to 11%.

Alternatively, if the DPM user was instead interested in the effect on population mortality where, among US males aged 13-17, smoking initiation was instead 5%, the DPM user would set the probability of transitioning from never tobacco user to smoker in age category 13-17 to 5%.

The distribution of the cohort into exposure groups may be constructed in a spreadsheet. However, to obtain variability estimates of the output using Markov chain Monte Carlo techniques, the DPM

is implemented in the WinBUGS computer program (version 1.4.3) (Lunn et al. 2000). Transition probabilities can be modeled as fixed (which is most appropriate for rates addressing a specific question of interest) or normally distributed (which is most appropriate for rates based on estimates from the literature), but are bounded between 0% and 100%. Default means are equal to the respective estimated transition probabilities, and default standard deviations are equal to 1%. These values can be changed by the DPM user.

6.5.1.2.2. Mortality

A Poisson model embedded within the DPM estimates the number of deaths among persons with a particular exposure history involving only the base case product. The estimates are based on person-years and deaths by age, years of exposure and years since cessation of exposure entered by the DPM user. Only survivors move on to the next age category. Specifically, r.ne, the mortality rate among persons who never used the base case or the alternative product, and r.bc and r.fbc, the mortality rates among current and former users of the base case product, respectively, are estimated as:

$$r.ne = e^{\beta_0+\beta_{age}age+\beta_{age^2}age^2}$$

$$r.bc = r.ne \times e^{\beta_{ybc}ybc+\beta_{aybc}age\times ybc}$$

$$r.fbc = r.bc \times e^{\beta_{yfbc}yfbc+\beta_{ayfbc}age\times yfbc}$$

where bc= base case product use, fbc=former base case product use, ybc=years of exposure to the base case product and yfbc=years since quitting the base case product.

To estimate mortality rates for the alternative product (ap), the DPM user enters the excess relative risk (ERR) for individuals with current exposure to the alternative versus the base case product, defined as the ratio of relative risks (RR) for the alternative and base case exposures:

$$ERR = \frac{RR.ap - 1}{RR.bc - 1}$$

The DPM then calculates age- and duration-specific mortality rates for the alternative product compared with the base case product, as follows:

Because $RR.\ ap - 1 = ERR\ (RR.bc - 1)$

and, therefore, $\frac{r.ap}{r.ne} - \frac{r.ne}{r.ne} = ERR\left(\frac{r.bc}{r.ne} - \frac{r.ne}{r.ne}\right)$ and $r.ap - r.ne = ERR(r.bc - r.ne)$,

the mortality rate for current users of the alternative product is

$$r.ap = ERR \times r.bc + (1 - ERR)r.\ ne.$$

Mortality rates for former users of the alternative product are calculated similarly, replacing bc with

fbc and ap with fap.

For users of the base case product who switch to the alternative product, mortality rates are the product of four factors: (i) risks from background, (ii) base case product use for the age range during which the base case product was used, (iii) alternative product use for the age range during which the alternative product was used, and (iv) former use of the base case product. Mortality rates for users of the alternative product who switch to the base case product are calculated similarly, but exclude risk for former use of the alternative product because the alternative product is assumed to have lower risks than the base case product. Mortality rates for persons switching to a different product and then quitting are calculated similarly, with former use replacing current use of the second product. Concurrent dual use is assumed to have the same mortality risk as use of the higher risk product. The derivation of the mortality rates is shown in Bachand and Sulsky, (2013).

The default prior distributions for the coefficients of the core Poisson model are non-informative normal distributions, with mean 0 and standard deviation 100.

6.5.1.2.3. Morbidity

To assess the overall impact of tobacco use on the public health, it is theoretically appropriate to consider both morbidity and mortality. However, the MRTP Guidance does not clearly define the term "morbidity," which raises conceptual difficulties with the recommendation of "including quantitative estimates of the effect . . . of the MRTP . . . on tobacco-related morbidity."

Morbidity can be defined as the incidence of a disease (e.g., cancer incidence), or it can mean the severity of the disease. Consider, for example, COPD, a disease which is a major concern associated with tobacco smoking. Because COPD is an irreversible, chronic condition, it is more appropriate to consider its incidence and severity rather than just the incidence among afflicted individuals when evaluating the burden of smoking-related disease. Likewise, diabetes is another condition in which the severity varies considerably. In some individuals, diabetes is reversible, but in others it is a chronic, severely debilitating, lifelong condition. Incidence and severity cannot easily be integrated to form an overall metric of "morbidity."

Morbidity data (whether measured as incidence or severity of disease) can be helpful in assessing a tobacco product's overall impact on population health. This is particularly true because mortality data may not otherwise capture the extent to which the population is impacted by diseases and/or conditions that are not rapidly lethal. For example, individuals who suffer from COPD or diabetes may be severely debilitated for decades, but their disease burden is not reflected in mortality statistics. Furthermore, disease severity may be affected by access to health care and, possibly other factors besides tobacco exposure. Likewise, for cancers with a relatively good prognosis, such as urinary bladder or squamous cell skin cancer, mortality data do not fully reflect the population- level impact because many more individuals are affected than eventually die from the disease. By contrast, most of the relevant tobacco-related cancers (i.e., those which account for most of the excess mortality among smokers) such as lung cancer, esophageal cancer, and pancreatic cancer, typically have a rather poor prognosis, thereby making mortality a reasonable proxy for incidence.

Mortality is generally regarded as the "hardest" and, therefore, the more reliable end-point. Data on mortality are readily available in most countries, including the United States, and have been

collected using standardized methods over many years. Even if "morbidity" is defined strictly as "disease incidence," the available data are inadequate to address the effect of changing tobacco exposures. For example, data on incidence of cancer can be obtained from population-based cancer registers. While registration has generally been done using standardized methods and validity issues related to completeness of registration, coding, etc. are typically well characterized, incidence rates for different tobacco exposure categories, or even cigarette exposure categories, are not usually available. To the best of Swedish Match's knowledge, there are no population-based registers in the United States to estimate the incidence of cardiovascular diseases or COPD, both of which account for a considerable proportion of the excess mortality experienced by smokers. Although such data may be available for selected groups of individuals, the external validity of such information is generally not well characterized. Reliable and comparable information on severity of disease by exposure category is even more scant.

Epidemiological studies on cancer and cardiovascular disease among snus users in Sweden have generally been based on morbidity data (with incidence as the main outcome measure) rather than mortality. This has only been possible because of the availability of population-based registers with high coverage of detected cases. These data have generally not supported an association with snus. Even the few individual studies which disagree with this general finding have typically not suggested *higher* risks with snus compared to cigarette smoking, although they may have suggested some risk increase compared to no tobacco use (Arefalk et al. 2012; Critchley and Unal 2004; Hansson et al. 2012; Hergens et al. 2007; Johansson et al. 2005; Lee 2007; Lee 2013; Roth et al. 2005).

Based on mechanistic considerations, it is widely accepted that snus is not associated with COPD. Evaluations of how smoking cessation affects COPD must be based on estimates of lung function or severity of symptoms rather than presence/absence of the condition, given that COPD represents an irreversible deterioration of lung function. There is little or no information on how any aspect of COPD morbidity is affected by smoking cessation through switching to snus versus complete tobacco cessation. However, it seems appropriate to assume that mortality from COPD would go down if smokers quit cigarettes through switching to snus. Indeed, it is widely accepted that COPD results from long term exposure from airborne irritants such as tobacco smoke and air pollution from certain occupational exposures and cooking fumes, for example. Genetics probably also play a major role. Of the HPHCs identified by FDA-CTP in smokeless tobacco (including Swedish snus), none has been suggested to be linked to the development of COPD unless inhaled. Expert panels (Levy et al. 2004) and institutional reports (SCENIHR 2008) have not considered the possibility that use of STP could be a significant risk factor for COPD. Thus, based on mechanistic considerations, snus is widely accepted not to be associated with COPD even in the absence of additional epidemiological confirmation.

In summary, even though considerations related to morbidity impact on the population are important, the data available to estimate morbidity (with the possible exception of cancer incidence) are inherently less reliable and are generally less available than those related to population mortality. An additional difficulty is the integration of different measures of morbidity into an overall "morbidity" metric.

The analyses presented in this section of the Application are based on estimates of how snus would affect population mortality in various uptake scenarios. The basic assumptions about the effects of snus on mortality were based on expert panel estimates for a low nitrosamine smokeless tobacco

product developed using a Delphi approach (Levy et al. 2004). Because this panel was convened before many of the key studies on Swedish snus became available (all of which showed essentially null results), panel member estimates were likely influenced by earlier data concerning some US smokeless products. It is therefore reasonable to assume that the panel's estimates represent a "worst case" scenario for Swedish snus. Citing a lack of relevant data, Levy et al. explicitly stated that they did not attempt to develop estimates for effects on morbidity (Levy et al. 2004). No other panel similar to the one convened by Levy et al, has published estimates on the effects of snus on morbidity.

The DPM is the most versatile tool available today that can be used to model the population impact of an MRTP. However, even the DPM in its present form does not allow modeling of cause-specific morbidity. Swedish Match is committed to supporting the further development of the model, and several enhancements to the DPM are currently underway—among them the incorporation of morbidity (i.e., incident disease) as an outcome measure. Significant challenges to that work include the need to obtain reasonable estimates on morbidity (similar to the Levy estimates for mortality) and to conceptualize how morbidity metrics accounting for disease incidence and severity could be integrated to form an overall metric.

The Tobacco Control Act does not require that an MRTP's "benefit to the population as a whole" be demonstrated by effects on both morbidity and mortality. There are also no special circumstances with Swedish snus that would invalidate mortality as a proxy for morbidity in the tipping point analyses presented in this Application. In light of these considerations, Swedish Match believes it is reasonable to limit quantitative estimates of the population-level impact of snus as an MRTP to effects on overall mortality without attempting to speculate on cause-specific morbidity.

6.5.1.2.4. Model Output and Applications

The DPM output includes the age-specific number of survivors under the base case and counterfactual scenarios, and their difference. Output values are estimated after each iteration and summarized over all iterations using means and 95% posterior intervals (i.e., the 2.5th and 97.5th percentile of the distribution). The model input and output are summarized in **Figure 6-8**.

The default output from the DPM is a comparison between survivors in the base case and counterfactual exposure scenarios. All possible exposure transitions can occur after conclusion of the fifth category of attained age, so age-specific numbers of survivors are displayed from that point forward. Results can be used to estimate tipping points, defined as the proportion of the population that must experience a reduction in harm to overcome the survival deficit arising from a proportion of the population experiencing an increase in harm, or vice versa. Tipping point analyses can be relatively simple (i.e., addressing only one harmful or beneficial exposure pattern and one exposure pattern expected to counteract the harm or benefit it produces) or complex (i.e., addressing multiple interacting exposure patterns). Model input values can be systematically changed to conduct sensitivity analyses.

6.5.1.3. Validation of the Model

The Kaiser Permanente (KP) cohort study provided age-, years of smoking- and years since quitting-specific mortality rates for men (Friedman et al. 1997), and, after some adjustments to

assure internal consistency[67] and to construct appropriate age categories, these were used in the embedded Poisson model. Any data set providing information on person-years and numbers of deaths by duration of exposure and cessation of exposure to a base case product (i.e., cigarettes) could have been used. The KP cohort study was selected for its relative sociodemographic diversity and because it provided person years and deaths by age and duration of smoking or smoking cessation.

There was no evidence of over- or under-dispersion in the Poisson model, and including interaction terms for (age×duration of smoking) and (age×duration of quitting) provided a model with excellent fit assessed both graphically and statistically (Pearson Chi-Square goodness of fit test p-value = 0.82). Fit was still good graphically and statistically (Pearson Chi-Square goodness of fit test p-value =0.2) when the KP data for women were used with the same model coefficients, although the y-intercept had to be adjusted to account for the women's lower baseline mortality risk.

The modeled mortality estimates were compared against mortality estimates using actual population life tables. To validate mortality estimates under the base case (i.e., no MRTP use), US mortality among men in 2006 was predicted using age-specific 1980 US smoking initiation (SAMHSA 1999) and cessation rates (Messer et al. 2007). Exposure data from 1980, as shown in **Table 6-57** were selected as pertinent to 2006 mortality data to allow for adequate induction time. Because the prevalence of smokeless tobacco use in US has been fairly low and stable, around 5% among men and much lower among women (CDC 1994), this approximates a population without MRTP exposure. The model results were then compared with the 2006 US life table for men (CDC 2009). As shown in **Table 6-58**, there was a close correspondence between the US life table-based numbers of survivors and the model results for the base case scenario.

To validate the counterfactual scenario estimates, Swedish snus (i.e., the proposed MRTP which is the subject of this Application) was used as an example MRTP. Swedish snus use has been common among Swedish men, especially since the 1970s, and thus ERR estimates were available that allowed estimation of all-cause mortality risk for users of snus compared to cigarette smokers. A counterfactual exposure scenario was defined (**Table 6-59**) based on estimated probabilities of transitioning between cigarettes, snus and dual use observed in Sweden (Lundqvist et al. 2009). For current snus use versus current smoking, a conservative estimate of ERR=0.11 (Levy et al. 2004) was employed. In the absence of data regarding the comparative mortality risks for former smokers vs. former snus users, the same ERR of 0.11 was used. Users of cigarettes and snus (i.e., dual users) are assumed to have the same excess risk as smokers, because the mortality risk estimated in the Poisson model is dependent on duration of smoking and not amount smoked. Mortality estimates based on the DPM results were compared to mortality estimates derived from the 2006 Swedish life table for men (Statistics Sweden 1982). **Table 6-60** shows close correspondence between the model results and the Swedish life table-based numbers of survivors for the counterfactual exposure scenario.

Importantly, development of the DPM was not based on any specific input data. The input values

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[67] For example, the mortality rate was lower in 35-49 year old former smokers than never smokers participating in the KP study and had to be adjusted. In addition, the KP data had to be adapted to be simultaneously stratified by age, duration of smoking, and years since quitting smoking.

specified above were used only to validate the predictions generated by the DPM. For validation of both the base case and the counterfactual exposure scenario, 10,000 iterations were used, after a burn-in of 2,000 iterations, and a Markov chain was considered to have converged if the Monte Carlo error was less than 5% of the sample standard deviation.

6.5.1.4. Discussion of the DPM

As discussed above, the DPM was designed to estimate the change in survival expected when an alternative exposure is added to a population. It was structured to test the effect on mortality if some people substitute a new exposure for an existing exposure, or if some people who would not have been exposed at all in the base case are instead exposed to the new product in the counterfactual scenario. The DPM was specifically developed to estimate changes in survival, at the population level, when proportions of potential or actual cigarette smokers substitute use of an MRTP for all or some of their cigarettes.

The partial or complete substitution of a higher risk product with a lower risk product, logically, should provide some health benefit. Evidence for the existence of health benefits for cigarette smokers who switch to Swedish snus is provided by correlations between changing patterns of tobacco use and changing morbidity and mortality patterns observed in Sweden, where Swedish snus has been commonly used by men for decades and the prevalence of cigarette smoking has declined over time (Foulds et al. 2003). It is necessary, however, to also analyze the likelihood of potential unintended adverse consequences occurring, if products are designated and marketed as MRTPs. Potential adverse consequences include the possibility that current smokers who would have otherwise given up cigarettes instead substitute MRTPs for some or all of their cigarettes, and that non-tobacco users might initiate MRTP use and then become cigarette smokers instead of remaining never tobacco users. The DPM can be used for this purpose by comparing the changes in mortality expected to follow from various potential changes in the distribution of use of cigarettes and snus.

The model validation exercises showed that, given a sufficient induction period and reasonable input data, the DPM accurately predicts life tables for a population with no snus use (i.e., the United States) and a population with widespread snus use (i.e., Sweden). Thus, the results of the validation indicate that the DPM can provide meaningful data to compare the health effects of different hypothetical exposure distributions.

Like all models, the DPM is built on simplifying assumptions, specifically: (i) it permits testing the addition of a new exposure, but not removal of an exposure that exists in the base case; (ii) the effects of using only two types of products are compared; (iii) it assumes that the rates of risk reduction associated with stopping use of the base case and the alternative products are proportional; (iv) mortality rates depend on the overall duration of product use or quitting, but not on the amount of each product used nor the sequence of exposures; (v) because the amount of exposure is not accounted for, the ERRs for current and former dual use versus current and former cigarette smoking cannot be modified by the user, and are set to 1; (vi) the DPM accommodates a large number of exposure patterns, but it does not allow for concurrent dual exposure to revert to exposure to either single product alone; (vii) only the direct effects of exposure to higher and lower risk products are considered - the DPM does not account for changes to second-hand smoke exposures due to changes in the proportions of cigarette smokers in the population; and (viii) the DPM requires user-specified input data, and the precision and validity of the outcome estimates

depend on the certainty and validity of the model input selected.

Notwithstanding its limitations, the DPM is the most comprehensive, flexible tool currently available to model tobacco-related health effects at the population level. Other dynamic models focusing on the risks associated with use of tobacco products have been described in the literature, but most were developed to estimate changes in population-level effects due to changes in proportions of never, current and former smokers resulting from increasing smoking cessation rates and/or decreasing smoking initiation rates. These models do not consider the effect of introducing a new product to a population (Hoogenveen et al. 2008; Kulik et al. 2012; Levy and Friend 2002; Tengs et al. 2001; Tengs et al. 2004; Tengs et al. 2005). Two published models were designed to estimate the effects of introducing an MRTP to a population of never, current and former smokers, but the range of questions they can address is limited because they hold smoking initiation and cessation rates constant and do not allow age-dependent transition probabilities (Apelberg et al. 2010; Mejia et al. 2010).

The main strengths of the DPM are its flexibility, its ability to account for uncertainty in the model input and output, its comprehensiveness, and its demonstrated validity. All DPM model input can be changed by the user, and the level of uncertainty in model input can be specified and is accounted for by the posterior intervals that estimate the variability of the results. Thus, the key benefit of using a model such as the DPM to investigate the potential effects of granting an MRTP designation is the ability of the DPM to hold constant all assumptions and factors other than the distribution of exposure or the comparative risk estimates. Because the DPM requires the user to specify the particular transition probabilities of interest and the risk associated with the new compared with the old exposure, the basis for the estimates of the effect of the MRTP designation are explicit.

6.5.2. Effect of Proposed MRTP on Population Health

The DPM was used to calculate all-cause mortality for a hypothetical population under different tobacco exposure scenarios, and these are described, in detail, in Appendix 6G. The scenarios were constructed to address the potential transitions and population subgroups that might lead to either negative or positive effects on the health of the population as a whole, estimated on the basis of changes in the number of survivors in the base case compared with counterfactual exposure scenarios.[68] In the base case, the only form of tobacco available is cigarettes. In the counterfactual scenario, the population may either smoke cigarettes or use Swedish snus, which is assumed to provide a lower all-cause mortality risk than cigarettes.

6.5.2.1. Model specification

The hypothetical cohort consisted of 1,000,000 male never tobacco users who were initially 12 years old. Follow-up was assessed from age 13 to age 72 in 5-year age intervals, with age- specific mortality rates for never, current and former smokers calculated from the Kaiser- Permanente Cohort Study data (Friedman et al. 1997) and the 2000 US census with coefficients modeled as fixed values. Follow-up could have continued beyond age 72, but the dwindling number of survivors at older ages in any exposure scenario reduces the value of further comparisons. For the base case, age category-specific exposure transition probabilities were based on 2008 cigarette

[68] MRTP Guidance.

smoking initiation rates[69] and smoking cessation[70] rates for 2005-2008 observed in the US (**Table 6-61**). Using recent smoking initiation and cessation rates to define the base case permits consideration of possible effects occurring in the future, after the introduction of a new product to the population, to be addressed. Smoking initiation and cessation rates were modeled as fixed values.

The excess relative risk (ERR) for current snus users versus current smokers was set to a conservative value of 0.11; this value is based on a published consensus estimate of the risk of current snus use compared to current smoking (Levy et al. 2004). There was no comparable estimate in the literature for former snus users versus former smokers, or for current or former dual users (i.e., concurrent use of both cigarettes and snus). We assumed the same ERR (0.11) for former snus users versus former smokers and that users of both products (dual users) had the same excess risk as smokers.

The model was set to run for 10,000 iterations after a burn-in of 2000 iterations. A Markov chain was considered to have converged if the Monte Carlo error was less than 5% of the sample standard deviation. Differences between the numbers of survivors in the base case compared with the counterfactual exposure scenario were estimated after each of the model iterations and the estimates were summarized over all iterations using means and 95% posterior intervals.

The results generated by the DPM were used to estimate tipping points. A tipping point is defined as the proportion of the population that experiences a beneficial change in tobacco exposure, i.e. one that increases the number of survivors relative to the base case that is necessary to offset the survival deficit due to a given harmful change in tobacco exposure. Because large shifts in tobacco use behaviors are unlikely, at least within short time periods, the magnitude of the tipping points allows for an assessment of how responsive the initial harm may be to the effect of possible alternative, beneficial exposure patterns. In interpreting the tipping points, however, it is important to bear in mind the relative sizes of the different population segments involved in the analysis – small changes in the proportion of a large group, such as non-smokers, affects a larger number of people, in absolute terms, than the same proportion of a small group, (e.g., those who successfully quit smoking cigarettes).

The tipping points were identified two different ways. A tipping point based on the point estimate was identified when the mean difference between survivors in the base case and counterfactual exposure scenarios was approximately zero. A tipping point based on statistical significance was identified when results changed from a statistically significant mean difference to a non-significant mean difference between survivors in the base case and counterfactual exposure scenario based on the 95% posterior intervals (PIs) around the mean difference (i.e., the 2.5th and 97.5th percentile of the distribution). The first method for identifying a tipping point, i.e., point estimate near zero, is more stringent than the second method because it requires a larger shift in the exposure patterns to be realized.

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69 http://www.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2010R/HTM/Sect4peTabs1to16.htm#Tab4.3B

70 http://www.samhsa.gov/data/2k10/172/172smokingcessation.htm

6.5.2.1.1. Analyses to address the MRTP Application Guidance

The MRTP Guidance highlights seven population segments and exposure patterns. Four of the seven can be analyzed using the DPM, namely, (i) tobacco users who switch from other commercially marketed tobacco products to the proposed product; (ii) tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk; (iii) tobacco users who opt to use the proposed product rather than cease tobacco use altogether; and (iv) non-users who initiate tobacco use with the proposed product, such as youth, never users, former users. In all analyses, the base case tobacco product is cigarettes and the proposed product is Swedish snus.

The three exposure patterns that cannot be analyzed with the DPM focus on use of medications approved to assist with cessation of tobacco use; health risks experienced by non-users; and dual use of the MRTP and cigarettes. Modeling the effects of an MRTP compared with pharmaceutical quit aids requires data on mortality risks associated with use of the medications; however these data do not exist. Non-combusted tobacco products, such as Swedish snus, have no direct health effects on non-users, and any reductions in the use of combusted tobacco products will also reduce environmental tobacco smoke, likely resulting in some benefit to the non-users in the population. In the DPM, dual use of the MRTP and cigarettes is considered to cause the same mortality risk as smoking, which may overestimate the risk to individuals who reduce their cigarette consumption in connection with MRTP use.

6.5.2.1.2. Counterfactuals Based on Tobacco Use Patterns Estimated for Sweden

An additional series of analyses provide estimates of the effect on US mortality if an MRTP were available and were used in patterns similar to the patterns of cigarette and snus use observed in Sweden in the 1990s. For the base case, exposure transition probabilities were based on US 2009 cigarette smoking initiation rates and smoking cessation rates for 2005 through 2008 (**Table 6-61**). The counterfactual exposure scenarios were selected to investigate potential effects on mortality in the US population if MRTP use were 10%, 25%, 50% and 100% as popular in the US as it was in Sweden in the 1990s (**Table 6-62**). Estimates were generated using an estimated ERR for MRTP compared to cigarette smoking of 0.11, as above, and also using an ERR half as large, i.e., 0.055. As described above, the model ran 10,000 iterations after a burn-in of 2,000 iterations and a Markov chain was considered to have converged if the Monte Carlo error was less than 5% of the sample standard deviation. Differences between the numbers of survivors in the base case compared with the counterfactual exposure scenario were estimated after each of the model iterations and the estimates were summarized over all iterations using means and 95% posterior intervals.

6.5.2.2. Results addressing the MRTP Application Guidance

6.5.2.2.1. Smokers who opt to use the proposed MRTP rather than cease tobacco use altogether, then continue using the proposed product or switch back to smoking

Mean survival differences and 95% posterior intervals between counterfactual and base case for counterfactual scenarios where 1%, 5% or 10% of base case smoking quitters switch to the MRTP (harmful transition) are shown in **Table 6-63**. We assumed no quitting among MRTP users and modeled three possible transitions following switching to MRTP use from smoking: No MRTP users revert to smoking, 50% of MRTP users revert to smoking in each age category; and all MRTP users revert to smoking in the next age category after switching.

As expected, as the proportion of base case smoking quitters switching to the MRTP increased (1% to 5% to 10%), we observed increasing and statistically significant survival deficits in the counterfactual scenarios. For example, if 1% of base case smoking quitters switch to the MRTP and none quit the MRTP or switch back to smoking cigarettes, there was a survival deficit of 38 (i.e., 38 additional deaths) in the counterfactual scenario compared with the base case. This deficit increased to 188 and 376 when 5% and 10% of base case smoking quitters switch to the MRTP and remain as MRTP users. Further, as the proportion of MRTP users switching back to smoking increased, so did the survival deficit. For example, when 1% of base case smoking quitters switch to the MRTP and 50% revert to smoking, the survival deficit in the counterfactual scenario increased from 38 to 172. The survival deficit in the counterfactual scenario was 208 when all of the MRTP users switched to smoking.

6.5.2.2.2. Smokers who opt to use the proposed product rather than cease tobacco use altogether, and smokers who opt to use the proposed MRTP rather than continuing to smoke

The negative consequences of switching to an MRTP instead of quitting smoking may be counterbalanced if some who would have continued smoking in the base case instead switch to the proposed MRTP. **Figures 6-9**, **6-10**, and **6-11** show the proportion of base case continuing smokers who must switch to the MRTP to overcome the survival deficit caused by 1%, 5% or 10% of base case smoking quitters switching to the MRTP in the counterfactual. **Figure 6-9** reflects the scenario where no MRTP users switch to smoking while **Figures 6-10 and 6-11** represent scenarios with 50% and 100% of MRTP users switching to MRTP use, respectively. For example, **Figure 6-9.3** shows that when 10% of base case smoking quitters switch to the MRTP and none quit the MRTP or switch to smoking, about 0.25% of base case continuing smokers must switch to the MRTP to overcome the statistically significant survival deficit. When more than 0.275% of base case continuing smokers switch to the MRTP, there are statistically significantly more survivors in the counterfactual than the base case. These tipping points, along with tipping points for other scenarios, are listed in **Table 6-64**. In the scenarios tested, the maximum proportion of base case continuing smokers who must switch to the MRTP to overcome a statistically significant survival deficit, 6.5%, is necessary when 10% of base case smoking quitters switch to the MRTP and 100% of MRTP users switch to smoking in the next age category in the counterfactual scenario.

6.5.2.2.3. Never tobacco users who opt to initiate the use of the proposed MRTP instead and remain as users of the MRTP or switch to smoking

In **Table 6-65**, mean survival differences and 95% posterior intervals between the counterfactual and base case are shown for counterfactual scenarios where 1%, 5% or 10 of base case never tobacco users initiate the use of the MRTP (a harmful exposure pattern). Following initiation of MRTP use, depending on the scenario, 0% MRTP users switch to smoking, 50% of MRTP users switch to smoking or 100% MRTP users switch to smoking. In some scenarios we varied the MRTP initiation rate to examine the potential effect on population health if the proposed MRTP were more attractive than cigarettes to youth (constant in the first three age categories versus twice as high in age category 1 as in age categories 2 and 3; we assumed no MRTP initiation in older age categories). Finally, we modeled scenarios where MRTP users quit at the same rate as US smokers quit smoking in 2005 through 2008 (**Table 6-61**) and subsequent resumption of MRTP use was either 25% or 50%.

As the proportion of base case never tobacco users initiating use of the MRTP increases from 1% to10%, i.e., as the number of tobacco users in the population increased, we observed increasing and statistically significant survival deficits in the counterfactual scenarios. For example, when MRTP initiation rates were constant in the first three age categories, no MRTP users switched to smoking or quit using MRTP, the survival deficit in the counterfactual compared with the base case was 641 if 1% of base case never tobacco users initiated the MRTP, 3,082 when 5% and 5,873 when 10% of base case never tobacco users initiated use of the MRTP. In addition, as the proportion of MRTP users switching to smoking increased, so did the survival deficit. For example, when 1% of base case never tobacco users initiated the MRTP, the survival deficit in the counterfactual increased from 641 (no MRTP users switch to smoking) to 1,927 when 50% of MRTP users switched to smoking. If all MRTP users switch to smoking, the survival deficit compared with the base case is 2,041. Survival deficits in the counterfactual were greater when the MRTP initiation rate was doubled in the first age category and when the proportion of persons resuming MRTP use after quitting increased from 25% to 50% (**Table 6-65**).

6.5.2.2.4. Never tobacco users who opt to initiate the use of the proposed product instead and remain as users of the MRTP or switch to smoking, and smoking initiators who opt to initiate the use of the proposed product instead of smoking; higher rates of MRTP adoption in the youngest age group

Tipping points for these harmful exposure patterns are shown in **Figures 6-11** to **6-14**, which show the proportion of base case smoking initiators who must instead initiate the use of the MRTP to overcome the survival deficit caused by 1%, 5% or 10% of base case never tobacco users initiating use of the MRTP in the counterfactual. **Figures 6-11** and **6-12** reflect the scenarios where no MRTP users switch to smoking and the MRTP initiation rate is constant in the first 3 age categories and doubled in age category 1, respectively. The latter is meant to model a scenario in which the MRTP is more attractive than cigarettes to youth. In Figures **6-13** and **6-14** no MRTP users switch to smoking and the MRTP initiation rate is constant in the first 3 age categories, but MRTP users quit at the same rates as smokers quit smoking (based on US smoking cessation rates in 2005-2008). Subsequently, 25% and 50%, respectively, resume MRTP use. The tipping points shown in

these figures are summarized in **Table 6-66**.

In the scenarios where none of the MRTP users switched to smoking, the maximum proportion of base case smoking initiators who must instead initiate the use of the MRTP to overcome a statistically significant survival deficit, 50%, is necessary when 10% of base case never tobacco users initiate the use of the MRTP, the MRTP initiation rate is doubled in the first age category and there is no quitting among MRTP users. In scenarios where 50% or 100% of MRTP initiators subsequently switch to smoking, no tipping points were found because the survival deficits caused in the base case never tobacco users initiating use of the MRTP, and the MRTP acting as a gateway, were greater than the total number of base case smoking initiators.

6.5.2.3. Results using Counterfactuals Based on Tobacco Use Patterns Estimated for Sweden

6.5.2.3.1. "Swedish counterfactual" vs. US base case

There was a statistically significant survival benefit if the US population used cigarettes and an MRTP in patterns similar to those observed in Sweden in the 1990s. If the ERR for the MRTP compared with cigarettes is assumed to be 0.11, then there are approximately 16,500 more survivors than if cigarettes were the only form of tobacco available, as in the base case. If the ERR is assumed to be half as large, 0.055, there are approximately 17,500 more survivors in the "Swedish counterfactual" compared to the US base case (**Table 6-66**).

6.5.2.3.2. Alternative "Swedish counterfactual" with reduced MRTP initiation vs. US base case

Reducing the probability of MRTP initiation by non-tobacco users and by those who would have become cigarette smokers in the base case to 10%, 25%, or 50% of the Swedish value, and leaving the probabilities of exposure transitions following MRTP initiation unchanged compared to the "Swedish counterfactual," affects the results very little. For ERR=0.11, the survival benefit of the counterfactual scenario versus the base case at the end of follow-up is approximately 16,600; 16,700 and 16,800, respectively (**Table 6-67**). For ERR=0.055, there are approximately 17,400 more survivors compared with the base case (**Table 6-67**). While these scenarios decrease the proportions of base case non-tobacco users initiating MRTP, the same proportional reduction is applied to base case smoking initiators. Thus, compared to the "Swedish counterfactual," there are more people who remain never tobacco users rather than initiating MRTP, resulting in fewer deaths compared to the "Swedish counterfactual." At the same time, there are also more current smokers and fewer persons who initiate tobacco use with MRTP instead of cigarettes, resulting in more deaths compared to the "Swedish counterfactual." The small increases and decreases in numbers of deaths due to these shifts in exposure are nearly balanced.

6.5.2.3.3. Alternative "Swedish counterfactual" with reduced MRTP initiation and gateway effect doubled, vs. US base case

Using the same probabilities of MRTP initiation (10%, 25% or 50% of the Swedish value) but doubling the gateway effect, such that twice the proportion of those who initiate tobacco use with the MRTP switch to cigarettes, again provides similar survival differences versus the base case

compared with those resulting from the "Swedish counterfactual" if ERR=0.11 (**Table 6-67**). Setting the ERR for MRTP vs. cigarette smoking to 0.055 increases the number of survivors compared with the base case to approximately 17,000 (**Table 6-67**). The small effect of doubling the gateway effect in the "Swedish counterfactual" can be explained by the fact that the proportion of the population initiating tobacco use with the MRTP and transitioning to cigarette smoking in the "Swedish counterfactual" is quite small (**Table 6-62**), so doubling that rate has little impact on survival.

6.5.2.3.4. Alternative "Swedish counterfactual" with reduced switching to MRTP

If the proportion of those who would have quit smoking in the base case who instead switch to the MRTP and the proportion of those who would have continued smoking in the base case who instead switch to the MRTP is reduced compared to the "Swedish counterfactual," the number of survivors at the end of follow-up is still larger than in the base case, but substantially smaller than in the "Swedish counterfactual." The difference ranges from about 7,000 for 10% of the proportion switching to MRTP in the "Swedish counterfactual" to about 12,000 for 50% of the proportion switching to MRTP in the "Swedish counterfactual" if ERR=0.11 (**Table 6-68**). As may be expected, when these scenarios are modeled with ERR=0.055, the difference in the number of survivors compared to the base case is increased somewhat. In the last age category of follow-up, there are just under 8,000 additional survivors compared with the base case when the proportion switching to MRTP is 10% of that in the "Swedish counterfactual," just under 10,000 when the proportion switching to MRTP is 25% of that in the "Swedish counterfactual," and about 13,000 when the proportion switching to MRTP is 50% of that in the "Swedish counterfactual" (**Table 6-68**).

6.5.2.3.5. Alternative "Swedish counterfactual" with reduced switching to MRTP and returning to smoking doubled, vs. US base case

Using the same probabilities of switching to MRTP (10%, 25% or 50% of the Swedish value) but doubling the proportion of MRTP users returning to smoking among those who initiate tobacco use with smoking but subsequently switch to MRTP provides smaller survival differences versus the base case compared with those resulting from the "Swedish counterfactual" if ERR=0.11(**Table 6-68**). Setting the ERR for MRTP vs. cigarette smoking to 0.055 slightly increases the number of survivors compared with the base (**Table 6-68**). The results are almost identical to the results from the scenario described in section 6.5.2.3.4. The proportion of MRTP users returning to smoking among those who initiate tobacco use with smoking who subsequently switch to MRTP is quite small in the "Swedish counterfactual" (**Table 6-62**), leading to the small effect of doubling this proportion in the analyses reported here.

While these scenarios decrease the proportion of the population switching to MRTP from cigarettes, the same relative decrease is applied to those who would have remained smokers in the base case and to those who would have quit smoking in the base case. Compared to the "Swedish counterfactual," these changes result in more smokers and fewer MRTP users, leading to more deaths compared to the base case than was estimated for the "Swedish counterfactual." While there are also more people quitting smoking rather than switching to MRTP, the absolute increase is too small to make a difference in the overall number of survivors, because the number of smokers who

would have quit smoking is much less than the number of smokers who would have continued to smoke. Overall, these exposure scenarios result in more deaths compared with the "Swedish counterfactual" and a smaller benefit compared to the US base case.

6.5.3. Conclusion

The DPM results confirm that the introduction of the Swedish snus, the proposed MRTP, can result in a net population-level benefit, particularly if it is adopted by a sufficient number of smokers. If introduction of an MRTP results in more tobacco users compared to the base case, however, a survival deficit may result. The size of the effect, positive or negative, depends on the particular exposure patterns evaluated. However, the premarket consumer perception study data included in this Application indicate that it is unlikely that a significant proportion of current non-tobacco users would start using snus as a consequence of the proposed label changes for the Snus Products.

Tipping point analyses indicate that if some who would have quit smoking in the base case switch to Swedish snus instead, a survival deficit results. This effect is counteracted, however, if a fairly small proportion, 1% or less, of those in the base case who would have continued to smoke switch to Swedish snus and do not revert to smoking. Tipping point analyses also indicate a survival deficit results if base case never tobacco users initiate Swedish snus instead, but this can be counterbalanced by base case smoking initiators initiating Swedish snus instead of cigarettes. If only 1% of base case never tobacco users initiate Swedish snus, less than 5% of base case smoking initiators must initiate Swedish snus to counteract the survival deficit. However, if 5% or 10% of base case never tobacco users initiate Swedish snus instead, at least 20% of base case smoking initiators instead must initiate Swedish snus to counterbalance the survival deficit. These apparently large percentage changes must be interpreted in light of the sizes of the exposure groups involved, however. Because the never tobacco users represent a large subgroup of the whole population, a small percent change affects a large number of individuals. Likewise, there are relatively few individuals who successfully quit smoking in the base case, so a large percentage of that population subgroup must shift to a different exposure for a population-level effect on survival to be observed. In modeling gateway effects, such that base case never tobacco users instead initiated tobacco use with the MRTP and then switched to smoking cigarettes, there was no statistically significant survival benefit in counterfactual scenarios consisting of base case smoking initiators choosing the MRTP instead of cigarettes, but other exposure patterns that include additional exposure groups can counterbalance this population level harm.

This conclusion is corroborated by analyses of counterfactuals based on the Swedish tobacco use patterns estimated for the 1990s compared with a base case defined by US smoking initiation rates from 2008 and cessation rates from 2005 through 2008. In each of the counterfactual exposure scenarios investigated, in which snus was used with similar frequency and in which snus was 10%, 25% and 50% as popular in the US as in Sweden, there was a substantial and statistically significant survival benefit compared with the US base case. The magnitude of the difference in the number of survivors vs. the base case was not greatly affected by the value selected for the ERR comparing the MRTP to cigarette smoking (0.11 or 0.055), by increasing the gateway effect or by reducing the MRTP initiation rate among those who would have otherwise remained as never tobacco users and those who would have initiated tobacco use with cigarettes. When the rate of switching to MRTP by those who would have continued to smoke and those who would have quit smoking in the base case was reduced compared to the rates estimated for the "Swedish counterfactual," there was still a statistically significant increase in the number of survivors in the

counterfactual vs. the base case, but the effect was smaller. The greater responsiveness of the results to changes that affected continuing smokers or those who would have quit smoking is a reflection of the relative sizes of the various population subgroups included in the analyses.

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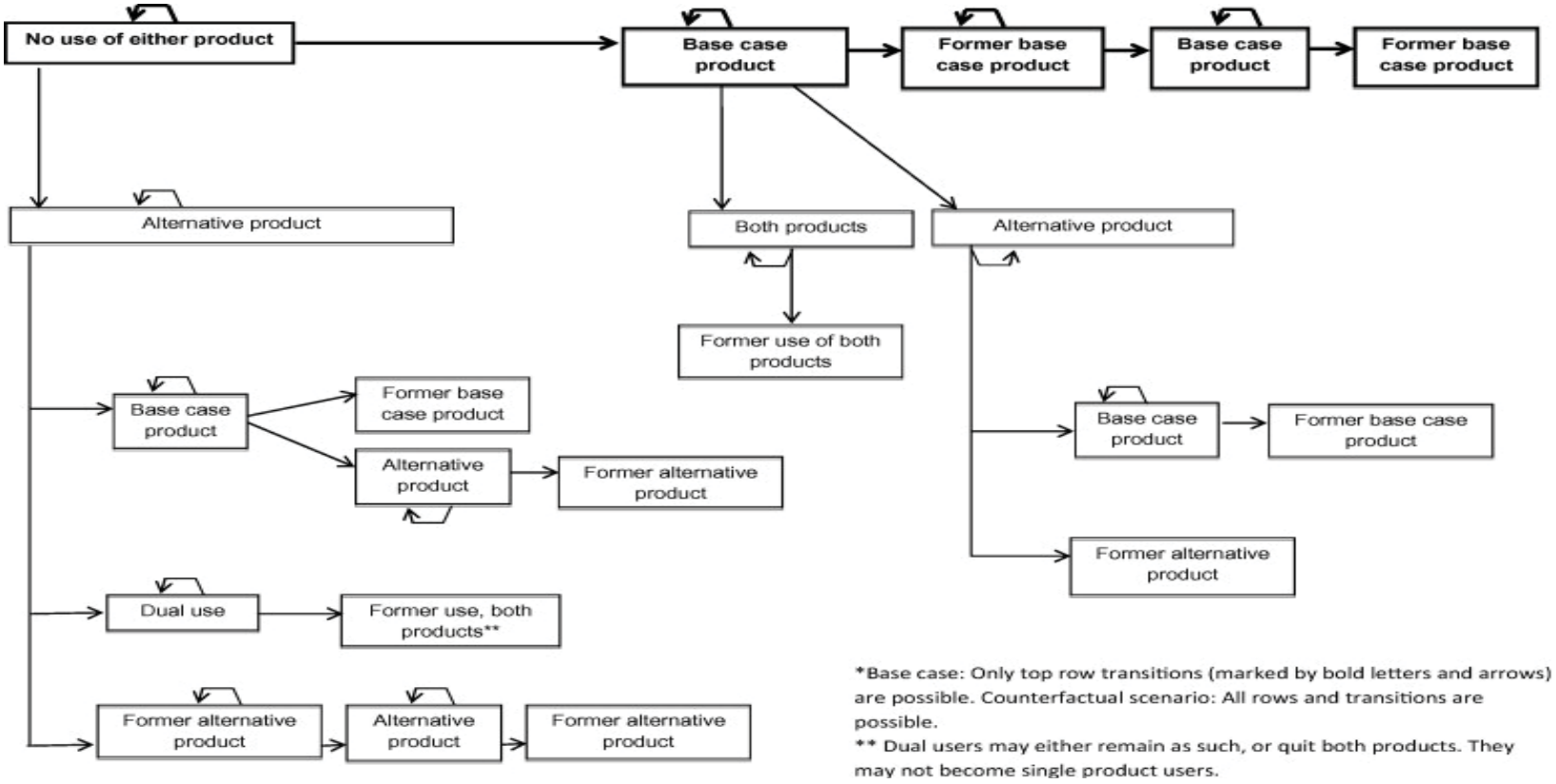
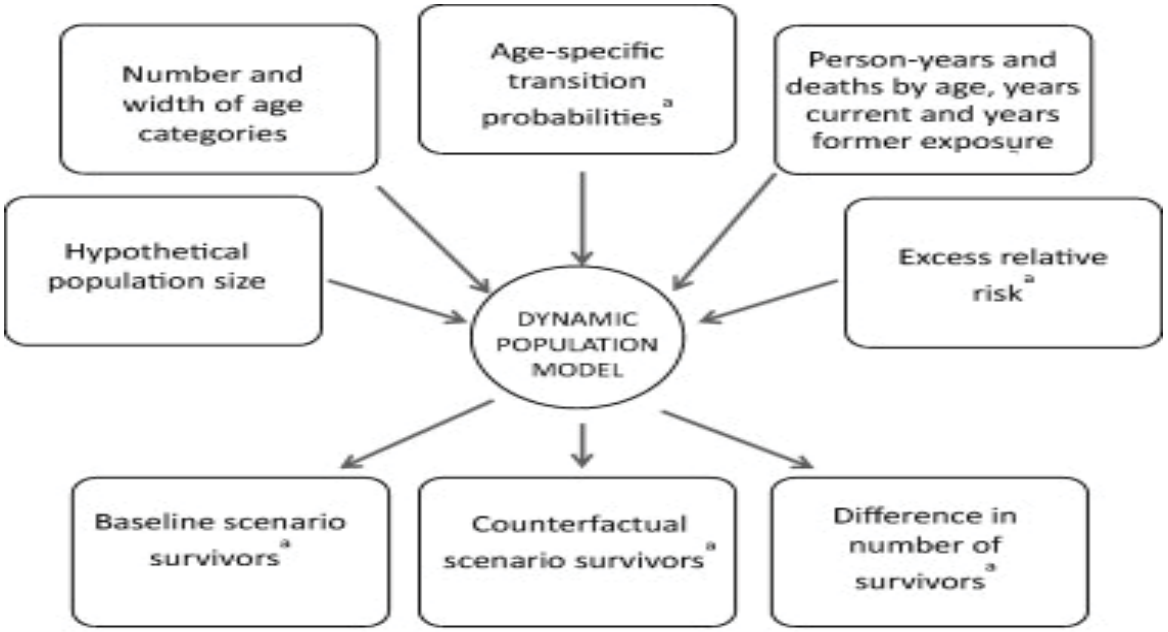


Figure 6-7: Schematic representation of the distribution of persons into exposure categories by the Dynamic Population Model; transitions for base case (top row, only) and counterfactual exposure scenarios (all rows)

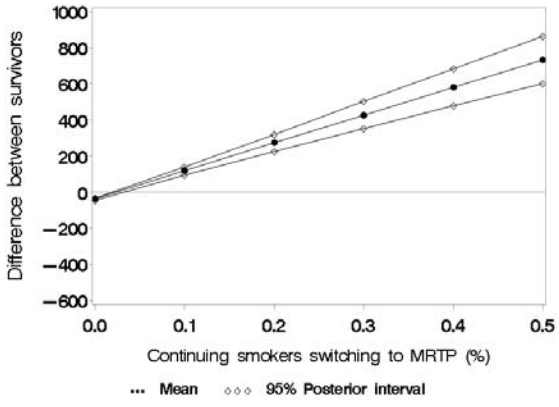
From: Annette M. Bachand , Sandra I. Sulsky. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology Volume 67, Issue 2 2013 246 – 251.



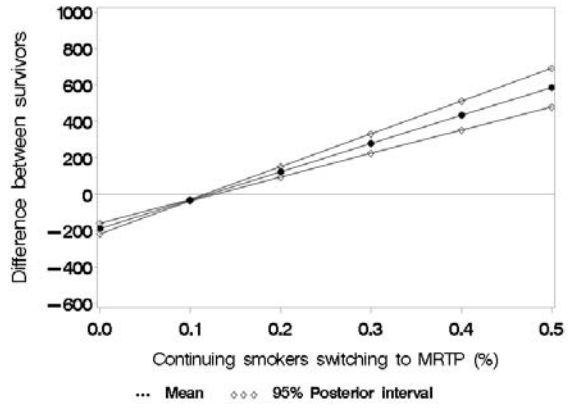
[a]Including estimated variability

Figure 6-8: Model input and output

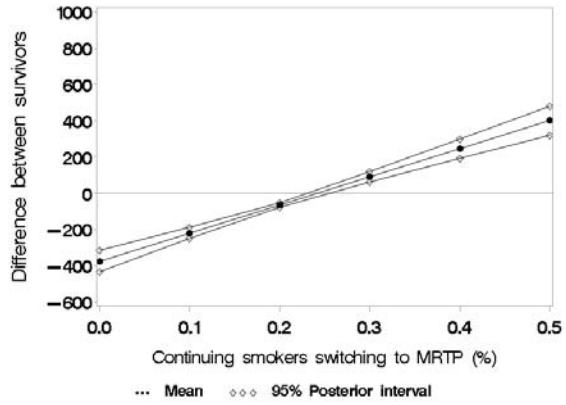
From: Annette M. Bachand , Sandra I. Sulsky. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology Volume 67, Issue 2 2013 246 – 251



(6-9.1) 1% of base case smoking quitters switch to the MRTP

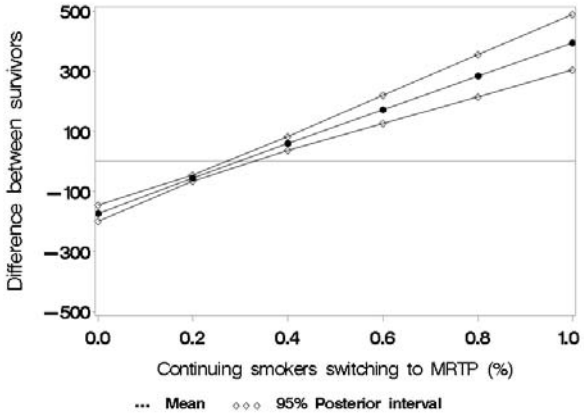


(6-9.2) 5% of base case smoking quitters switch to the MRTP

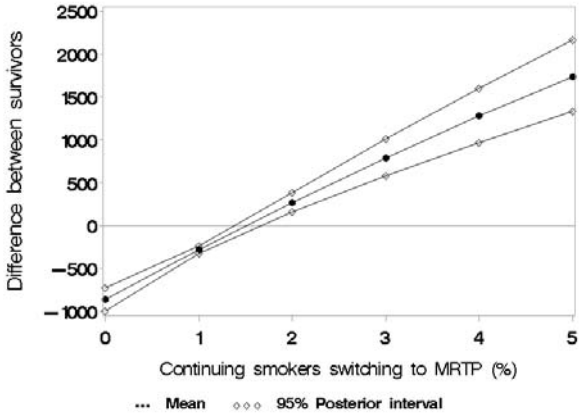


(6-9.3) 10% of base case quitters switch to the MRTP

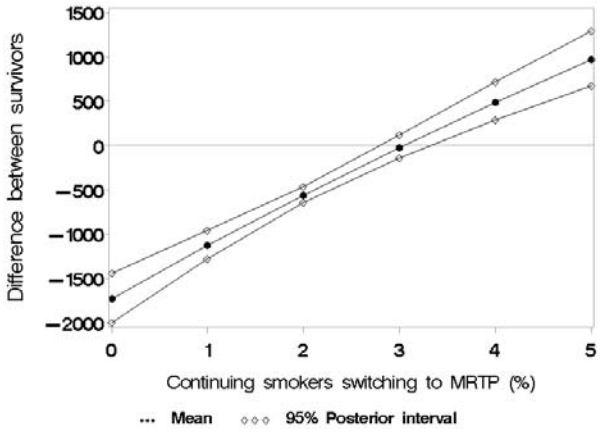
Figure 6-9: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP and continue MRTP use (results shown for age category 68-72)



(6-10.1) 1% of base case smoking quitters switch to the MRTP

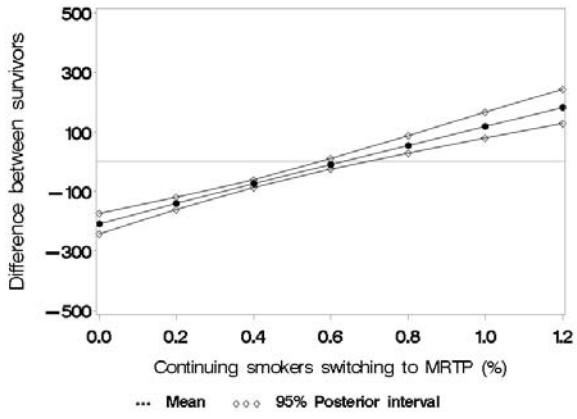


(6-10.2) 5% of base case smoking quitters switch to the MRTP

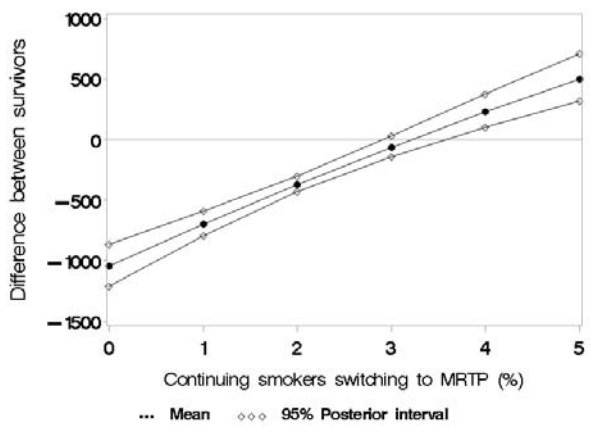


(6-10.3) 10% of base case quitters switch to the MRTP

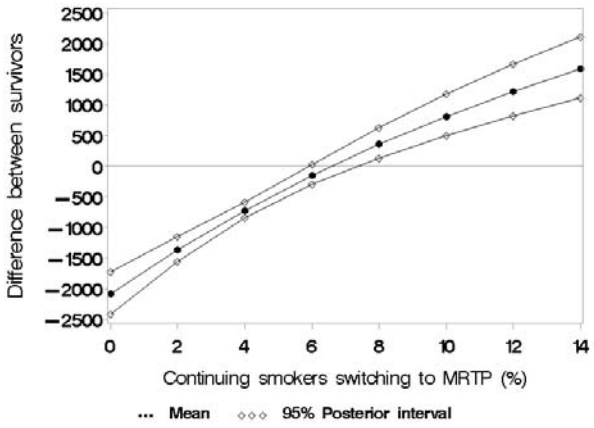
Figure 6-10: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; in subsequent age categories 50% of switchers revert to smoking and 50% remain MRTP users (results shown for age category 68-72)



(6-11.1) 1% of base case smoking quitters switch to the MRTP

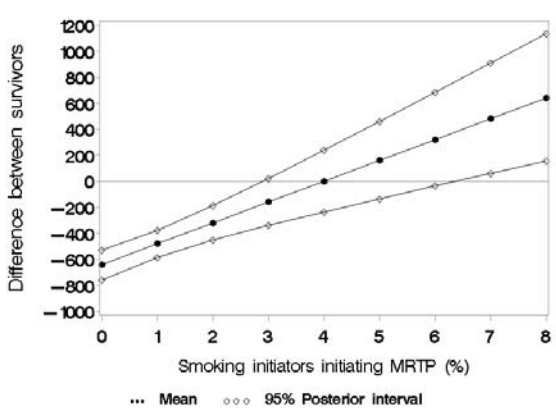


(6-11.2) 5% of base case smoking quitters switch to the MRTP

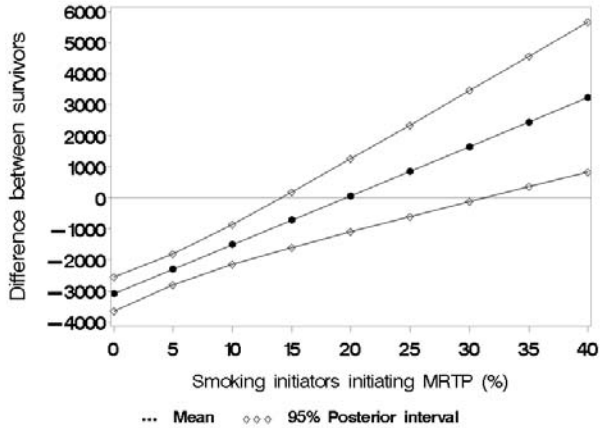


(6-11.3) 10% of base case quitters switch to the MRTP

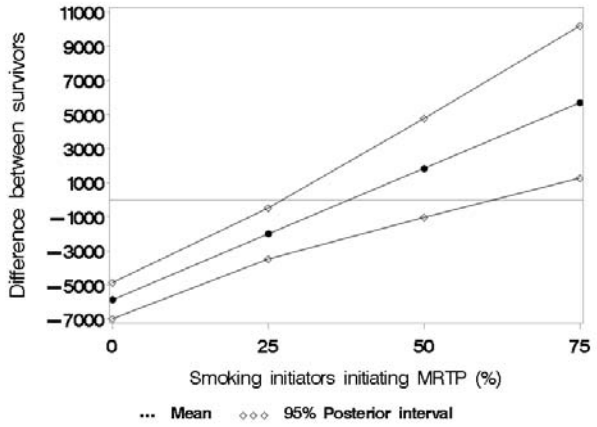
Figure 6-11: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category (results shown for age category 68-72)



(6-12.1) 1% of base case never tobacco users initiate the MRTP

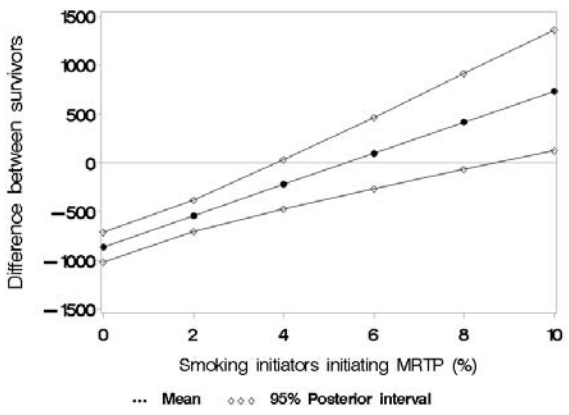


(6-12.2) 5% of base case never tobacco users initiate the MRTP

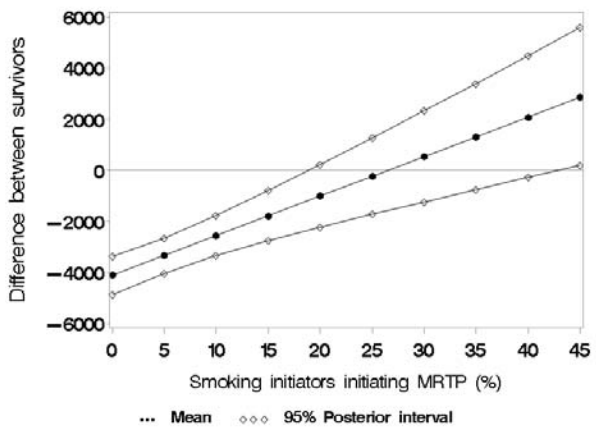


(6-12.3) 10% of base case never tobacco users initiate the MRTP

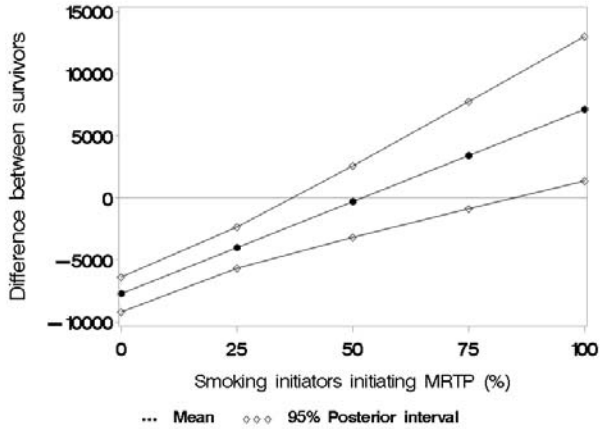
Figure 6-12: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)



(6-13.1) 1% of base case never tobacco users initiate the MRTP

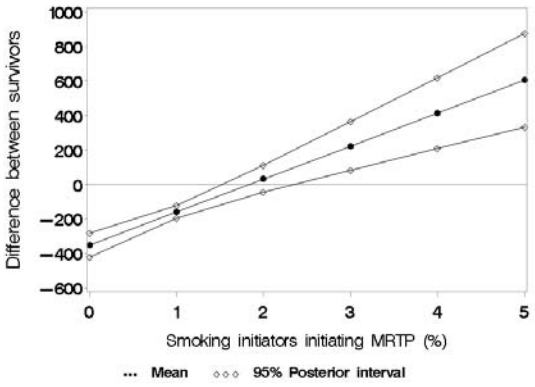


(6-13.2) 5% of base case never tobacco users initiate the MRTP

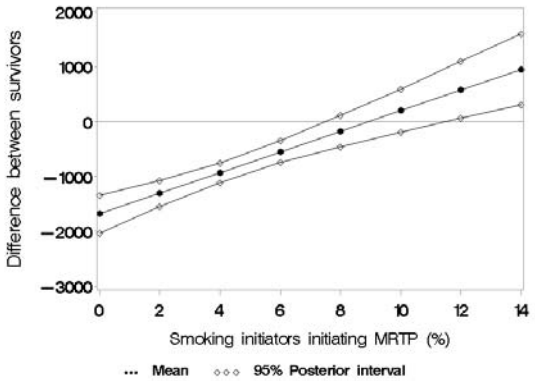


(6-13.3) 10% of base case never tobacco users initiate the MRTP

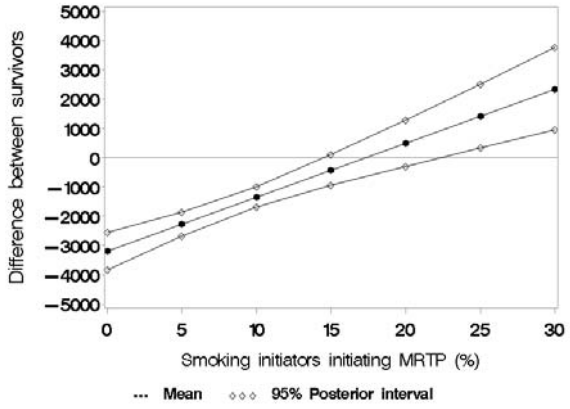
Figure 6-13: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, and 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category; no initiation thereafter (results shown for age category 68-72)



(6-14.1) 1% of base case never tobacco users initiate the MRTP

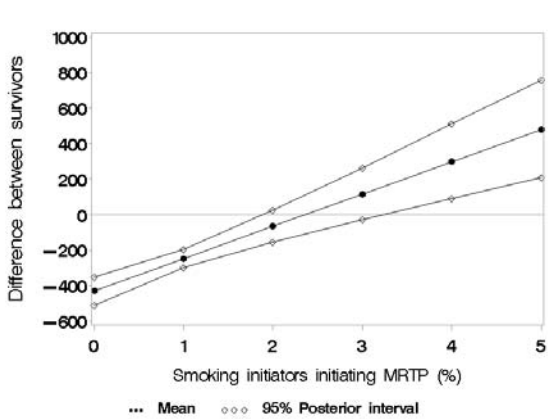


(6-14.2) 5% of base case never tobacco users initiate the MRTP

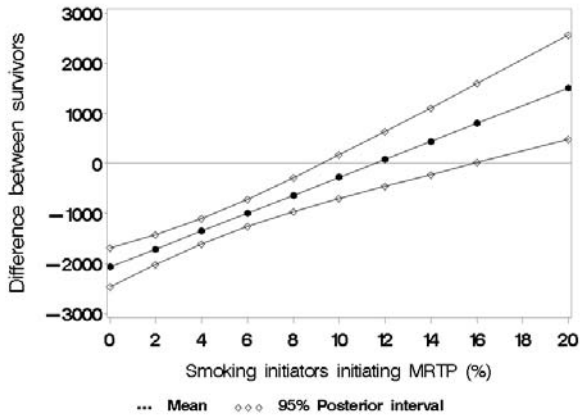


(6-14.3) 10% of base case never tobacco users initiate the MRTP

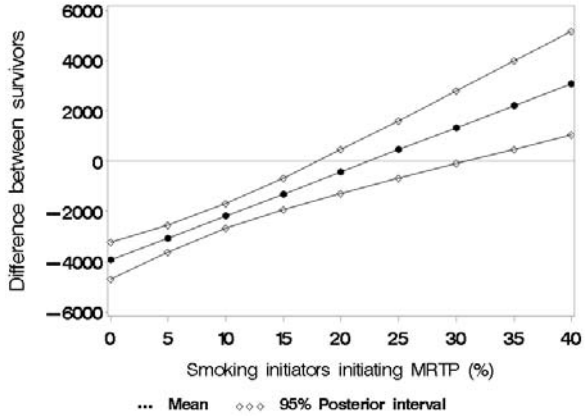
Figure 6-14: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, and 10% of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)



(6-15.1) 1% of base case never tobacco users initiate the MRTP



(6-15.2) 5% of base case never tobacco users initiate the MRTP



(6-15.3) 10% of base case never tobacco users initiate the MRTP

Figure 6-15: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up and 95% posterior intervals; 1%, 5%, and 10% of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

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estimated for Sweden, modeled with ERR=0.11 and ERR=0.055 (results shown for age category 68-72)

Table 6-68: Mean difference in number of survivors with 95% posterior intervals (95% PI) for various counterfactual exposure scenarios involving switching to MRTP based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055 (results shown for age category 68-72)

Table 6-57: Estimated smoking initiation and cessation probabilities (based on US rate data for men and women, 1980)

Age category	Smoking initiation rate[1]	Smoking cessation rate[2]
13-17	11.25	2.5
18-22	10.00	4.5
23-27	1.25	4.5
28-32	0.25	4.5
33-37	0.00	5.0
38-42	0.00	5.5
43-47	0.00	5.5
48-52	0.00	7.5
53-57	0.00	8.5
58-62	0.00	8.5
63-67	0.00	8.5
68-72	0.00	8.5

[1] Based on: Office of Applied Studies, National Household Survey on Drug Abuse (NHSDA), 1999, Appendix D, table 4.2 (http://www.samhsa.gov/data/NHSDA/tobacco/appendixd.htm)

[2] Based on: Messer et al., 2007

Table 6-58: Validation of base case exposure scenarios based on US tobacco use patterns in 1980. Age-specific number of survivors estimated from 2006 US life table versus model-based estimates (starting with 1,000,000 12-year old male never tobacco users)[a]

Age category	Survivors based on US life table	Survivors based on base case (US)
38-42	957,654	957,100
43-47	940,866	939,200
48-52	915,745	914,300
53-57	880,470	879,800
58-62	832,268	832,000
63-67	764,922	765,600
68-72	674,217	674,300

[a] Age group 38-42 is the first age group where all possible transitions have occurred

Table 6-59: Transition probabilities used to approximate Swedish tobacco use patterns, ca. 1990.

Probability of:	
Initiating MRTP instead of remaining never tobacco user	**0.05**
Initiating MRTP instead of initiating smoking	**0.05**
Gateway effect (switching to smoking/dual use from MRTP) among persons who initiated tobacco use with MRTP	**0.01**
Quitting MRTP among persons who initiated tobacco use with MRTP	**0.19**
Continued MRTP use among persons who initiated tobacco use with MRTP	**0.77**
Switching to MRTP instead of quitting	**0.02**
Switching to MRTP instead of continuing to smoke	**0.10**
Switching to smoking from MRTP among persons who initiated tobacco use with MRTP	**0.015**
Quitting MRTP among persons who initiated tobacco use with smoking	**0.217**
Continued MRTP use among persons who initiated tobacco use with smoking	**0.768**

Table 6-60: Validation of counterfactual exposure scenarios based on approximate Swedish tobacco use patterns, ca 1990. Age-specific number of survivors estimated from the 2006 Swedish life table versus model-based estimates (starting with 1,000,000 12 year-old male never tobacco users)[a]

Age category	Survivors based on Swedish life table	Survivors based on exposure scenario (Sweden)
38-42	980,999	979,274
43-47	972,889	970,010
48-52	959,782	957,276
53-57	936,838	935,677
58-62	902,590	902,104
63-67	846,884	847,362
68-72	764,275	762,582

[a] Age group 38-42 is first age group where all possible transitions have occurred

Table 6-61: Estimated smoking initiation and cessation probabilities (based on US rate data for men and women, 2005-2008)

Age interval	Smoking initiation[1]	Smoking cessation[2,4]
13-17	13.75	N/A[3]
18-22	10.00	9.00
23-27	1.00	9.50
28-32	0.00	14.00
33-37	0.00	14.00
38-42	0.00	14.00
43-47	0.00	14.00
48-52	0.00	14.00
53-57	0.00	14.00
58+	0.00	14.00

[1]http://www.samhsa.gov/data/NSDUH/2K10ResultsTables/NSDUHTables2010R/HTM/Sect4peTabs1to16.htm#Tab4.3B

[2]http://www.samhsa.gov/data/2k10/172/172smokingcessation.htm

[3]No smoking cessation allowed in 13-17 years age interval, as smoking duration among quitters in this age interval would only be 2.5 years (on average)

[4]The oldest age category for which smoking cessation data were provided was defined as "35 and older". Thus, the last seven age categories were assigned the same smoking cessation rate.

Table 6-62a: Transition patterns to develop various counterfactual exposure scenarios involving MRTP initiation based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055

	MRTP initiation		Transitions following MRTP initiation		
Scenario	**Harmful transition:** Probability of initiating MRTP instead of remaining NT user	**Beneficial transition:** Probability of initiating MRTP instead of initiating smoking	Probability of gateway effect (switching to smoking/dual use)	Probability of quitting MRTP	Probability of continued MRTP use
Sweden	0.05	0.05	0.01	0.19	0.77
Variations					
Probabilities of transitions following MRTP initiation unchanged compared to Sweden and:					
Probability of MRTP initiation reduced to					
10% of Swedish value	0.005	0.005	0.01	0.19	0.77
25% of Swedish value	0.0125	0.0125	0.01	0.19	0.77
50% of Swedish value	0.025	0.025	0.01	0.19	0.77
Gateway effect doubled and:					
Probability of MRTP initiation reduced to					
10% of Swedish value	0.005	0.005	0.02	0.19	0.76
25% of Swedish value	0.0125	0.0125	0.02	0.19	0.76
50% of Swedish value	0.025	0.025	0.02	0.19	0.76

Table 6-62b: Transition patterns to develop various counterfactual exposure scenarios involving switching to MRTP based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055

	Switching to MRTP		Transitions following MRTP initiation		
Scenario	**Harmful transition:** Probability of switching to MRTP instead of quitting all tobacco use	**Beneficial transition:** Probability of switching to MRTP instead of continuing smoking	Probability of gateway effect (switching to smoking)	Probability of quitting MRTP	Probability of continued MRTP use
Sweden	0.02	0.10	0.015	0.217	0.768
Variations					
Probabilities of transitions following switching to MRTP use unchanged compared to Sweden and:					
Probability of switching to MRTP reduced to					
10% of Swedish value	0.002	0.010	0.015	0.217	0.768
25% of Swedish value	0.005	0.025	0.015	0.217	0.768
50% of Swedish value	0.010	0.050	0.015	0.217	0.768
Returning to smoking doubled and:					
Probability of switching to MRTP reduced to					
10% of Swedish value	0.002	0.010	0.03	0.217	0.753
25% of Swedish value	0.005	0.025	0.03	0.217	0.753
50% of Swedish value	0.010	0.050	0.03	0.217	0.753

Table 6-63: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up (age category 68-72) and 95% posterior intervals; some base case smoking quitters switching to MRTP

% of base case smoking quitters switching to MRTP		1%			5%			10%	
% MRTP users switching to smoking[1,2]	Mean	95%	PI	Mean	95%	PI	Mean	95%	PI
0%	-38	-43	-32	-188	-217	-158	-376.30	-433	-317
50%	-172	-199	-144	-862	-996	-721	-1,724	-1,992	-1,442
100%	-208	-242	-173	-1,041	-1,210	-865	-2,081	-2,419	-1,730

[1] Remaining subjects continue MRTP use for at least one additional age category
[2] No quitting among MRTP users

Table 6-64: Tipping points for base case continuing smokers switching to MRTP versus base case smoking quitters switching to MRTP

Base case smoking quitters switching to MRTP		1%			5%			10%		
		Approximate proportion of base case continuing smokers switching to MRTP needed for								
% reverting to smoking	% continuing MRTP use	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit
0%	100%	<0.01%	0.025%	>0.05%	<0.1%	0.125%	>0.15	<0.2%	0.25%	>0.275%
50%	50%	<0.25%	0.3%	>0.4%	<1.25%	1.5%	>1.75	<2.75%	3.0%	>3.5%
100%	0%	<0.5%	0.6%	>0.8%	<2.5%	3.0%	>4.0	<5.75%	6.0%	>8%

Table 6-65: Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow- up (age category 68-72) and 95% posterior intervals; some base case base case never tobacco users initiate MRTP

% of base case never tobacco users initiating MRTP			1%			5%			10%		
MRTP initiation in age categories 1-3	% MRTP users switching to smoking[1]	% MRTP quitters[2] resuming MRTP	Mean	95%	PI	Mean	95%	PI	Mean	95%	PI
Constant	0%	No quitters	-641	-757	-528	-3,082	-3,646	-2,541	-5,873	-6,950	-4,838
Doubled in 1st age category	0%	No quitters	-862	-1022	-708	-4,109	-4,872	-3,375	-7,730	-9,163	-6,347
Constant	0%	25%	-350	-423	-280	-1,679	-2,026	-1,343	-3,183	-3,839	-2,549
Constant	0%	50%	-431	-513	-352	-2,071	-2,465	-1,692	-3,936	-4,681	-3,216
Constant	50%	No quitters	-1,927	-2,427	-1,429	-9,282	-11,700	-6,875	-17,700	-22,320	-13,100
Constant	100%	No quitters	-2,041	-2,626	-1,455	-9,833	-12,660	-7,001	-18,760	-24,150	-13,340

[1] Remaining subjects continue MRTP use for at least one additional age category

[2] Same cessation rates as US smoking cessation rates, 2005-2008

Table 6-66: Tipping points for base case never tobacco users initiating MRTP versus base case smoking initiators initiating MRTP; table entries are the proportion of base case smoking initiators initiating MRTP necessary to eliminate the survival deficit caused by some base case never tobacco users initiating MRTP instead

Base case never tobacco users initiating MRTP		1%			5%			10%		
		Approximate proportion of base case smoking initiators initiating MRTP needed for								
% switching to smoking	% continuing MRTP use	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit	Stat. sign. survival deficit	No survival deficit or benefit	Stat. sign. survival benefit
0%[1]	100%	<3.0%	4.0%	>7.0%	<14%	20%	>30%	<25%	40%	>60%
0%[2]	100%	<4.0%	5.0%	>9.0%	<20%	25%	>45%	<35%	50%	>80%
0%[1,3]	100%	<1.5%	2.0%	>2.5%	<7%	9%	>12%	<14%	18%	>25%
0%[2,4]	100%	<1.75%	2.5%	>3.5%	<9%	12%	>16%	<18%	24%	>30%
50%[1,#]	50%	<60.0%	-	-	≤100%	-	-	≤100%	-	-
100%[1,#]	0%	<100.0%	-	-	≤100%	-	-	≤100%	-	-

[1] Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter; no MRTP quitting

[2] MRTP initiation rate doubled in the first age category; no initiation after age category 3; no MRTP quitting

[3] Some MRTP users subsequently **quit** (same age-specific smoking cessation rates as were used in the base case (US 2006 estimates) are applied to the MRTP users) and 25% of MRTP quitters resume MRTP

[4] Some MRTP users subsequently **quit** (same age-specific smoking cessation rates as were used in the base case (US 2006 estimates) are applied to the MRTP users) and 50% of MRTP quitters resume MRTP

[#] Too few smoking initiators to reach a tipping point

Table 6-67: Mean difference in number of survivors with 95% posterior intervals (95% PI) for various counterfactual exposure scenarios involving MRTP initiation based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055 (results shown for age category 68-72)

	ERR=0.11			ERR=0.055		
Scenario	Mean	95%	CI	Mean	95%	CI
Sweden	16,448	13,398	19,424	17,506	14,422	20,532
Variations						
Probabilities of transitions following MRTP initiation unchanged compared to Sweden and:						
Probability of MRTP initiation reduced to						
10% of Swedish value	16,784	13,815	19,708	17,428	14,364	20,450
25% of Swedish value	16,724	13,733	19,649	17,439	14,370	20,457
50% of Swedish value	16,627	13,612	19,577	17,459	14,382	20,476
Gateway effect doubled and:						
Probability of MRTP initiation reduced to						
10% of Swedish value	16,735	13,765	19,652	17,377	14,317	20,394
25% of Swedish value	16,601	13,619	19,516	17,313	14,248	20,321
50% of Swedish value	16,385	13,388	19,313	17,209	14,149	20,212

Table 6-68: Mean difference in number of survivors with 95% posterior intervals (95% PI) for various counterfactual exposure scenarios involving switching to MRTP based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055 (results shown for age category 68-72)

	ERR=0.11			ERR=0.055		
Scenario	Mean	95%	CI	Mean	95%	CI
Variations						
Probabilities of transitions following switching to MRTP use unchanged compared to Sweden and:						
Probability of switching to MRTP reduced to						
10% of Swedish value	7,253	5,774	8,720	7,823	6,397	9,245
25% of Swedish value	9,037	7,250	10,802	9,702	7,953	11,454
50% of Swedish value	11,770	9,522	13,980	12,580	10,335	14,806
Returning to smoking doubled and:						
Probability of switching to MRTP reduced to						
10% of Swedish value	7,208	5,736	8,669	7,777	6,359	9,191
25% of Swedish value	8,928	7,158	10,675	9,589	7,858	11,324
50% of Swedish value	11,560	9,344	13,739	12,363	10,147	14,558

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6.6 Tabulated Index of Studies

Consistent with the MRTP Guidance, Swedish Match has prepared a tabulated index of all studies and analyses submitted in support of this Application. The tabulated index is organized according to the following five key areas of investigation:

- Health Risks of the Tobacco Product;
- Effect on Tobacco Use Behavior among Current Users;
- Effect on Tobacco Use Initiation among Non-Users;
- Effect of Marketing on Consumer Understanding and Perceptions; and
- Effect on the Population as a Whole.

The index is further organized by study type (i.e., product analyses, nonclinical studies, studies in adult human subjects, and secondary data analyses and modeling) and identifies each study and analysis by name, section and page numbers. The index also includes, where appropriate, a hypertext link to each study and analysis and/or a citation to the relevant peer-reviewed literature.

7. SCIENTIFIC STUDIES AND ANALYSES

7.1 Product Analyses

Consistent with the MRTP Guidance, copies of all Product Analysis documents submitted in support of this Application were provided to CTP concurrent with submission of the Application.

7.2 Nonclinical Studies

Consistent with the MRTP Guidance, copies of all Nonclinical Study documents submitted in support of this Application have been provided to CTP concurrent with submission of the Application.

7.3 Human Studies

Consistent with the MRTP Guidance, copies of all Human Study documents submitted in support of this Application have been provided to CTP concurrent with submission of the Application.

7.4 Secondary Data Analysis and Modeling

Consistent with the MRTP Guidance, copies of all Secondary Data Analysis and Modeling documents submitted in support of this Application have been provided to CTP concurrent with submission of the Application.

7.5 Other

Consistent with the MRTP Guidance, copies of all other documents submitted in support of this Application have been provided to CTP concurrent with submission of the Application.

8. FOREIGN LANGUAGE CERTIFICATION

English and Swedish are the business languages of Swedish Match, and the Company has corporate offices in both Stockholm, Sweden and in Richmond, Virginia.

Swedish Match conducts business in English on a regular basis and therefore, as was previously agreed upon with CTP, the Company has translated foreign language documents into English for purposes of this Application.

Where applicable, and consistent with the MRTP Guidance, Swedish Match has provided the original foreign language document, its English translation, and the following omnibus certification that each respective translation into English is accurate.

I, Lars-Erik Rutqvist, certify that Company staff and/or outside contractors hired by the Company, who speak and read both English and Swedish have translated from Swedish to English all foreign language documents submitted by Swedish Match in support of this Application. I further certify that each respective English translation is complete and accurate.

Lars Erik Rutqvist, M.D., Ph. D.
Senior Vice President Scientific Affairs
Swedish Match AB
Maria Skolgata 83
SE-118 85 Stockholm
Sweden

9. POSTMARKET SURVEILLANCE AND STUDIES

9.1 Development of Swedish Match Postmarket Program

9.1.1. Program Objectives

Swedish Match has established the foundation for a postmarket surveillance and study program ("Postmarket Program") to satisfy the requirements of Section 911(g)(2)(C)(ii) of the Act and to address the recommendations set forth in the MRTP Guidance. Swedish Match considers the Postmarket Program to be part of a broader product stewardship effort that is based on traditional Company practices, such as GOTHIATEK®; the funding of health and safety research, including clinical trials; and an enduring commitment to transparency and inclusiveness, including the involvement of external, independent reviewers.

The primary objective of the Postmarket Program is to evaluate the benefit to the population as a whole of the labeling changes proposed in this MRTP Application. (b) (4) The focus of the Postmarket Program is to collect evidence to address the key public health questions of who is using the Swedish Match Snus Products and, importantly, how the products are being used.

A second objective of the Postmarket Program is 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. If the requested MRTP orders are granted, Swedish Match is committed to working with CTP and serving in a pilot capacity in the building and testing of a reporting mechanism.

Swedish Match intends to build on the processes established in preparing this MRTP Application in continuing to develop the Postmarket Program and the postmarket surveys central thereto. In particular, Swedish Match will continue to seek the input of external experts, including most importantly, the Swedish Match MRTP Advisory Panel. The Postmarket Program will also seek to benefit from and complement ongoing research initiatives, including the PATH Study. Moreover, as with the premarket consumer perception research, the Company will use its considerable market research experience and expertise to develop and implement a program that blends marketing concepts with regulatory science principles, resulting in a collection of evidence that will support decision-making and future research.

9.1.2. Postmarket Surveys

Swedish Match's postmarket surveys will build on the information and experience derived from Swedish Match's premarket consumer perception survey, as described in Section 6.4 of this Application. Indeed, questions from several sections of the premarket consumer perception survey will also be included in the postmarket surveys. The postmarket surveys will include additional 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 DPM discussed in Section 6.5 of this Application.

Swedish Match expects that the precise configuration of the postmarket survey will evolve substantially over the next year, as CTP reviews this Application and as new tobacco research data on consumer perceptions and behavior indicators become available.[71] Of particular interest is the ongoing Population Assessment of Tobacco and Health Study ("PATH Study"), which will undoubtedly help inform the scope and configuration of the postmarket surveys.

In sum, the Postmarket Program, and the postmarket surveys in particular, will be comprehensive and will include a range of elements and influences. In accordance with Section 911(i)(2) of the Act, Swedish Match will submit a final protocol within 30 days following the issuance of the MRTP orders. This final protocol will be fully developed during FDA's 360-day review period of this MRTP Application.

9.1.3. Marketing Expertise and Resources

In developing the Postmarket Program, Swedish Match has relied, and will continue to rely, upon a range of internal and external inputs, including:

- internal marketing research expertise and resources;
- scientific literature pertaining to product postmarket surveillance in general and tobacco harm reduction products specifically;
- evidence gained from and research conducted to complement the PATH Study; and
- external review of the proposed Postmarket Program by the Swedish Match MRTP Advisory Panel and other independent experts.

Swedish Match devotes considerable attention and resources to market research. Snus-related market research has been conducted in Sweden for decades and has increased in the United States as the product category has grown. Much of the research focuses on consumer behavior and perceptions and seeks information on tobacco initiation, dual use, and the likelihood that users who may have otherwise quit using tobacco products may instead use snus.

Swedish Match has historically relied on a range 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. (b) (4)

[redacted]

[71] A key attribute of an effective surveillance program is flexibility, and a program needs to adapt to changing information needs or operating conditions (Klaucke et al. 1988). Flexibility is particularly important in tobacco science where research activity is increasing exponentially.

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9.1.4. Review of the Scientific Literature

Swedish Match drew upon the scientific literature on postmarket surveillance in general, and articles and reports specific to tobacco harm reduction and the MRTP provisions in the Tobacco Control Act, to develop the Postmarket Program.

The 2001 IOM Report *Clearing the Smoke* highlighted the significance of postmarket surveillance for harm reduction or modified risk tobacco products. In the Principal Recommendations section, the IOM recommends the development of a surveillance system that can assess the impact of promotion and use of harm reduction products on the public health, with elements necessary to assess population impact, including " . . . attitudes, beliefs, product characteristics, distribution and usage patterns, marketing messages . . . , incidence of initiation and quitting . . ." (IOM 2001, p. 8). The Proposed Surveillance System Enhancements section further recommends that such a program should " . . . maximize the ability to assess the public health impact of the introduction of these products, with the explicit goal of maximizing the health of the public." (IOM 2001, p. 188). The IOM also suggests that ancillary prospective studies of representative populations could inform the public health impact of modified risk products, and that such studies would ideally be set up prior to the introduction of the these products (IOM 2001, p. 191). All of the IOM's aforementioned recommendations are consistent with Swedish Match's approach to building a Postmarket Program on the foundation established by the Company's premarket consumer perception research.

The scientific literature on behavior indicators and public perception of tobacco products has increased significantly since the issuance of *Clearing the Smoke*. Several articles (Hamilton et al. 2004; Hughes et al. 2005; Shiffman et al. 2007) have addressed the public health impact of consumer product awareness and identified evidence collection methods that would be appropriate for postmarket surveillance. Swedish Match relied on these and other publications in developing its Postmarket Program, and the Company anticipates that the number of such articles will significantly increase as researchers understand the opportunities presented by the MRTP review process. Swedish Match will continue to monitor the research literature and integrate the evidence into the postmarket surveillance program, consistent with the approach described in a 2012 article in Nicotine & Tobacco Research (O'Connor 2012) that discusses the need "to integrate postmarketing surveillance methods and practices and propose[] research opportunities for the scientific community as the FDA moves toward applying regulatory science to MRTPs."

9.1.5. Evidence Gained from, and Research Conducted to Complement, the PATH Study

The PATH Study is a national longitudinal study of tobacco use and how it affects the health of people in the United States. The study examines many of the areas that comprise Swedish Match's postmarket survey, including the core questions of who is using products and how the products are being used.

Data generated from the PATH Study will inform the further development of Swedish Match's Postmarket Program, particularly as it relates to the PATH Study's investigation of all the following:

(b) (4)

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9.1.6. External Review by independent experts

One of the fundamental premises guiding the development of the Postmarket Program was to build on the processes established in preparing this MRTP Application. One of the most effective components in the development of this Application has been the contribution made by external experts who provided their input and review. This was primarily accomplished through the Swedish Match MRTP Advisory Panel, and the Panel has had, and will continue to have, a significant role in assisting with the development of the Postmarket Program. In addition, and after CTP has accepted the MRTP Application for filing, Swedish Match will reach out to the research and public health communities to determine how best to promote discussion and idea generation leading to a standard for postmarket surveillance in the tobacco space.

The Postmarket Program outlined below builds on the Company's existing market research activities and has a quantitative approach. As a result of discussions within the Swedish Match MRTP Advisory Panel, the Company will consider supplementing the quantitative data with focused qualitative research initiatives to complement the PATH Study's investigations, as noted above.

9.2 Draft – Preliminary Outline of Postmarket Survey Protocol

Swedish Match sets forth below a draft outline of the postmarket survey protocol to be used as part of the Postmarket Program. We invite CTP's comments on this preliminary draft and, as noted above, expect to continue to refine this protocol during the pendency of this Application's review.

Objective:
(b) (4)

Hypotheses:
(b) (4)

Background Information:
Large-scale epidemiological studies in Sweden link the decline in the incidence of lung cancer among Swedish men to their having switched from smoking cigarettes to using Swedish snus. In addition, a large body of epidemiology and clinical data have demonstrated no correlation between the use of Swedish snus and oral cancer, and no increased risk of cardiovascular disease in snus users.

Swedish Match conducted a large web-based premarket consumer perception survey of 13,203 respondents to assess their perceptions and understanding based on (i) the customary smokeless tobacco warnings required by Section 3(d) of the CSTHEA, as amended by Section 204 of the Tobacco Control Act, and (ii) the modified risk warnings proposed in Swedish Match's MRTP Application. The overall results of the Premarket Consumer Perception Study demonstrated that the proposed warning labels for the Snus Products were unlikely to produce unintended negative consequences for the population as a whole, or the former smoker, imminent quitter, minority, low income, or youth subgroups. Study results demonstrated subjects' comprehension and understanding of the proposed warning labels and supported the conclusion that the modified risk claims were not misleading, but rather promoted a better understanding of the actual health risks of snus as compared to cigarettes.

Based on the extensive Swedish Experience evidence and the diagnostic learnings gleaned from premarket consumer perception study, Swedish Match proposed to modify the warnings for its Swedish snus products sold in the United States to include only the following two statements:

- WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes.

- WARNING: This product is addictive.

FDA approved Swedish Match's MRTP Application for the Snus Products on [date]. The purpose of this study is to evaluate changes in consumer perception and use patterns of Swedish snus and other tobacco products following introduction of the modified risk tobacco products to the market.

Study Design:

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(b) (4) (b) (4)
(b) (4) .

Study Endpoints:
[to be determined]

Statistical Analysis:

Methodologies

(b) (4)

Quality Control of the Survey Data Collection

(b) (4)

(b) (4)

Critical Quality Assurance

Figure 9-1 provides an overview of the various phases required to successfully conduct the (b) (4) research that the Postmarket Program contemplates.

Figure 9-1. Critical Quality Assurance Steps

(b) (4)

In the (b) (4) phase, (b) (4) perform three of eight Critical Quality Assurance Steps required to successfully conduct research (b) (4) .

1. ***Representative Sample.*** (b) (4)

   (b) (4)

   (b) (4)

(b) (4)

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Figure 9-2. SSI and M/A/R/C Quota Controls

(b) (4)

2. ***Questionnaire Design.*** (b) (4) (b) will be used in the (b) (4) survey. Examples of (b) (4) include the following:

(b) (4)

(b) (4)

All questionnaires are then reviewed (b) (4) .

3. ***Testing the Survey to Ensure Accuracy of the Questionnaire.*** (b) (4)

Additional Critical Quality Assurance Steps continue during the (b) (4) phase.

4. (b) (4)

(b) (4)

The following table is an example of (b) (4)

(b) (4)

Table 9-1. (b) (4)

(b) (4)

5. (b) (4)

6. (b) (4)

7. (b) (4)

(b) (4)

During the (b) (4) **Collection** phase, additional (b) (4) as part of the Critical Quality Assurance Steps continues. These additional (b) (4) steps include the following:

- (b) (4)

8. Adherence *to* (b) (4) *Guidelines for Marketing Research* – (b) (4) (b) (4) follows (b) (4) guidelines[72] for conducting research (b) (4) . (b) (4)

Protection of Human Subjects:
The study protocol will be developed in conjunction with Swedish Match's MRTP Advisory Panel. Swedish Match believes that informed consent is not required because the postmarket study will not involve the use of test articles (i.e., regulated tobacco products) and, hence, does not constitute a "clinical investigation" for purposes of FDA's Good Clinical Practice regulations.

Timeline:
Survey results are expected to be available in February 2015.

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72 *See* (b) (4)

9.3 References

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10. PREMARKET REVIEW

On March 17, 2011, Swedish Match submitted SE Reports to FDA for the Snus Products which are the subject of this MRTP Application. The SE Reports, along with their associated amendments, set forth the basis for Swedish Match's determination that the products are substantially equivalent, within the meaning of Section 910 of the Act, to tobacco products commercially marketed in the United States as of February 15, 2007.

Because the SE Reports were submitted prior to March 23, 2011, each of the Snus Products may continue to be legally marketed unless and until FDA issues an order that the tobacco product is not substantially equivalent to its predicate tobacco product. No such order has been issued to date, and all ten (10) Snus Products are currently able to be lawfully marketed in the United States.

Notwithstanding the foregoing, FDA currently considers the label of a tobacco product to be a "part" of that product, such that any modification to the label (e.g., adding modified risk claims) automatically makes the product a "new tobacco product" subject to premarket review. Thus, this MRTP Application includes certain SE information for each of the Snus Products, as modified to include, among other things, certain proposed modified-risk claims in their respective labels. In accordance with Section 911(l)(4) of the Act, Swedish Match has submitted SE and MRTP information for the Snus Products in a single submission, and further understands that FDA intends to review the entire submission within 360 days.

SE Reports have been submitted for each of the following Snus Products:

10.1 General Loose (SKU 4852)

10.2 General Dry Mint Portion Original Mini (SKU 4800)

10.3 General Portion Original Large (SKU 4880)

10.4 General Classic Blend Portion White Large – 15 ct (SKU 4877)

10.5 General Classic Blend Portion White Large – 12 ct (SKU 4878)

10.6 General Mint Portion White Large (SKU 4352)

10.7 General Nordic Mint Portion White Large – 15 ct (SKU 4876)

10.8 General Nordic Mint Portion White Large – 12 ct (SKU 4875)

10.9 General Portion White Large (SKU 4881)

10.10 General Wintergreen Portion White Large (SKU 4882)